COVER PAGE SU-G-01 TRIAL PROTOCOL

Official trial title	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
NCT number	NCT04881461
Document date	12-Nov-2021

Clinical trial protocol

Trial ID: SU-G-01

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

Sponsor: ALK-Abelló A/S
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DK-2970 Hørsholm

Investigational medicinal product: 5-grass mix SLIT-drops

Phase: III

Regulatory trial identifier number(s):

EudraCT No: 2020-000455-12

Document status: Final

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Version number: 4.0

Protocol synopsis

Trial ID EudraCT no.	SU-G-01 2020-000455-12
Title of trial	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
Main objectives	Primary objective: • To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and in use of symptom-relief medication during the 2nd Peak Grass Pollen Season (PGPS) Key secondary objectives: • To measure the impact of treatment with 5-grass mix SLIT-drops compared to placebo on health-related quality of life as a result of grass pollen-induced rhinoconjunctivitis during the 2nd PGPS • To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and in use of symptom-relief medication during the 1st PGPS • To measure the impact of treatment with 5-grass mix SLIT-drops compared with placebo on health-related quality of life as a result of their grass pollen-induced rhinoconjunctivitis during the 1st PGPS
Primary estimand	The primary estimand is the absolute difference between the 5-grass SLIT-drops and placebo treatment policies based on the average total combined score (TCS) during the 2nd PGPS in the population is defined by the trial inclusion and exclusion criteria, in the hypothetical situation that all subjects complete treatment for the planned duration.
Secondary estimand	The secondary estimand is the absolute difference between 5-grass SLIT-drops and placebo treatment policies based on the average TCS during the 2nd PGPS, in a population defined by the trial inclusion and exclusion criteria, regardless of whether subjects complete treatment for the planned duration.
Primary endpoint	The primary efficacy endpoint is the average daily allergic rhinoconjunctivitis TCS during the 2nd PGPS
Secondary endpoints	• The average weekly overall rhinitis quality of life questionnaire (RQLQ) score during the 2nd PGPS • The average daily allergic rhinoconjunctivitis TCS during the 1st PGPS

	• The average weekly overall RQLQ score during the 1st PGPS
Trial design	A phase III randomised, parallel-group, double-blind, placebo-controlled trial of 5-grass mix SLIT-drops in adults with grass pollen-induced moderate to severe allergic rhinoconjunctivitis, with or without asthma, conducted over two grass pollen seasons All randomised subjects should receive daily treatment continuously from at least 16 weeks before the anticipated start of the 1st entire grass pollen season (EGPS) through the 2nd EGPS, corresponding to approximately 26 months of treatment At least 9 in-clinic visits and up to 3 phone contacts are planned for each subject
Main assessments	<u>Efficacy assessments:</u> Rhinoconjunctivitis symptoms assessment (Nose symptoms; runny nose, blocked nose, sneezing, itchy nose; Eye symptoms; gritty feeling of the eyes, red/ itchy eyes and watery eyes) Rhinoconjunctivitis rescue medication <u>Safety assessments:</u> Adverse events Clinical laboratory tests Vital and clinical signs [redacted]
Main criteria for inclusion	• Male or female aged ≥18 years on the day informed consent is obtained • A clinical history of grass pollen-induced allergic rhinoconjunctivitis for two years or more with or without asthma • A clinical history of severe allergic rhinoconjunctivitis symptoms (interfering with usual daily activities or sleep) induced by grass pollen, which remain troublesome despite symptomatic treatment with antihistamines, nasal steroids or eye drops during the previous grass pollen season • Positive specific immunoglobulin E (IgE) (defined as ≥class 2, ≥0.70 kU/l) against grass: *Phleum pratense* • Positive skin prick test to *Phleum pratense* at screening
Main criteria for exclusion	• Has a clinically relevant history of symptomatic seasonal and/or perennial allergic rhinoconjunctivitis and/or asthma caused by an allergen other than grass pollen, to which the subject is exposed, which could potentially overlap with the efficacy assessment periods

	• Within the last 3 months before the randomisation visit, has had an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalisation, or treatment with systemic corticosteroids • SLIT treatment with any grass pollen AIT for more than 1 month within the last 5 years. In addition, any SLIT treatment with grass pollen AIT within the previous 12 months • SCIT treatment with any grass AIT reaching the maintenance dose within the last 5 years. In addition, any SCIT treatment with grass AIT within the previous 12 months • Ongoing treatment with any allergy immunotherapy product • Uncontrolled or severe asthma requiring daily use of more than 800 mcg budesonide or equivalent at screening
Investigational medicinal products	ALK 5-grass mix SLIT-drops The 5-grass mix SLIT-drops contains 5 different grass species: *Dactylis glomerata L* (cat grass / cock's foot / orchard grass), *Phleum pratense L.* (timothy), *Lolium perenne L*. (ryegrass), *Anthoxanthum odoratum L* (sweet vernal / vernal grass), *Poa pratensis L.* (Kentucky bluegrass) The treatment schedule for the allergens included in this trial will be as follows: • Initiation: 50 SRU/day for five consecutive days followed by 150 SRU/day for five additional consecutive days • Maintenance: 300 SRU/day (once a day) from day 11 The investigational treatment must be taken continuously during the trial
Duration of treatment	Treatment will be initiated after the end of the entire 2021 grass pollen season and will continue until the end of the 2023 entire grass pollen season corresponding to approximately 26 months of treatment
Number of subjects to be enrolled	440 subjects to be randomised
Number and distribution of trial sites	Estimated 50-65
Statistical methods	Statistical analyses will be performed using SAS software, version 9.4 or later (Cary, North Carolina, SAS Institute Inc.). All efficacy analyses will be performed based on the full analysis set employing hierarchically testing to control the family-wise error rate at 5% level. All endpoints will be tested on a 5% significance level, and all tests and confidence intervals will be 2-sided.

	Using the framework proposed in the ICH E9(R1) addendum, two estimands are defined: primary estimand - trial product estimand and secondary estimand - treatment policy estimand. The main estimator and sensitivity estimator(s) for both estimands will be based on an identical method of statistical analysis, although the actual data used in each analysis may vary according to the different strategies taken for the handling of IEs and missing data. The absolute treatment difference between two treatments will be estimated based on the full analysis set by using model of Mixed Model of Repeated Measurements with relevant endpoint in 1st year and in 2nd year as the response variables, treatment, visit number, interaction of treatment and visit number and asthma indicator as fixed variables and trial site as a random class effect. The estimated difference in adjusted means between the two groups will be presented together with the associated 2-sided 95%-confidence interval and the p-value for the test of no difference. Missing data will be imputed using method of unrestricted random sampling with replacement. The average score will be imputed, but not the daily/weekly values. Rubin's multiple imputation strategy with 1000 imputations will be used. Seed used for imputation will be 12345. Safety evaluation will include description of AEs, and descriptive data analysis of laboratory assessments, and vital signs. The safety evaluation will be based on the safety analysis set (all randomised subjects who received at least one dose of IMP).
International coordinating investigator	[redacted]
Sponsor's name/address	ALK Abelló A/S, Bøge Allé 1, DK-2970 Hørsholm Denmark

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Table of abbreviations

AE	Adverse event
AIT	Allergy immunotherapy
ALT	Alanine aminotransferase
ARC	Allergic rhinoconjunctivitis
AST	Aspartate aminotransferase
BP	Blood pressure
CRA	Clinical research associate
CRO	Clinical research organisation
DMS	Daily medication score
DSS	Daily symptoms score
eCRF	Electronic case report form
EGPS	Entire grass pollen season
EMA	European medicines agency
[redacted]	[redacted]
ESI	Events of special interest
EudraCT	European Union drug regulating authorities clinical trials database
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
HAS	Haute Autorité de Santé
IB	Investigators brochure
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IEC	Independent ethics committee
IgE	Immunoglobulin E
IMP	Investigational medicinal product
IRB	Institutional review board
IRT	Interactive response technology
LABA	Long-acting B-agonist
LSLV	Last subject last visit
MAA	Marketing authorisation application

MAOIs	Monoamine oxidase inhibitors
MCID	Minimal clinically important difference
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed Model of Repeated Measurements
NPPs	Named patient products
PGPS	Peak grass pollen season
PP	Per protocol
QoL	Quality of life
QPPV	Qualified person responsible for pharmacovigilance
RCT	Randomised controlled trial
RQLQ	Rhinitis quality of life questionnaire
SABA	Short-acting β_2-agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software; computer software for statistical programming
SCIT	Subcutaneous allergy immunotherapy
SDTM	Study Data Tabulation Model
SLIT	Sublingual allergy immunotherapy
SLIT-drops	Sublingual allergy immunotherapy drops
SLIT-tablet	Sublingual allergy immunotherapy tablet
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPT	Skin prick test
SRU	Standardized reactivity unit
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse events
TCS	Total combined score
WHO	World Health Organisation

Table of definitions

Anaphylaxis	The definition of anaphylaxis (**Sampson H.A.et al. 2006**) includes any 1 of the following 3 criteria: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus, or flushing, or swollen lips, tongue, or uvula) AND either respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced Peak Expiratory Flow (PEF), hypoxemia) or reduced BP* or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence) 2. Two or more of the following that occur rapidly after exposure to a likely allergen for the subject (minutes to several hours): a) Involvement of the skin-mucosal tissue (e.g. generalised hives, itch-flush, swollen lips, tongue, or uvula) b) Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c) Reduced BP* or associated symptoms (e.g. hypotonia [collapse], syncope, incontinence) d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting) 3. Reduced BP after exposure to known allergen for the subject (minutes to several hours): low systolic BP* or greater than 30% decrease in systolic BP *Low systolic BP is defined as less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years
Completed subject	A randomised subject is considered completed if he/she has not discontinued the trial before visit 9
Completion date	For each completed subject, the date of the last scheduled procedure/end of trial visit (visit 9)
Concomitant medication	All medications being continued by a subject on entry into the trial and all medications given in addition to the background treatment during the trial
Date of last contact	Date of the last contact, either by telephone or in a visit
End of trial	The overall end of the trial is defined as the date of last follow-up phone visit (TC follow-up) for the last subject in the trial
Estimand	A precise description of the treatment effect reflecting the clinical question of interest posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared **(ICH 2020)**.
Grass pollen season	• Start date: The first day of 3 consecutive days with (non-missing) pollen count larger than or equal to 10 grains/m3 • Stop date: The last day before 3 consecutive days with (non-missing) pollen count less than 10 grains/m3 • Peak: The 15 days period with the highest average pollen count during the entire grass pollen season
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products with a marketing authorisation used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form

Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated **(ICH 2020)**.
IRT	Automated system to be used for managing randomisation, subject enrolment and trial supply management in this trial
LSLV	Last scheduled physical visit for any subject (visit 9)
Life-threatening asthma	Asthma worsening that requires intubation and/or is associated with hypercapnia requiring non-invasive ventilator support
Primary completion date	Date of the last data collection for the primary endpoint (ClinicalTrials.gov) is the last scheduled physical visit for any subject (visit 9)
Rescue medication	Medicinal products provided by ALK when the efficacy of the IMP is not sufficient or likely to cause an adverse event (AE) to the subject or to manage an emergency situation in relation to grass pollen allergy symptoms in agreement with the EMA Definition of IMPs and Use of AMPs Consultation Document **(EMA 2016)** The rhinoconjunctivitis rescue medication in this trial is: • Antihistamine tablets • Antihistamine eye drops • Corticosteroid nasal spray
Source documents	Source documents are original documents, data, and records from which the subjects' electronic case report form (eCRF) data are obtained. These include, but are not limited to, hospital records (from which medical history and concomitant medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence
Systemic corticosteroids	Oral, intramuscular, or intravenously administered corticosteroids
TEAE	TEAEs are defined as adverse events with start date and/or time on or after the time of first IMP administration and no later than 7 days after last IMP administration
Trial completion	The trial is completed once the integrated clinical trial report (ICTR) is signed
Trial discontinuation date	Date of subject trial discontinuation. In case of subjects lost to follow-up, the discontinuation date is defined as the date the investigator/sponsor decides to discontinue the subject

Protocol versions

Date	Version	Description of document	Rationale for amendment
29-Jan-2020	1.0	Final Protocol	N/A
11-Mar-2020	2.0	Final Protocol	Version update to align with IB
23-Oct-2020	3.0	Final Protocol	Key changes: • To address EMA recommendations in the 'Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic' **(EMA 2020)** • FEV_1 removed from screening visit 1 and from subsequent visits after randomisation visit 2 • Oropharyngeal exam removed from screening visit 1 and from subsequent visits after randomisation visit 2 • Addition of retention TC between visits V5 and V6 • Removal of visit schedules/content from section 10. This section is not mandatory, is repetitive to the flow chart and assessments and creates a risk for error • Estimand has been added as per ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (Step 5) **(ICH 2020)**
12-Nov-2021	4.0	Final Protocol	Key changes • List of appendices updates • Flowchart: Time window for V4 and V7 expanded to allow up to 14 days prior to EGPS. Footnote 1 updated with 'optional' referring to TC1 and updated year of randomisation to 2021. • 3.4: End of trial definition updated to the date of the last follow-up phone visit (TC follow-up) for the last subject in the trial. • 7.: Table 2 updated due to reassessment of criticality of restricted and prohibited concomitant medication. • 11.4: clarification on stratification added to medical history: A subject should be stratified as asthmatic if they have been diagnosed and/or treated for asthma in adulthood. • 11.14: Assessments reordered to ease readability • 12.1: Deletion of bullet stating that events defined as efficacy endpoints should not be recorded as AEs. • 12.1: Addition of bracket in sentence: Selected AEs (non-serious or serious) will be considered ESIs • 12.3 and 12.3.1 Specification of ESI forms and procedures • 15.11.4 Correction of undefined reference • Appendix 3 updated due to change of central lab and CRO legal entity and contact details

Flow chart

Visit ID:	Protocol section	V1	V2	TC1	V3	V4	V5	TC2	V6	V7	V8	V9	TC Follow-up	Unsched-uled visit
Visit: V=Site Visit TC=Telephone Contact		Screening	Random-isation	Optional between V2 and V3[1]	1st off-season	1st pre-EGPS[2]	1st on-season	Retention between V5 and V6	2nd off-season	2nd pre-EGPS[2]	2nd on-season	End of trial	Post-treat-ment	
Time Window		At least 3 days before V2	At least 16 weeks before start of 1st EGPS[2]	November 2021	January 2022	14 to 0 days before start of 1st EGPS[2]	7 to 0 days before expected PGPS[3]	4-12 weeks before V6	January 2023	14 to 0 days before start of 2nd EGPS[2]	7 to 0 days before expected PGPS[3]	1 to 7 days from end of 2nd EGPS[2]	4 to 10 days after V9	As necessary
Informed consent	**11.1**	X												
Demography and body measurements	**11.3**	X												
Smoking habits	**11.5**	X												
Medical history	**11.4**	X												
In-/exclusion criteria	**4.1/4.2**	X	X											
Randomisation	**6**		X											
Urine pregnancy test[4]	**11.10**	(X)	(X)		(X)	(X)	(X)		(X)	(X)	(X)	(X)		(X)
Physical examination	**11.8**	X										X		(X)

[1] An optional retention telephone contact for those subjects randomised between start of August and end of November 2021
[2] EGPS- entire grass pollen season (see Appendix 5)
[3] PGPS- peak grass pollen season (see Appendix 5)
[4] For females of child-bearing potential, urine pregnancy tests should be performed at each visit and if a menstrual period is missed.

Visit ID:	Protocol section	V1	V2	TC1	V3	V4	V5	TC2	V6	V7	V8	V9	TC Follow-up	Unsched-uled visit
Visit: V=Site Visit TC=Telephone Contact		Screening	Random-isation	Optional between V2 and V3[1]	1st off-season	1st pre-EGPS[2]	1st on-season	Retention between V5 and V6	2nd off-season	2nd pre-EGPS[2]	2nd on-season	End of trial	Post-treat-ment	
Oropharyngeal examination	**11.8**		X											(X)
Vital signs	**11.12**	X	X		X	X	X		X	X	X	X		(X)
Lung function test	**11.7**		X											(X)
Blood and urine samples for safety laboratory assessments	**11.13**	X										X		(X)
Blood sample for specific IgE	**11.14**	X												
[redacted]	**11.14**	X			X	X			X			X		(X)
Blood sample for biobanking[5]	**11.15**	(X)										(X)		
SPT	**11.11**	X	(X)											(X)
Intake of IMP at clinic	**9.1**/**9.2**		X											
Instruct the subject in use of IMP	**9.1**/**9.2**		X											
Record previous and concomitant medication	**11.6**	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess and/or record AEs	**12.2**	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess eosinophilic eosophagitis	**11.9**	X	X		X	X	X		X	X	X	X		(X)
Dispense IMP	**8.1**		X		X	X	X		X	X	X			(X)

[5] Only if biobanking specific informed consent has been signed and according to country specific regulations.

Visit ID:	Protocol section	V1	V2	TC1	V3	V4	V5	TC2	V6	V7	V8	V9	TC Follow-up	Unsched-uled visit
Visit: V=Site Visit TC=Telephone Contact		Screening	Random-isation	Optional between V2 and V3[1]	1st off-season	1st pre-EGPS[2]	1st on-season	Retention between V5 and V6	2nd off-season	2nd pre-EGPS[2]	2nd on-season	End of trial	Post-treat-ment	
Dispense rescue medication	**8.2**					X	(X)			(X)	(X)			(X)
Trial medication collection, compliance check compliance and drug accountability	**8.5**				X	X	X		X	X	X	X		X
[redacted]	**11.17**		X									X		
Issue and instruct in use of E-diary/LogPad	**11.16**				X									
Instruct in use of E- diary/LogPad	**11.16**					X	(X)			X	(X)			
eDiary completion: • [redacted]	**11.16.5**						X[6]							
eDiary completion: • RQLQ	**11.16.4**				X	X…….X[7]				X…….X[7]				
eDiary completion: • Symptoms • Medication	**11.16.1**/ **11.16.2**					X…….X[7]				X…….X[7]				
eDiary completion: • [redacted]	**11.16.3**					X…….X[7]				X…….X[7]				
Review eDiary recordings	**11.16**						X		X	X	X	X		(X)
Collect eDiary												X		

[6] The [redacted] will be performed at the defined end of the EGPS for each region (see Appendix 5)

[7] Rhinoconjunctivitis symptoms scores, use of rescue medication and [redacted] will be collected daily and RQLQ will be collected weekly during the EGPS until the defined end of the EGPS for each region (see Appendix 5)

1 INTRODUCTION

1.1 Disease background and current treatment modalities

Disease Background

Allergic rhinoconjunctivitis (ARC) represents a global health problem, with grass pollen induced ARC being the most prevalent pollen allergy. An estimated 15 to 40% of the global population are affected **(Brozek et al. 2017)** and the number appears to be rising **(Linneberg et al. 2007)**. Although the prevalence of seasonal ARC (hay fever) varies, studies including more than 100,000 subjects have documented a high prevalence of ARC in Western European countries. If left untreated, ARC is considered to be one of the major risk factors for the development of asthma **(Corren 2007)**. In 2013, data from the World Health Organization (WHO) showed the prevalence of asthma in the European Union to be 9.4% for children and 8.2 % for adults **(Selroos et al. 2015)**. Allergy immunotherapy (AIT) is a well-established therapy for improving ARC symptoms and limiting the progression of the disease by preventing the development of asthma and new allergen sensitisations **(Jutel et al. 2016)**.

Current Treatment Modalities

The therapeutic management of allergy currently involves one or more of the following approaches:

- Allergen avoidance
- Symptomatic medication
- Specific immunotherapy

The strategy of allergen avoidance is difficult for an airborne allergen such as grass pollen, and while symptomatic medications may offer short-term relief of symptoms, they do not treat the underlying cause of allergy and hence cannot provide long-term remission. Furthermore, a significant number of people with allergic rhinitis continue to experience residual allergic symptoms despite use of symptomatic pharmacotherapy **(Feliziani et al. 1995; Niggemann et al. 2006)**. Only specific immunotherapy targets the underlying allergic disease and, as such, has the potential to produce long-term remission as well as to prevent the development of new sensitisation and asthma. Traditionally, immunotherapy has been administered subcutaneously and due to the requirement for injectable delivery and the safety profile, its administration has been restricted to a clinical setting. The development of immunotherapy as sublingual drops and as tablets has provided a safer and more convenient alternative to the subcutaneous route **(Durham & Penagos 2016)**, allowing home administration by the patient.

Sublingual immunotherapy (SLIT) administered as drops or tablets is an approved form of AIT shown to be effective in the treatment of severe grass pollen-induced ARC **(Dretzke et al. 2013)**.

The French National Authority for Health (Haute Autorité de Santé; HAS) have requested the demonstration of treatment benefit of allergen products specifically prepared for individuals (or named patient products (NPPs)) that are currently marketed in France. The SLIT NPP developed by ALK and currently registered under the French nominative authorisation APSI[8] in France, is OSIRIS®.

[8] In France the NPP status is named allergènes préparés spécialement pour un individu (APSI [allergens specially prepared for individuals])

1.2 Stage of development

OSIRIS® is a SLIT-drop product that has been available to patients in France since 1992. OSIRIS® has been available in selected European countries as SLIToneULTRA® since 2012.

OSIRIS® and SLIToneULTRA® have the same composition of excipients (sodium chloride, sodium bicarbonate and glycerol), however they differ in their presentation: OSIRIS® is available in vials of 3000 SRU/10 ml with a syringe to deliver the volume corresponding to 300 SRU each day, whereas SLIToneULTRA® is available as single-dose containers of 0.5 ml containing 50 SRU, 150 SRU or 300 SRU per 0.5 ml. OSIRIS® and SLIToneULTRA® 5-grass mixes contain 20% each of the homologous grass species *Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis* and *Anthoxanthum odoratum.*

In agreement with the HAS, SLIToneULTRA® five-grass mix has been selected as the investigational medicinal product in this trial because of the similarity of the formulations and due to the single-dose delivery in a clinical trial setting. SLIToneULTRA® five-grass mix will be referred to hereafter by the generic name 5-grass mix SLIT-drops.

1.3 Trial rationale

The rationale for conducting this trial is to generate further clinical data on the efficacy and safety of 5-grass mix SLIT-drops based on a request from HAS requiring Marketing Authorisation Application (MAA) holders of NPPs available in France to provide more clinical evidence to support reimbursement in France. As well as assessing the sum of rhinoconjunctivitis symptom severity in combination with intake of rescue medication, this trial will also assess in a robust manner, the effect on quality of life of AIT in subjects suffering from grass pollen allergic rhinitis.

ARC is the main driver for prescription of NPPs in France, even exceeding NPP prescriptions for allergic asthma, and as such, ARC has been selected as the target condition for this trial. ARC has been widely documented as having a strong impact on quality of life (QoL) of patients with this disease (**Bousquet et al. 2008; Bousquet et al. 2001**). It follows then, that demonstration of QoL improvement on this trial will bring additional, relevant data to support the benefit of clinical treatment.

1.4 Benefit-risk assessments

SLIT has been shown to be effective for the treatment of severe grass pollen-induced AR **(Dretzke et al. 2013)** and is recommended by international guidelines for treatment of severe AR **(Brozek et al. 2017; Canonica et al. 2009; GINA Executive Committee 2018)**. SLIT can be administered in the form of drops or tablets; sublingual drops represent a convenient treatment regimen for home use allowing for gradual up-dosing to the recommended maintenance dose.

To date, no clinical trials have been conducted on SLIToneULTRA® 5-grass mix. However, two clinical trials (03-ITS-2001-Fr and OS-G-01) and two non-interventional studies (NI-SU-X-02 and NI-XX-01) have been conducted with closely related SLIToneULTRA® and OSIRIS® grass products **(de Blay et al. 2007; Moral et al. 2016; Nittner-Marszalska et al. 2013; Paul-Ehrlich-Institut 2019)**. These 4 trials support the efficacy and safety for SLIToneULTRA® 5-grass-mix, since all of the grass species used in these trial products are within the same homologous group.

Of these four trials conducted with SLIToneULTRA® and OSIRIS® grass products, one investigated efficacy and all investigated safety. Further information can be found in the current edition of the IB.

In the efficacy trial, **(de Blay et al. 2007)** demonstrated a trend in favour of treatment with OSIRIS® 3-grass mix compared with placebo based on the sum of rhinoconjunctivitis and asthma symptom and rescue medication scores. This difference was not statistically significant, however treatment was administered only three times a week and the active group contained significantly more subjects with asthma at inclusion than the placebo group. A *post hoc* analysis on subjects without asthma showed that subjects in the active treatment group had statistically significant better overall clinical scores compared with subjects in the placebo group.

In all four SLIToneULTRA® and OSIRIS® trials, 389 subjects received grass treatment **(de Blay et al. 2007; Moral et al. 2016; Nittner-Marszalska et al. 2013; Paul-Ehrlich-Institut 2019)**. In general, treatment was found to be well-tolerated: The majority of adverse events were mild or moderate local events and no treatment-related serious adverse events were reported.

This safety profile is consistent with post-marketing data available in the ALK global safety database for 5-grass mix SLIT-drops where broad market exposure exists for SLIT-drops. For SLIToneULTRA® and OSIRIS® (all product/allergen variants) the registered cumulative patient exposure as of 31-Jan-2020 is approximately 1,570,000 treatment years and for grass products alone, the total exposure is approximately 316,000 treatment years. For 5-grass mix SLIT-drops, the cumulative patient exposure is approximately 1,800 treatment years. Systemic allergic reactions, including anaphylactic shock, have been identified as an important identified risk and eosinophilic oesophagitis as an important potential risk. Only 5 cases of anaphylactic shock (1 concerning use of SLIToneULTRA® 5-grass-mix) and 2 potentially related cases of eosinophilic oesophagitis have been reported in the cumulative post-marketing experience of the SLIT drops, thus the safety concerns are considered of very low risk (for further details, please refer to the current edition of the IB).

In addition, published literature commonly describes SLIT administration as safe and SLIT-related reactions as mild and sometimes as self-resolving **(Ciprandi & Marseglia 2011)** and no mortalities related to SLIT administration have been reported **(Leatherman et al. 2015)**.

The purpose of the present trial is to investigate the clinical efficacy of the 5-grass mix SLIT-drops compared with placebo based on the total combined rhinoconjunctivitis symptoms and medication intake, with daily treatment and stratified treatment allocation based on a pre-existing diagnosis of asthma. In addition, the treatment benefit in terms of improvement in quality of life will be investigated using the rhinitis quality of life questionnaire (RQLQ) tool **(Juniper et al. 1999)**. Both treatment groups will be provided rescue medication to treat rhinoconjunctivitis symptoms during the trial. Subjects will be medically monitored and provided with appropriate treatment if warranted.

In conclusion, subjects in the present trial may benefit from improvement in grass pollen allergic symptoms and medication use as well as from improvement in RQLQ. It is not considered that treatment with the trial product will expose subjects to any risks that unduly jeopardise their health. Thus, the benefits of trial participation outweigh the risks.

1.4.1 Considerations regarding COVID-19

Regarding the pandemic of COVID-19, it is important to highlight that subjects' safety is always first priority. Participating in this trial, including receiving treatment with AIT, is not expected to increase subjects' risk of contracting communicable diseases, including COVID-19. The examinations and procedures (e.g. lung function, SPT, blood sampling) included in this trial are of minimal burden to subjects and do not include assessment outside what standard medical evaluation of allergic subjects would include. If regional circumstances related to COVID-19 change, local guidance should be followed (see appendix 6).

1.5 Ethical considerations

This clinical trial will follow the principles of the Helsinki Declaration 1964 and subsequent amendments and clarifications **(World Medical Association 2013)**. The trial will be approved by local independent ethics committees (IECs)/institutional review boards (IRBs) and health authorities before initiation.

A placebo group will be used as a control-group in the trial. A placebo group is considered ethically justifiable since subjects in both treatment groups will be provided with rescue medication to treat their rhinoconjunctivitis symptoms during the trial. Furthermore, subjects will be medically monitored during the trial and provided with appropriate treatment if warranted. Finally, subjects can withdraw from the trial at any time if they find the treatment intolerable and without giving reason.

2 OBJECTIVES, ESTIMANDS AND ENDPOINTS

2.1 Primary objective

The primary objective is to compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and in use of symptom-relief medication during the 2nd Peak Grass Pollen Season (PGPS).

2.2 Secondary objectives

2.2.1 Key secondary objectives

- To measure the impact of treatment with 5-grass mix SLIT-drops compared to placebo on health-related quality of life as a result of grass pollen-induced rhinoconjunctivitis during the 2nd PGPS.
- To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and in use of symptom-relief medication during the 1st PGPS.
- To measure the impact of treatment with 5-grass mix SLIT-drops compared to placebo on health-related quality of life as a result of their grass pollen-induced rhinoconjunctivitis during the 1st PGPS.

2.2.2 Supportive secondary objectives

- To measure the impact of treatment with 5-grass mix SLIT-drops compared to placebo on health-related quality of life as a result of their grass pollen-induced rhinoconjunctivitis during the 1st Entire Grass Pollen season (EGPS) and during the 2nd EGPS.
- To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms and in use of symptom-relief medication during the 1st EGPS and during the 2nd EGPS.
- To compare the efficacy of 5-grass mix SLIT-drops to placebo in relieving grass rhinoconjunctivitis symptoms during the 1st and during the 2nd PGPS, and during the 1st EGPS and during the 2nd EGPS.

- To compare the efficacy of 5-grass mix SLIT-drops to placebo in use of symptom-relief medication during the 1st and during the 2nd PGPS, and during the 1st and during the 2nd EGPS.

2.3 Exploratory objectives

2.4 Primary estimand

The primary estimand is the absolute difference between the 5-grass SLIT-drops and placebo treatment policies based on the average TCS during the 2nd PGPS, in a population defined by the trial inclusion and exclusion criteria, in the hypothetical situation that all subjects complete treatment for the planned duration regardless of whether they take rescue medication.

This estimand will be referred to as the ‘trial product estimand’. The trial product estimand assesses the anticipated effect of the 5-grass SLIT-drops if it is taken as instructed. This estimand is considered to be of most relevance to the patient, as it describes the potential benefit they could obtain from the 5-grass SLIT-drops if they adhere to treatment for the planned duration. Adherence to treatment is considered important in immunotherapy since the optimal effect of immunotherapy is expected when taken consistently for a longer period.

2.5 Secondary estimand

The secondary estimand is the absolute difference between 5-grass SLIT-drops and placebo treatment policies based on the average TCS during the 2nd PGPS, in a population defined by the trial inclusion and exclusion criteria, regardless of whether subjects complete treatment for the planned duration or take rescue medication.

This estimand will be referred to as the ‘treatment policy estimand’. The treatment policy estimand assesses the treatment effect regardless of adherence to treatment and provides a broad perspective of the treatment effect in clinical practice in the selected population of patients. This estimand is in line with the ‘intention to treat’ principle and provides a robust assessment of the efficacy of the 5-grass SLIT-drops.

2.6 Estimands for key secondary and supportive secondary objectives

The trial product estimand and treatment policy estimand, specified for the primary objective in Sections **2.4** and **2.5** respectively, are defined for each of the key secondary and supportive secondary objectives in a similar manner.

2.7 Primary endpoint

The primary efficacy endpoint is the average daily allergic rhinoconjunctivitis total combined score (TCS) during the 2nd PGPS.

2.8 Secondary endpoints

2.8.1 Key secondary endpoints

- The average weekly overall rhinitis quality of life questionnaire (RQLQ) score during the 2nd PGPS.
- The average daily allergic rhinoconjunctivitis TCS during the 1st PGPS.
- The average weekly overall RQLQ score during the 1st PGPS.

2.8.2 Supportive secondary endpoints

- The average weekly overall RQLQ score during the 1st EGPS.
- The average weekly overall RQLQ score during the 2nd EGPS.
- The average daily allergic rhinoconjunctivitis TCS during the 1st EGPS.
- The average daily allergic rhinoconjunctivitis TCS during the 2nd EGPS.
- The average daily allergic rhinoconjunctivitis DSS during the 1st PGPS.
- The average daily allergic rhinoconjunctivitis DSS during the 2nd PGPS.
- The average daily allergic rhinoconjunctivitis DSS during the 1st EGPS.
- The average daily allergic rhinoconjunctivitis DSS during the 2nd EGPS.
- The average daily allergic rhinoconjunctivitis DMS during the 1st PGPS.
- The average daily allergic rhinoconjunctivitis DMS during the 2nd PGPS.
- The average daily allergic rhinoconjunctivitis DMS during the 1st EGPS.
- The average daily allergic rhinoconjunctivitis DMS during the 2nd EGPS.

2.9 Exploratory endpoints

3 TRIAL DESIGN

3.1 Summary of trial design

This is a phase III randomised, parallel-group, double-blind, placebo-controlled trial of 5-grass mix SLIT-drops in adults with grass pollen-induced moderate to severe allergic rhinoconjunctivitis, with or without asthma, to be conducted in conformance with Good Clinical Practices (GCP). The trial will be conducted over two grass pollen seasons.

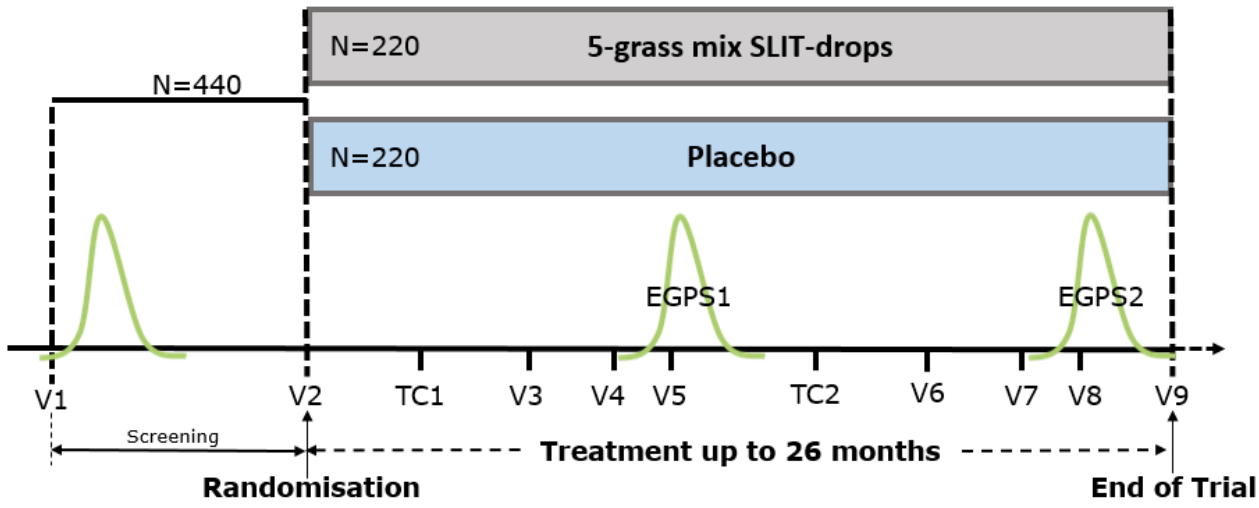
A total of 440 adults will be randomised (1:1) to receive either ALK sublingual solution of grass allergy extracts for immunotherapy (5-grass mix SLIT-drops) or placebo once daily.

All subjects should receive daily treatment continuously from at least 16 weeks before the anticipated start of the 1st EGPS through the 2nd EGPS, corresponding to approximately 26 months of treatment (see **Figure 1**). The subjects will be asked to complete a RQLQ diary one time in January 2022 during the off-season for grass and tree-pollen. Subjects will be asked to fill in a daily diary for the EGPS to capture information on rhinitis and/or conjunctivitis symptoms, use of symptom-relieving medications and impact of rhinitis and/or conjunctivitis on daily life and quality of life. Subjects will also be asked to fill in a weekly RQLQ diary during the EGPS.

Data for the primary endpoint: the average daily allergic rhinoconjunctivitis TCS during the 2nd PGPS, will be collected by the subjects completing questions related to their daily symptoms and medication use in an electronic diary. No interim analysis is planned.

Routine safety surveillance will be conducted throughout the trial. The follow-up visit will be conducted via a telephone call approximately one week after the End of Trial visit.

Figure 1 Trial design



EGPS: Entire grass pollen season

3.1.1 Definition of pollen seasons

The grass pollen seasons vary across regions both in intensity and duration although the seasonal pollen index start and stop dates of grass pollen is predictable **(Sofiev 2017)**. The definitions of the

grass pollen season start, stop and grass pollen peak are provided in **Table 1**. The grass pollen expected start and stop dates for each region are specified in Appendix 5.

Table 1 Grass pollen season definitions

Start date	The first day of 3 consecutive days with (non-missing) pollen count larger than or equal to 10 grains/m^3.
Stop	The last day before 3 consecutive days with (non-missing) pollen count less than 10 grains/m^3.
Peak	The 15 days period with the highest average pollen count during the entire grass pollen season.

The actual pollen plots of the grass pollen season will be reviewed in order to validate the pollen counts in the season described in the above criteria. The final pollen seasons will be defined prior to database lock and further specified in the statistical analysis plan (SAP).

eDiary data will be collected during the expected EGPS season. The expected dates for each country are provided in Appendix 5. More precise dates for some regions are specified since larger countries can have different EGPS start and stop dates from north to south. If monitoring of the weather effecting the grass pollen season identifies a prolongation of the expected stop date of the EGPS for any country or region in Appendix 5, the effected site will be notified and the eDiary will be updated to allow for additional data collection.

3.2 Discussion of design

The design for the present trial is based on the recommendation from the EMA guideline on the clinical development of products for AIT for the treatment of allergic diseases **(EMEA 2008)**, as recommended in the WHO position paper on AIT for development of SLIT **(Bousquet et al. 1998)**, and based on the experience from previous ALK trials with AIT.

The primary endpoint TCS is the sum of the average rhinoconjunctivitis DSS and the average DMS during the 2nd PGPS. The primary endpoint analysis is from the peak grass pollen season in order to minimise the effect of natural variation that exists over the entire grass pollen season. As symptom-relieving medications are allowed in the trial, it is reasonable to adjust the reported symptom score to account for the symptom-relieving medications used, in order to get a more accurate representation of symptomatology.

Scientific recommendations for ARC trials currently describe a primary outcome reflecting a combined symptom and medication score severity with secondary outcome measures including validated symptom scores and/or health related QoL questionnaires **(Pfaar et al. 2014)**. However, in order to make additional claims on QoL, hierarchical testing will be employed on this trial with efficacy endpoints including symptom and medication scores and RQLQ QoL scores.

The symptom score has been designed based on EMA guidance documentation **(EMEA 2008)** and on scoring from previous and ongoing ALK trials. The medication score proposed for this trial has been used in numerous clinical trials performed with the authorised products GRAZAX®/GRASTEK® and RAGWITEK® **(Blaiss et al. 2011) (Nelson et al. 2011) (Creticos et al. 2013) (Maloney et al. 2014)** and was developed by the sponsor based on recognised guidelines **(EMEA 2008) (Canonica et al. 2007)**, as well as on thorough discussions with key opinion leaders and specialists within the field of allergy.

Clinical development experience with grass AIT has shown that the treatment effect during the first PGPS is strongly linked to the duration of the pre-seasonal exposure to AIT. Results from clinical

trials using the SLIT tablet GRAZAX® with grass pollen allergen (GT-02, GT-07 and GT-08), showed significant effect on improvement of symptom and medication scores following a pre-seasonal treatment period of at least 8 weeks prior to the start of the PGPS. This improvement continued over time **(Calderon et al. 2007)**. Furthermore, clear time-dependent increases in allergen-specific antibody responses have been observed during the first 8 weeks of daily dosing, with elevated levels sustained over a longer period **(Malling et al. 2006)**. Based on this data and the cumulative clinical development experience with grass AIT, the GRAZAX® Summary of Product Characteristics (SmPC) recommends initiation of treatment of at least 16 weeks prior to expected initiation of the GPS. Following this, a pre-season exposure of at least 16 weeks has been included in this trial in order to see a treatment effect during the first EGPS.

The trial is designed to be conducted over two grass pollen seasons in accordance with **(EMEA 2008)** concerning sustained clinical effect. In order to demonstrate robust QoL data, subjects in this trial will be treated with investigational medicinal product (IMP) for up to 26 months and will be assessed over two extended grass pollen seasons.

A double-blinded set-up has been chosen to minimise the potential bias resulting from differences in management, treatment or assessment of subjects and/or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.

A placebo arm has been introduced to establish the superiority of the IMP compared to placebo with respect to reducing the TCS.

3.3 Justification of dose

Efficacy of SLIT-drops has been found to be dose-dependent in clinical trials where the dose was increased gradually from 50 to 150 SRU/day over 10 days to reach the minimum recommended maintenance dose of 300 SRU (see section **8.1**) **(Braun et al. 2010)**. This up-dosing titration schedule will be used for the current trial and was previously assessed with *Phleum pratense* OSIRIS® sublingual solution and found to be well-tolerated**(Nittner-Marszalska et al. 2013)** . Based on the results of immunological data, 300 SRU was established as the optimal tested dose for maintenance treatment. The 300 SRU dose is currently used in daily clinical practice **(Didier et al. 2015)** because it is considered safe and efficient **(Canonica et al. 2009)**.

3.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed the last scheduled visit (V9).

The end of the trial is defined as the date of the last follow-up phone visit (TC follow-up) for the last subject in the trial.

4 TRIAL POPULATION

Subjects randomised in this trial will be adults ≥18 years of age, with a clinical history of allergic rhinoconjunctivitis (with or without asthma) as diagnosed by a physician and having had symptoms despite treatment with antihistamines or nasal steroids during the two previous grass pollen seasons.

Subjects meeting all the inclusion criteria and none of the exclusion criteria will be considered eligible for the trial.

4.1 Inclusion criteria

Subjects are eligible to be included in the trial only if all the following criteria apply:

I1. Written informed consent obtained before any trial related procedures are performed

I2. Male or female aged ≥18 years on the day informed consent is obtained

I3. For female subjects of childbearing potential,[9] a negative pregnancy test and willingness to practice appropriate contraceptive methods[10] until the follow-up visit must be confirmed

I4. A clinical history of grass pollen-induced allergic rhinoconjunctivitis for two years or more with or without asthma[11]

I5. A clinical history of severe allergic rhinoconjunctivitis symptoms (interfering with usual daily activities or sleep) induced by grass pollen, which remain troublesome despite symptomatic treatment with antihistamines, nasal steroids or eye drops during the previous grass pollen season

I6. Positive specific immunoglobulin E (IgE) (defined as ≥class 2, ≥0.70 kU/l) against grass: *Phleum pratense*

I7. Positive skin prick test (SPT)[12] to *Phleum pratense* at screening

I8. The subject must be willing and able to comply with the trial protocol

[9] Females, after the first menstrual period. Females who are post-menopausal are considered not to be of child-bearing potential. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[10] For the purpose of this protocol the following contraceptive methods are considered appropriate: oral contraceptives, transdermal patches or depot injection of a progestogen drug (starting at least 4 weeks prior to IMP administration); double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent; IUD, IUS, implant, or vaginal ring (placed at least 4 weeks prior to IMP administration); or male partner sterilisation (vasectomy with documentation of azoospermia) prior to the female subject's entry into trial and is the sole sexual partner for that female subject. Sexual abstinence is acceptable as contraceptive if it is true abstinence and in line with the usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. *However, national requirements regarding contraception should always be followed.*

[11] If medical records are not available, verbal history from subject can be used to fulfill this criterion and this must be documented in the medical records by the investigator.

[12] A positive Skin Prick Test (SPT) is defined in the SPT Guideline. For subjects in Europe, a positive SPT is defined as a wheal size ≥3 mm. If medication that could interfere with the skin prick test, according to **Table 7** has not been washed out and the positive control is <3 mm for subjects in Europe, the skin prick test can be repeated after the interfering medication has been washed out.

4.2 Exclusion criteria

Subjects are excluded from the trial if any of the following criteria apply:

E1. Previous participation in this trial. Participation is defined as screening

E2. Has a clinically relevant history of symptomatic seasonal and/or perennial allergic rhinoconjunctivitis and/or asthma caused by an allergen other than grass pollen, to which the subject is exposed, which could potentially overlap with the efficacy assessment periods

E3. Within the last 3 months before the randomisation visit, has had an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalisation, or treatment with systemic corticosteroids

E4. Reduced lung function: FEV_1 <70% of predicted value after adequate pharmacologic treatment[13]

E5. SLIT treatment with any grass pollen AIT for more than 1 month within the last 5 years. In addition, any SLIT treatment with grass pollen AIT within the previous 12 months

E6. SCIT treatment with any grass AIT reaching the maintenance dose within the last 5 years. In addition, any SCIT treatment with grass AIT within the previous 12 months

E7. Ongoing treatment with any allergy immunotherapy product

E8. Uncontrolled or severe asthma requiring daily use of more than 800 mcg budesonide or equivalent at screening

E9. Severe chronic oral inflammation

E10. Any nasal or naso/oropharyngeal condition that could confound the efficacy or safety assessments (e.g. hypertrophy of the pharyngeal/palatine tonsils, clinically relevant nasal polyps, a history of paranasal sinus surgery or surgery of nasal turbinates)[14]

E11. Has a diagnosis of eosinophilic oesophagitis

E12. At randomisation, current symptoms of, or treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infectious process (serous otitis media is not an exclusion criterion)

E13. A relevant history of systemic allergic reaction e.g. anaphylaxis with cardiorespiratory symptoms, generalised urticaria or severe facial angioedema that in the opinion of the investigator may constitute an increased safety concern

E14. Any clinically relevant chronic disease incl. malignancy that in the opinion of the investigator would interfere with the trial evaluations or the safety of the subject

E15. Active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance

E16. Immunosuppressive treatment (ATC code L04 or L01) ≤ 90 days prior to the screening visit

[13] Lung function will be measured according to the ATS/ERS spirometry recommendations (Reddel et al. 2009). The subjects will be included based on spirometry values measured at the site and reported by the site according to the site's pre-programmed spirometric reference equations. The reference equations and values used should be documented on every pulmonary function report.
[14] If in doubt, nasal endoscopy is recommended

E17. Treatment with medications with potential impact on efficacy endpoints (e.g. treatment with anti-IgE drugs within 130 days/5 half-lives of the drug (which ever longest) or treatment with antidepressant or antipsychotic medications with antihistaminic effect)

E18. A history of allergy, hypersensitivity or intolerance to the IMP (except to the active ingredient) or any of the background treatment provided in this trial

E19. Female who is pregnant or breast-feeding

E20. Has a business or personal relationship with trial staff or sponsor who is directly involved with the conduct of the trial

4.3 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not eligible for participation according to in/exclusion criteria and subsequently not randomly assigned to trial intervention/entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants in order to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, medical history, adverse events, eligibility criteria and screen failure details.

4.3.1 Rescreening

Screen failures may not be rescreened.

5 SUBJECT DISCONTINUATION

5.1 Discontinuation from IMP treatment

Subjects must be discontinued from IMP treatment under the following circumstances:

- If a subject becomes pregnant
- The subject experiences severe or persistent symptoms of oesophagitis or has a confirmed diagnosis of eosinophilic oesophagitis
- The subject's asthma becomes difficult to control
- If, in the investigator's opinion, continuation with IMP treatment would be detrimental to the subject's well-being
- If treatment is unblinded for the subject or investigator

For all subjects discontinued from IMP, efforts must be made to have subjects attend and complete all scheduled visit procedures to collect the data for the primary and key secondary endpoints. Subjects must be educated about the scientific importance of their data, even if they discontinue trial product.

5.2 Discontinuation from trial

The subject will be advised in the informed consent form that he/she has the right to discontinue from the trial at any time without prejudice.

Subjects must be discontinued from the trial under the following circumstances:

- If, in the investigator's opinion, continuation in the trial would be detrimental to the subject's well-being
- If informed consent is withdrawn

If found required by ALK after discussion with the investigator, subjects may be discontinued from the trial under the following circumstances:

- If subject is treated with prohibited medication as defined in Table 2
- In case of protocol deviation, violation of eligibility criteria or deviation from the treatment plan specified in the protocol (e.g. incorrect administration of the IMP)
- Simultaneous or previous participation (within 30 days of randomisation) in other clinical trials of an approved or non-approved investigational medicinal product

In case a subject discontinues from the trial, the discontinuation page in the electronic case report form (eCRF) should be completed. On the discontinuation page the investigator should record the date of the discontinuation from the trial, the person initiating the discontinuation, and the primary reason for discontinuation. If an adverse event (AE) is involved in a discontinuation, this must be recorded as the primary reason. In all cases, the primary reason for discontinuation must be recorded in the eCRF and in the subject's medical records. A follow-up visit on the subject is necessary to establish trial-related AEs that must be reported in accordance with the appropriate procedures.

5.3 Lost to follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the site. Reasonable effort should be made to contact any subject who does not return to the site for scheduled visits during the course of the trial in order to complete assessments and retrieve any outstanding data and medication/supplies. Should the subject continue to be unreachable, he/she will be considered lost to follow-up, and the effort taken to contact the subject should be documented in the subject's medical record.

Data obtained until discontinuation will be used for statistical analyses.

5.4 Replacement of subjects

Subjects who discontinue IMP treatment or from the trial will not be replaced.

6 RANDOMISATION AND TREATMENT BLINDING/UNBLINDING

6.1 Subject ID number

All subjects enrolled must be identifiable throughout the trial. Each subject will be allocated a 5-digit subject number in combination with a 3-digit site number to create a unique subject id (e.g. 101-50001).

The subject number will be generated when the subjects' data are entered into the eCRF at the screening visit. Only the investigator is able to reconcile the unique subject number with the identity of the data subject.

6.2 Randomisation

The randomisation list will be generated by a trial-independent statistician and will not be accessible to trial personnel involved in the conduct of the trial, until the database has been locked. The treatment allocation will be stratified based on pre-existing diagnosis of asthma in order to ensure equal treatment distribution of subjects with or without asthma.

The randomisation codes will only be made available for the trial data manager and statistician when the clinical database has been locked and all protocol deviations have been identified and evaluated.

6.3 Treatment blinding/unblinding

A double-blind setup will be used, the active IMP and their matching placebo will be similar in appearance and taste and will be packaged identically to maintain the treatment blind. The treatment will be blinded to the subject, the investigator/site personnel and sponsor personnel or delegates who are involved in the treatment administration or clinical evaluation of the subject.

The treatment for a particular subject may be unblinded by the investigator in a medical emergency situation if knowledge of the IMP is necessary for the optimal treatment of the subject. If possible, the trial site must contact ALK prior to unblinding the subject's treatment. However, in case of an emergency, unblinding and appropriate treatment should be the very first action by the site. Unblinding may also be done by the Qualified Person Responsible for Pharmacovigilance (QPPV).

The randomisation code breaking will be performed via interactive response technology (IRT) for this trial. The time, date and reason for unblinding as well as the initials of the person breaking the randomisation code must be recorded.

The IRT will notify the Clinical Research Assistant (CRA) and the sponsor’s safety department immediately after the randomisation code is broken. The subject must be discontinued from the trial after the randomisation code is broken.

It may also be necessary to unblind an individual subject’s treatment by the sponsor/safety department, for the purposes of expedited reporting to the authorities and/or ethics committees (e.g. in case of a suspected unexpected serious adverse reactions (SUSAR)). In that situation, blinding of other sponsor personnel and of the investigator and subject must be maintained during the trial.

6.4 Subject card

All subjects who have signed the informed consent form will be given a subject card by the investigator or qualified designee, identifying them as participants in a clinical trial. The card will contain trial site information (including direct telephone number) to be utilised in the event of an emergency.

7 RESTRICTED AND PROHIBITED CONCOMITANT MEDICATION

Restricted and prohibited concomitant medications are listed in Error! Reference source not found.. For medication that could possibly interfere with the SPT performed at screening please refer to **Table 7**.

All concomitant medications must be appropriately documented in the eCRF. The use of any concomitant medication must relate to the documented medical history, prophylaxis or an AE of the subject.

Table 2 Restricted concomitant medications

Product	Time window	Reason
An investigational product other than the IMP	≤ 30 days or 5 half-lives of the product (which ever longest) before visit 2 and until end of trial	Possible interaction between IMPs. Interferes with efficacy and safety evaluations
Antihistamine, routine use and preventive use to treat anticipated adverse events (rescue medication antihistamines provided by sponsor are permitted for treatment of acute allergic symptoms, see section **8.2**) - Oral, intravenous, nasal or ocular	 From V4 until 01 Sep 2022 and from V7 until 01 Sep 2023	 Interferes with rhinoconjunctivitis efficacy assessments.
Antidepressant medications -Antidepressant medication with antihistaminic effect	≤ 14 days before visit 2 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments Interferes with safety evaluation
Antipsychotic medications -Antipsychotic medication with antihistaminic effect	≤ 7 days before visit 2 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments due to antihistaminic effect. Interferes with safety evaluation
Glucocorticosteroids -unless provided by the sponsor (see section **8.2**) -does not include inhaled corticosteroids - topical (nasal or ocular) - with systemic effect:[15] - any oral tablets (OCS is allowed in cases of asthma exacerbation)	 From V4 until 01 Sep 2022 and from V7 until 01 Sep 2023 60 days before visit 4 and until end of trial	 Interferes with rhinoconjunctivitis efficacy assessment. Interferes with safety evaluation

[15] Treatment with systemic prednisolone with daily doses below 20 mg should not be discontinued. Estimated equipotent doses (i.v. or p.o.); 20 mg Hydrocortisone = 5 mg Prednisolone = 5 mg Prednisone = 4 mg Methylprednisolone = 0,75 mg Dexamethasone **(Liu et al. 2013)**

- any parenteral formulations (intravenous, intra-articular or intramuscular) or depot formulations regardless of treatment days and dose	≤ 90 days from visit 4 and until end of trial	
Systemic immunosuppressive treatment (ATC code L04, L01) *other than glucocorticosteroids	≤ 90 days before visit 2 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments.
Biologic treatments, including, **but not limited to**: anti-IgE -, anti-IL5 -, anti-IL5R and anti-IL4R treatment (e.g. omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab)	≤130 days or 5 half-lives of the product (which ever longest) prior to visit 2 and until end of trial	Safety of subject. Interferes with rhinoconjunctivitis efficacy assessments.
Immunotherapy with any other allergen(s)	From screening visit 1 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments. Interferes with safety evaluation
Inhaled, topical (nasal or ocular) or oral nedocromil or cromolyn sodium	≤ 14 days before visit 4 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments
Monotherapy of Long-acting B-agonist (LABA) (LABA in combination with ICS is allowed)	From visit 2 and until end of trial	Interferes with safety evaluation
Nasal or ocular decongestants	≤ 3 days before visit 4 until 01 Sep 2022 and ≤ 3 days before visit 7 until 01 Sep 2023	Interferes with rhinitis efficacy assessments

8 TRIAL PRODUCTS

8.1 IMP

The IMP provided in this trial is 5-grass mix SLIT-drops or placebo.

All IMPs are manufactured and provided by ALK. The placebo is similar to the active treatment with regards to appearance, smell and taste.

Please refer to **Table 3** and the Trial Supplies Catalogue provided by ALK for details regarding IMP and background treatment.

Table 3 IMP details

IMP name:	Active treatment 5-grass mix SLIT-drops	Placebo
Active ingredients:	Allergen extracts from the five grass species: *Dactylis glomerata L* (cat grass /cock's foot/orchard grass), *Phleum pratense L.* (timothy grass), *Lolium perenne L.* (perennial rye-grass), *Anthoxanthum odoratum L* (sweet vernal/vernal grass), *Poa pratensis L.* (Kentucky bluegrass/meadow grass)	None
Dosage form:	SLIT-drops Sublingual solution	SLIT-drops Sublingual solution
Excipients:	Glycerol, carbonate, sodium chloride	Glycerol, carbonate, sodium chloride
Route of administration:	Sublingual	Sublingual
Dose/strength:	Initiation: 50 SRU/day for five consecutive days followed by 150 SRU/day for five additional consecutive days. Maintenance: 300 SRU/day from day 11.	N/A
Dosing instruction:	One single-dose container (0.5 ml) once daily. First dose will be dispensed at site at visit 2 (randomisation visit)	One single-dose container (0.5 ml) once daily. First dose will be dispensed at site at visit 2 (randomisation visit)

Each subject will be randomly assigned to receive active treatment or placebo.

IMP dispensing

The treatment will start at visit 2 (randomisation visit). Hereafter, IMP will be dispensed at visits 3-8. The first dose will be administered under medical supervision for at least 30 minutes after intake.

8.2 Rescue medication

During the trial, subjects may experience allergy symptoms that require additional treatment. Rhinoconjunctivitis pharmacotherapy for allergic rhinitis or conjunctivitis will be provided by the

sponsor to subjects as pre-defined, open-labelled rescue medication and may be used in addition to the IMP to which the subjects have been randomised if needed.

For the rhinoconjunctivitis symptoms the subject will be provided with:

- Oral antihistamine tablets (Desloratadine, 5 mg)
- Nasal corticosteroid spray (Mometasone furoate, 50 µg/dose)
- Antihistamine eye drops (Olopatadine eye drops, 1 mg/ml)

The allergy pharmacotherapy provided to the subject should be used according to the product's labelling (e.g. SmPC). The dosage instructions are described in **Table 4**.

Table 4 Schedule for rhinoconjunctivitis pharmacotherapy

Rhinoconjunctivitis pharmacotherapy	**Subject dosage instructions**
Rhinitis	
Oral antihistamine, tablets	1 tablet once daily as needed for control of allergic rhinitis symptoms
Nasal corticosteroids	2 puffs in each nostril once daily as needed for control of allergic rhinitis symptoms. Dose can be reduced to 1 spray in each nostril when the treatment has become effective
Conjunctivitis	
Antihistamine eye drops	1 drop in the affected eye(s) twice daily, morning and evening as needed in case of persisting allergic conjunctivitis symptoms
*Oral antihistamine has an effect on the conjunctivitis symptoms and will be counted in both the rhinitis and the conjunctivitis medication score	

Repeat supply of any rescue medication will be done at scheduled visits as needed.

8.3 Packaging and labelling

The IMP will be supplied in foil bags containing five single-dose containers each. The foil bags will be packed in specific boxes containing a sufficient number of single-dose containers to cover the treatment periods between the dispensing visits and the End of Trial visit.

IMP will be packaged and labelled according to EU Annex 13 and national requirements. The IMP will be uniquely numbered.

Rescue medication will be sourced as commercially available products in a member state of the EU or EEA. The products will be labelled with an additional label including trial specific information.

Packaging and labelling will be outsourced. See Appendix 3 – List of Suppliers.

8.4 Handling and storage

The trial products provided by ALK (IMP, rescue medication and SPT) are to be used only for this trial and not for any other purpose.

The trial products must be stored in a secure, limited-access location separate from normal clinic stocks and according to label specifications. Trial products returned by the subject must be stored separate from other medication, e.g. unused IMP that has not yet been dispensed.

Site storage conditions for IMP, rescue medication and SPT must be monitored by the site staff for adherence to label specifications and reviewed by the CRA during monitoring visits.

Temperature monitoring must be done using a calibrated, stationary and continuously recording system. As a minimum a calibrated min/max thermometer is required.

8.5 IMP and rescue medication accountability

The investigator or appropriate delegated staff must maintain records of the IMP and rescue medication delivered to the trial site from ALK. The site must maintain records of:

- Inventory at the site
- Dispensing to each subject
- Returns by each subject to site
- Returns by site to ALK

These records must include dates, quantities, batch/serial numbers, expiry dates and the unique IMP code number assigned to the subject. Investigators must maintain records that document adequately that the subjects were provided the doses specified by the protocol and must reconcile all IMP and rescue medication received from ALK.

All IMP and rescue medication accountability logs and records will be verified by the CRA during the monitoring visits in accordance with the monitoring plan.

Full drug accountability will be performed for the IMP. Subjects must be instructed to bring all unused IMPs to the site at every drug accountability visit. Compliance will be assessed by foil bag counts. If IMP compliance is less than 80% or more than 100%, the investigator should discuss the reason and educate the subject to comply with the protocol.

Full drug accountability will not be performed on rescue medication. Subjects must be instructed to bring all unused rescue medication to the site at relevant visit. At the final visit, the investigator must return a copy of the completed drug accountability form to the ALK-appointed CRA or to the ALK address provided.

The investigator must not destroy any IMP or rescue medication without written agreement with ALK.

8.6 Reporting of technical complaints

Any technical complaint related to the trial products provided by ALK (IMP, rescue medication, SPT) must be reported to ALK. The information must be accompanied by samples or a picture of the item.

9 TREATMENT

9.1 Treatment administration

The solution from the single-dose containers should be administered once daily. Place the entire content of the single-dose container under the tongue (sublingual) and keep it there for 2 minutes before swallowing.

Eating and drinking should be avoided for the next 5 minutes.

9.2 Precautions in relation to first dosing

The first intake of IMP should be at the clinic with a subsequent 30 minutes observation period. An oropharyngeal examination should be performed prior to the first IMP dosing and should be repeated after 30 minutes.

For subjects with severe oral inflammation (e.g. oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction or following tooth loss, initiation of IMP treatment should be postponed to allow healing of the oral cavity.

For subjects with symptoms of or in treatment for upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infections, initiation of IMP treatment should be postponed until the condition has improved. If first dosing is postponed, the first intake of IMP should still be at the clinic with a subsequent 30 minutes observation period.

9.3 Treatment of severe allergic reactions/anaphylaxis

If, following exposure to an allergen, multiple organ systems are adversely affected, anaphylaxis is a likely event/diagnosis. Adrenaline auto-injectors are intended for immediate self-administration for an anaphylactic reaction, including symptoms/signs of upper airway obstruction. A list of symptoms that may be present during anaphylaxis include flushing, apprehension, syncope, tachycardia, thread or unobtainable pulse associated with a fall in blood pressure (BP), vomiting, diarrhoea and abdominal cramps, wheezing, dyspnoea due to laryngeal spasm, lower airway obstruction, pruritus, rashes (such as urticaria), or angioedema. Self-injectable adrenaline should be administered promptly when significant respiratory and/or cardiovascular symptoms accompany an allergic reaction.

Subjects experiencing symptoms of an anaphylactic reaction without access to an adrenaline auto-injector must immediately call their local emergency number.

In the event of symptoms of anaphylaxis and regardless of use of self-injectable adrenaline, the subject must immediately call the local emergency number and the 24-hour investigational site emergency number indicated in the informed consent and on the subject identification card. An unscheduled visit will be arranged to further evaluate the subject. The investigator or designee must notify the sponsor within 24 hours of first becoming aware of the use of self-injectable adrenaline. The symptoms and/or circumstances that triggered symptoms of anaphylaxis and/or the use of self-injectable adrenaline must be clearly recorded on the eCRF.

9.4 Temporary interruption and discontinuation of treatment

Treatment may be discontinued for up to 7 days for the following reasons:

- In case of oral surgery, including dental extraction and shedding of a tooth, to allow healing of the oral cavity
- Inflammatory conditions in the oral cavity
- Upper airway viral infection in an asthmatic subject
- Other reasons if deemed necessary by the investigator

Interruptions should be kept to a minimum, however the event causing the interruption should be resolved before re-initiating the treatment. If IMP is interrupted for more than 7 days in a row, the investigator should be contacted before restarting the treatment. The investigator should evaluate based on the length of the IMP interruption and previous experienced AEs if the subject should

start up treatment again at the clinic or if it is ok that the subject starts up at home, or if IMP should be discontinued permanently.

ALK should be notified in case of IMP discontinuation due to an AE.

9.5 Post-trial treatment

After the end of the trial, the investigator must advise trial subjects on access to appropriate and available treatment. Post-trial treatment will not be sponsored by sponsor.

10 VISIT SCHEDULE

Not applicable for this trial.

11 TRIAL PROCEDURES

This section outlines the trial procedures that will be performed during the trial.

The tasks listed below must be performed by a physician:

- Obtainment of informed consent
- Evaluation of inclusion and exclusion criteria
- Physical examination
- Assessment of AEs/SAEs
- Assessment of FVC, FEV_1, and laboratory results
- Decision to unblind treatment for individual subjects

Review of completed diaries, questionnaires, laboratory reports etc. must be documented either on the documents or in the subject's source documents. If clarification of entries or discrepancies in the diary or questionnaires is needed, the subject must be asked to clarify, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.

11.1 Informed consent

All subjects must provide informed consent in accordance with the origins of the Declaration of Helsinki **(World Medical Association 2013)** and the applicable laws of the country. The written informed consent must be obtained before any trial activities are performed, including any period for wash-out of concomitant medication.

It is the responsibility of the principal investigator or a sub-investigator to obtain the written informed consent from the subject.

The investigator must explain the nature of the trial, its purpose, the assessments involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail and provide the subject with a copy of the information sheet and the consent form. Information to a subject can be delegated to a nurse, but the investigator must be available for questions and both the nurse and the investigator must sign the consent form to document this.

The subject must be given sufficient time to consider the trial before deciding whether to participate. Each subject must be informed that participation in the trial is voluntary and that he/she may withdraw from the trial at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject must sign and date the informed consent form before entering the trial (i.e. before any trial related activity). The investigator must give a copy of the signed informed consent to the subject. The investigator should keep the original.

If information becomes available that may be relevant to the subject's willingness to continued participation in the trial the subject information sheet will be updated by ALK and approved by an IEC/IRB and the Competent authorities. The subject must be informed in a timely manner about the updated subject information sheet and written informed consent must be obtained.

11.2 Consent to collection of blood samples for storage in biobank

Storage of blood samples in a biobank is planned for this trial (see section **11.15**). The subject should consent to long-term storage of the sample on a separate consent form prior to collection of the sample(s) as described in section **11.1**. Participation in this part of the trial is optional. Subjects who do not wish to participate with biobanking can still participate in this trial.

11.3 Demographics and body measurements

The following data will be recorded:

- year of birth[16]
- Age
- Race[17]
- Sex
- Height
- Weight

11.4 Medical history

The relevant medical history must be recorded in the eCRF.

The asthma history should include a detailed description of all asthma exacerbations including information on visits to emergency rooms, hospitalisations and changes in asthma treatment during the past 2 years.

In addition, a detailed allergy history including recording of the subject's history of rhinitis, conjunctivitis or rhinoconjunctivitis, atopic dermatitis and food allergy including start and stop date as well as cause of condition (if available). A subject should be stratified as asthmatic if they have been diagnosed and/or treated for asthma in adulthood.

11.5 Smoking habits

Information on exposure to cigarette smoke (active and passive) will be collected in the eCRF.

11.6 Concomitant and previous medication

The subjects' use of concomitant medication including allergy and asthma medication must be recorded. Relevant previous medication should also be recorded. This includes previous allergy and asthma pharmacotherapy taken for the past 2 years. Other previous medication taken by the subject should also be recorded if considered relevant by the investigator.

Medication not provided as a part of this trial should be kept to a minimum during the trial. However, if considered necessary for the subject's well-being, concomitant medication may be given at the discretion of the investigator according to the local standard of care. See section **7** for restricted and prohibited concomitant medication on this trial.

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[16] Collection of month if allowed according to local regulations

[17] Collection of race is required for calculation of FEV_1 "The predicted FVC and FEV_1 will based on the Quanjer equation **(Quanjer et al. 1993)**. If the subject self-reports his/her race as Black, appropriate adjustments will automatically be made for race by programming the spirometer using the formula: FEV_1 predicted x 0.87 = FEV_1 predicted adjusted for race"

At each visit the investigator should ask the subject about use of concomitant medication. All concomitant medication must be documented in the subject's medical records and in the eCRF. Furthermore, each change in concomitant medication (e.g. new treatment, discontinuation of treatment and change in dosage/routine) during the trial must be documented in the same way.

11.7 Lung function

The assessment of the lung function will include measurements of forced vital capacity (FVC), FVC percent predicted, FEV_1 and FEV_1 percent predicted for all subjects at randomisation visit 2 and as per investigator discretion during the trial. A 6-hour wash-out of SABA will be required before measurement of lung function. Lung function measurements will be performed with a spirometer available at the clinic. FVC and the derived FEV_1 is measured as 3 valid measurements and the highest value will be entered in the eCRF.

Lung function will be measured according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) spirometry recommendations (**Reddel et al. 2009**). The spirometry values will be reported by the site according to the site's pre-programmed spirometric reference equations. The reference equations and values used should be documented on every pulmonary function report.

11.8 Physical examination

The physical examination should be performed by a physician and should be based on the body systems as described in **Table 5**.

Table 5 Physical examination

Body system	Minimum examinations to be completed
General appearance	As applicable
Skin	Inspection of skin
Head (ears, eyes, nose and throat)	Ears - Inspection of auricles and external canal (otoscopy is not required) Eyes - Inspection of conjunctivae and eyelids, examination of pupils including reaction to light Nose - Inspection of nasal mucosa Oral cavity - oropharyngeal inspection of lips, tongue, tonsils and uvula will be performed for signs of mouth irritation, oedema, and any other abnormalities. Oropharyngeal inspection is performed before and after administration of IMP at randomisation V2 and as per investigator discretion during the trial
Respiratory	Auscultation/stethoscopy of the lungs
Heart	Auscultation/stethoscopy of the heart
Lymph nodes	Examination of lymph nodes (cervical, axillary, and inguinal lymph nodes)
Abdomen	If applicable
Urogenital	
Musculoskeletal and neurological	
Other abnormality	

Physical examination of optional body systems not performed should be marked as not done (ND) in the eCRF.

Significant findings that are present at screening must be recorded as medical history in the eCRF. Significant findings found at the following visits, which meet the definition of an AE, must be recorded on an AE page in the eCRF.

11.9 Eosinophilic Oesophagitis

At each visit, subjects/caregivers will be asked whether any of the following has occurred since the last clinic visit:

- food impaction requiring medical intervention
- dysphagia/difficulty swallowing requiring the subject to drink large quantities of water to swallow food
- choking or gagging with meals
- persistent (8 weeks or more) dysphagia
- a sensation of food becoming lodged in the throat
- persistent (8 weeks or more) vomiting without evidence of infection
- persistent (8 weeks or more) early satiety
- unexplained weight loss in combination with other gastrointestinal symptoms

If a subject present any of the above, the investigator should consider referring the subject to a gastroenterologist for evaluation. If there is a clinical suspicion of eosinophilic oesophagitis, subjects must be referred to a gastroenterologist.

11.10 Pregnancy test

For female subjects of childbearing potential, a urine pregnancy test will be performed at all regular visits. For female subjects who have their first menstrual period during the trial, a urine pregnancy test will be performed at all subsequent visits. Further, the test will be performed during the trial, if a menstrual period is missed.

The urine pregnancy tests will be performed by dipstick at the trial site.

11.11 Skin prick test

Skin Prick tests (SPTs) must be performed according to the guideline provided by ALK. No data are available for SPT in pregnant subjects, therefore a urine pregnancy test must be performed before the SPT.

Subjects enrolled in the trial will be tested for the allergens listed in **Table 6**. All allergens are supplied by ALK.

SPT positive control is histamine hydrochloride 10 mg/ml.

See the SPT guideline for further details on SPT.

Table 6 Skin prick test

Country	Allergen
All Countries	Positive control – Histamine Negative control – Saline HDM – *Dermatophagoides pteronyssinus* HDM – *Dermatophagoides farinae* Cat - *Felis domesticus*

	Dog - *Canis familiaris* Mould - *Alternaria alternata* Grass – *Phleum pratense* Weed - *Artemisia vulgaris* Tree – *Betula verrucosa* Tree - *Cupressus arizonica*

Some medications may affect the outcome of the SPT and should be washed out before performing the SPT (see **Table 7**). If medication that could interfere with the SPT has not been washed out and the positive control is <3 mm for subjects in Europe, the SPT must be repeated after the interfering medication has been washed out and before randomisation at V2.

Table 7 Medications with a possible interference with SPT

Drug	**Recommended wash-out period prior to performing SPT**
Antihistamine	
• Oral, intravenous or topical (skin)	3 days
• Long-acting (astemizole)	100 days
Tricyclic antidepressant medications and antidepressant medication with antihistaminic effects (e.g. doxapine, mianserine)	14 days
Antipsychotic medications with antihistaminic effects (e.g. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)	7 days
Glucocorticosteroid[18]	
• Local application (on the skin area used for SPT)	21 days
• Oral	30 days
• Short-acting parenteral	30 days
• Long-acting parenteral (intra-articular or intramuscular)	90 days
Pizotifene	7 days

11.12 Vital signs

Vital signs will include measurement of blood pressure and heart rate in a seated position (after ≥3 minutes of seated inactivity).

Significant findings that are present at screening must be recorded as medical history in the eCRF. Significant findings found at the following visits, which meet the definition of an AE, must be recorded on an AE page in the eCRF.

[18] Treatment with systemic prednisolone with daily doses below 20 mg should not be discontinued. Estimated equipotent doses (i.v. or p.o.); 20 mg Hydrocortisone = 5 mg Prednisolone = 5 mg Prednisone = 4 mg Methylprednisolone = 0,75 mg Dexamethasone **(Liu et al. 2013)**

11.13 Blood and urine sampling

The following types of blood samples will be drawn during the trial, totalling an approximate blood volume of 39 ml (if the subject consents to the biomarker sample, the total blood volume will be approximately 49 ml):

Purpose	Volume	Number of samples
Safety / Haematology	2 ml	2
Safety / Blood chemistry	2.5 ml	2
Screening / IgE	5 ml	1
[redacted]	[redacted]	[redacted]
Total volume	39 ml	

The following urine samples will be drawn:

Purpose	Volume	Samples during the trial.
Safety/Urinalysis	10 ml	2
Pregnancy tests	NA	at each visit, if applicable

The following samples will only be drawn if specific consent has been obtained from the subject.

Purpose	Sample type	Volume	Number of samples during the trial
Long term storage - biomarker sample	Blood	5 ml	2
Total volume		10 ml	

11.14 Laboratory assessments

All laboratory assessments will be performed centrally at one or more certified laboratories selected by ALK.

The clinical laboratory values will be reported to the investigator by the laboratory and he/she must immediately review them for clinical significance.

Laboratory assessments are described in a separate laboratory manual that also details blood sampling and shipment procedures.

The following laboratory variables will be measured:

Haematology - Automated differential

Haemoglobin, erythrocytes, haematocrit, mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), platelets, leucocytes, neutrophils, lymphocytes, monocytes, eosinophils and basophils

Blood chemistry

Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), albumin, alkaline phosphatase, aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), potassium, sodium and total bilirubin

Urinalysis

bilirubin, glucose, haemoglobin, ketone, leukocytes, nitrite, pH, protein, specific gravity and urobilinogen

IgE

To assess the inclusion criteria in order to confirm the diagnosis of allergy against grass, blood samples will be drawn at the screening visit (visit 1) for determination of specific IgE against the following allergens: *Phleum pratense*

These samples will be analysed together with the samples for the safety laboratory assessments (see above), and the results will be reported to sites for assessment of subject eligibility.

[redacted]

11.15 Long-term storage of samples

Blood sample for storage in Biobank

This blood sample will only be drawn if the subject consents to long-term storage of a blood sample.

If long-term sampling is accepted, a 5.0 ml blood sample will be drawn at visits 1 and 9 where blood sampling is already planned. The subject will consequently only donate an extra blood sample and no additional venipuncture is required.

The purpose of the biobank blood samples is to continue the research into the immunological processes involved in the observed clinical effects in subjects treated with allergy immunotherapy, and which today is not fully understood. One of the goals of this research is to identify one or more surrogate markers, which can predict clinical efficacy in the individual subject, i.e., which can help ensuring optimal treatment for future subjects with allergies. The surrogate markers may be antibody levels, cytokine profiles, cell surface markers, specific set of proteins or metabolites or combinations hereof, etc. Although the exploratory biomarker analyses will help to increase our understanding, the efforts described in this protocol are strictly research based. Thus, as the complex interactions between allergy immunotherapy, rhinoconjunctivitis and asthma are currently not characterised to a level that translates to a meaningful clinical advantage, individual results from the exploratory biomarker analyses will not be given to the subjects. For the same reasons, individual results will not be added to the subjects' medical records.

The subjects will have no direct benefit from the exploratory biomarker analyses.

The samples will be stored at ALK after end of trial and until marketing authorisation approval or until the research project terminates, but no longer than 25 years from end of trial after which they will be destroyed.

If ALK publishes results obtained from biomarker studies based on samples obtained in the trial, the results will be published in such a way that it cannot be tied to an individual subject.

11.16 Electronic diary and patient reported outcome questionnaires

During the trial, the subject will complete an eDiary. The eDiary is a hand-held electronic device that will be issued to the subjects at visit 3. Subjects will be instructed by the investigator in how to fill in the eDiary.

The following items will be provided in the eDiary at pre-specified intervals during EGPS (see the flow chart and Appendix 5):

- Rhinoconjunctivitis quality of life questionnaire (RQLQ)
- Rhinoconjunctivitis symptoms
- Use of rhinoconjunctivitis rescue medication for treatment of rhinoconjunctivitis
- [redacted]

[redacted]

11.16.1 Symptom assessment: Rhinitis and conjunctivitis symptoms

Subjects should be instructed by the investigator or delegated staff on how to complete symptom assessments and record the results in the diary on a daily basis – in the evening.

A total of 6 allergic symptoms, 4 rhinitis and 2 conjunctivitis symptoms should be measured on a scale from no symptoms to severe symptoms.

The subject should be instructed in the symptom score using the following definitions:

0 - No symptoms - no sign/symptom evident
1 - Mild symptoms - symptom clearly present, but minimal awareness; easily tolerated
2 - Moderate symptoms - definite awareness of symptom that is bothersome but tolerable
3 - Severe symptoms - symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping

The 6 symptoms are classified in 2 groups as follows:

Nose symptoms:

- Runny nose
- Blocked nose
- Sneezing
- Itchy nose

Eye symptoms:

- Gritty feeling/red/itchy eyes
- Watery eyes

11.16.2 Medication assessment

Subjects are provided with open-label rhinoconjunctivitis rescue medication to be used as needed for treatment of their rhinoconjunctivitis symptoms not controlled by the IMP. Subjects should be instructed to report their use of rhinoconjunctivitis rescue medication via the daily diary. As suggested in an European Academy of Allergy and Clinical Immunology (EAACI) position paper on standardisation of clinical outcomes **(Pfaar et al. 2014)** the subjects should be instructed to start with antihistamine tablets and/or eye-drops. Treatment with nasal steroids should only be initiated if antihistamines and/or eye drops do not alleviate the symptoms.

The medication use will be scored as shown in **Table 10**.

[redacted]

11.16.4 Rhinoconjunctivitis quality of life questionnaire

The quality of life will be assessed by the standardised RQLQ(S) questionnaire **(Juniper et al. 1999)** included in the electronic diary. RQLQ questionnaire contains 28 questions that are scored in 7-point scale (0 = not impaired at all; 6 = severely impaired). Questions are divided in 7 domains (activity limitations). The overall RQLQ score is derived by taking the average of 7 domain scores.

[redacted]

11.17 Paper questionnaire

Health-related quality of life assessment

The health-related quality of life will be assessed using the [redacted].

12 SAFETY PROCEDURES

Information about AEs, whether reported by the subject, discovered by the investigator by reviewing eDiary records, detected through physical examination, laboratory test or other means, must be collected and recorded on the AE form and followed up as appropriate. Evaluation of AEs including severity, causality, outcome and seriousness assessments must be performed by a physician.

Any AE occurring from the time the informed consent was signed by the subject and until the last follow-up phone contact must be recorded and reported on the AE page in the eCRF. This includes all AEs, even AEs occurring before the subject is administered the IMP and whether or not AEs are observed in connection with the trial assessments and conduct of the trial.

12.1 Definitions

Adverse events
An AE is any untoward medical occurrence in a clinical trial subject, and which does not necessarily have a causal relationship with the administered IMP.

An AE can therefore be any unfavourable and unintended sign (including e.g. an abnormal laboratory finding or medication error), symptom or disease, whether or not considered related to the IMP.

The following events should not be recorded as AEs:

- A pre-planned procedure, e.g. a surgical intervention, unless the condition for which the procedure was planned has worsened since the informed consent form was signed.
- Pre-existing conditions documented as medical history. However, any worsening in severity or frequency of a pre-existing condition during the clinical trial period must be regarded as an AE.

Serious adverse events

An SAE is any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe)
- Requires in-subject hospitalisation, regardless of duration, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is judged to be medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above)

Events of medication error, overdose and abuse
Medication error, misuse, overdose and abuse of IMP(s) must always be collected in line with adverse event reporting, with or without associated AEs.

- Medication error: Any unintended failure in the medication treatment process that leads to, or has the potential to lead to, harm to the subject.
- Overdose: Any cumulative dose taken in one day that exceeds the dose intended by this protocol, regardless of whether the dose has caused any AEs
- Abuse: Persistent or sporadic, intentional excessive use which is accompanied by harmful physical or psychological effects
- Misuse: Intentional and inappropriate use

Events of special interest (ESI)
Selected (non-serious or serious) AEs will be considered ESIs. ESIs are events that are considered critical for the evaluation of the product's safety profile and for which additional data will be collected. ESIs for this trial are:

- Systemic allergic reactions including anaphylaxis
- Events treated with adrenaline/epinephrine
- Severe local swelling of the mouth and/or throat
- Eosinophilic oesophagitis

Significant laboratory event
A significant laboratory event should be recorded as an AE if one of the following is applicable:

- It is clinically significant (medical judgement by investigator)
- It leads to a change or discontinuation of treatment
- It fulfils a seriousness criterion
- It indicates a potential safety risk to the subject
- If Hy's law is fulfilled; AST and/or ALT ≥3 times upper normal limit and bilirubin ≥2 times upper normal limit and ALP is not >2 times upper normal limit

12.2 AE assessments

12.2.1 Severity

The severity of an AE is a clinical observation assessed by the investigator using the following definitions:

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

12.2.2 Causal relationship to IMP

The causal relationship between an AE and the IMP is assessed by the investigator using the following definitions:

- Possible: A reasonable possibility of a causal relationship between the event and the IMP.
- Unlikely: The event is most likely caused by a different aetiology than the IMP.

For SAEs assessed as unlikely and possible related to IMP, the most likely alternative aetiology should be provided.

12.2.3 Outcome

The outcome of an AE is assessed by the investigator using the following definitions:

- Recovered: Fully recovered or the condition has returned to baseline
- Recovered with sequelae: As a result of the AE the subject suffered persistent disability/incapacity. If the sequela qualifies as a SAE, the AE must be reported as such
- Not recovered: The condition has not returned to baseline however, symptoms may have improved
- Fatal: Event that results in death
- Unknown: The outcome is unknown. This term should only be used when no other definition is possible e.g. the subject is lost to follow-up

12.3 Collection, recording and reporting of AEs

AEs must be recorded on the AE form in the eCRF with the initial eCRF report containing as much information as possible. One single AE form must be used per AE from start to resolution. For SAEs and ESIs, additional information will be collected. For each of the 4 pre-defined ESIs, the

investigator must fill out a specific eCRF ESI form with additional questions, in order to ensure that all relevant data is captured.

If the same type of AE occurs more than 1 day in a row with the same pattern (e.g. itching in the mouth for 5-10 minutes after intake of IMP) it is considered a recurrent AE. The AE form should be filled in with the start date and the description. If the AE no longer reoccurs after IMP intake, the AE form should be completed with a stop date. If the AE then re-appears on a subsequent day, a new AE form should be filled in.

The investigator should record the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs. Further, the diagnosis of the underlying disease should be reported instead of a procedure performed due to the disease (e.g. if a subject undergoes surgery due to appendicitis, appendicitis, and not the surgery performed, should be reported as the AE).

12.3.1 Reporting of SAEs

The investigator must report all SAE (initial as well as follow-up) to ALK within 24 hours after obtaining knowledge of the information. SAEs will automatically be sent to ALK via the eCRF system. In case the eCRF system is unavailable during the 24-hour reporting timeline, SAEs (including relevant data e.g. demography, medical history, concomitant medication) must be reported by email or fax to ALK. For all ESIs, additional information specific to the ESI in question will be collected in the eCRF.

Any specific eCRF ESI form and non-serious AEs should be reported within 5 working days after obtaining knowledge of the information.

If requested, please forward supporting documents to ALK via fax. Please state the trial ID and the subject and site ID on all documents.

IMPORTANT: Any information that could reveal the identity of the trial subject must be hidden or removed in the source documentation. Also, information that is not relevant for the subject and the subject's condition must be hidden or removed.

Email address:	<[redacted]>
Fax number:	[redacted]
Emergency phone:	[redacted]

The assessment of listedness is performed by ALK according to the reference safety information in the current version of the IB.

ALK will inform the regulatory authorities and IECs/IRBs in accordance with local requirements in force and the ICH guidelines for GCP **(ICH 1996)**.

12.3.2 Follow-up on AEs and SAEs

SAEs must be followed up until resolution and until all queries have been resolved. The investigator must respond to SAE follow-up requests from ALK without delay and no later than 7 days after receiving the request.

For chronic diseases ongoing SAEs can be closed at the end of trial (visit 9) with the term "not recovered" (as evaluated upon medical evaluation by the investigator or the sponsor).

The investigator must ensure that the worst-case severity and seriousness of an event is kept throughout the trial.

Non-serious AEs must be followed up until resolution or until the end of trial (visit 9).

12.3.3 Reporting of medication errors, including overdose, abuse and misuse

Medication errors, including events of overdose, abuse or misuse must be reported on an AE form within 7 calendar days of obtaining the information. Reporting of overdoses must be based on actual IMP exposure. For overdose cases, the descriptive terms accidental or intentional overdose should be used. If an event is classified as an SAE, it must be reported as such.

12.3.4 Reporting of significant laboratory events

All laboratory reports must be reviewed by the investigator for significance.

Significant laboratory events present at screening should be recorded in the medical history section in the CRF. Significant laboratory events found at the following visits, and which meet the definition of an AE, must be recorded on an AE form.

A significant laboratory event should be recorded as an AE if one of the following is applicable:

- It is abnormal and clinically significant (medical judgement by investigator).
- It leads to a change or discontinuation of treatment.
- It fulfils a seriousness criterion.
- It indicates a potential safety risk to the subject.
- If Hy's law is fulfilled; AST and/or ALT ≥3 times upper normal limit and bilirubin ≥2 times upper normal limit and ALP is not >2 times upper normal limit

12.3.5 Reporting of pregnancies

The investigator must report information on pregnancy and pregnancy follow-up information including pregnancy complications, delivery and health of the infant until the age of one month within 14 calendar days of obtaining the information, using the pregnancy notification form and pregnancy follow-up form.

Complications in relation to pregnancy must be reported as AEs. In case of spontaneous abortion, any malformation of the foetus, foetal death, stillbirth or a congenital anomaly/birth defect/developmental delay, the event must be reported and followed up as an SAE.

Any abnormalities observed in a child (up to two years of age) and suspected to be related to intra-uterine exposure to the IMP should be reported to ALK.

12.3.6 Reporting of SAE and pregnancies after end of trial

SAEs that in the opinion of the investigator are related to IMP that are brought to the attention of the investigator after the last follow-up phone contact must be reported immediately by using the contact details listed in this section.

All pregnancies occurring in trial subjects while exposed to IMP that are brought to the attention of the investigator after the last follow-up phone contact must be reported within 14 days by using the contact details listed in this section.

12.4 Safety surveillance

Safety surveillance will be performed by ALK at pre-specified intervals to evaluate safety data and perform ongoing evaluation of AEs, SAEs, and laboratory data.

12.5 DMC

A data monitoring committee (DMC) will not be established for this trial.

12.6 Pregnancy

Female subjects must be advised to notify the investigator immediately if they become pregnant. If a female subject becomes pregnant, she must discontinue IMP intake but may continue to be enrolled in the trial.

The investigator must report any pregnancy reported during the trial to ALK. Subjects will be informed that the investigator will report any pregnancy during the trial to ALK and that she will be asked to provide information about her pregnancy, delivery and health of her infant until the age of one month. If deemed relevant to collect information from the male partner, a separate informed consent has to be obtained.

13 EARLY TERMINATION OF TRIAL

ALK reserves the right to terminate the trial due to the following:

- Safety concerns
- Proven lack of efficacy from other completed trials with the same IMP

If the trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or ALK should promptly inform the pertinent IEC/IRBs and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

Early trial termination may be the result of any single criterion specified below:

- IMP-related death of an individual
- IMP-related anaphylactic shock in at least 2 subjects defined as:

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus, or flushing, swollen lips, tongue, or uvula) AND medically confirmed reduced BP with associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence).

14 DATA HANDLING

The diary in the trial will be an eDiary. The site will be trained in the use of eDiary by sponsor representatives. The sites will then train the subjects in how to fill in the eDiary.

An eCRF will be used for this trial. The data is entered by trained site investigator/staff into the eCRF according to guidelines. A completed eCRF is required for each subject who signs an informed consent. All eCRFs must be completed in English.

The completed eCRFs and eDiaries are the property of the sponsor and must not be made available in any form to third parties (except for authorised representatives of appropriate governmental health or regulatory authorities) without written permission of the sponsor.

14.1 eCRF

Data generated by the trial site and relevant for the trial will be recorded in the eCRF.

The sponsor or its representative will supply sites with access to the eCRF. The sponsor will make arrangements to train the site staff in the use of the eCRF. There will be no access to the eCRF without documented training in the system.

All eCRF data must be verified and approved by an investigator at the site.

The CRA will review the eCRF for completeness and accuracy and instruct the personnel at the trial site to make any required corrections or additions according to an eCRF completion guideline.

The information entered into the database is systematically checked and errors or omissions will result in queries, which will appear in the eCRF for resolution. Concomitant medications entered into the database will be coded using the World Health Organisation Drug Reference List (WHO Drug, September 1, 2019 or higher).

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 22.1 or higher).

14.2 eDiary

Starting at visit 3, an eDiary will be dispensed and data will be entered by the subject. The subject will be trained in the eDiary by the investigator or designee. In addition, a training video with information on the eDiary will be available for the subjects. The data will be reviewed by the investigator.

During the trial, data will be entered in an eDiary by the subject and transferred to the eDiary vendor database on a daily basis. If the subject has missed more than 2 days in a row the investigator/designee will be notified by email and must contact the subject. In addition, if the total compliance for a period is less than 80% the investigator/designee must contact the subject and retrain the subject in the use of the eDiary. The aim is for the overall compliance for a subject in the trial not to be below 80%.

There will be no other source documentation for these data other than the vendor database.

After database lock, all access to the eDiary will be set as "read only". The sponsor will extract blinded data from the eDiary system. The investigator will be provided with an electronic copy of the diary data collected at the specific site at the latest 3 months after end of trial, by the vendor. The eDiary data will be subject to periodic review by the sponsor. Findings during the review of the eDiary data will be evaluated by the investigator and updates/correction to the data can only be executed by the investigator or if raised by sponsor only executed after confirmation and approval by the investigator.

Documentation of the data load from the eDiary vendor to ALK will be described in the data management report.

14.3 Query handling

Query handling at the trial site will be performed according to the guidelines for the eCRF and eDiary systems. Queries are created by programmed validation checks according to an edit check specification. Queries will also be created based on manual data checks.

All data changes/query decisions are created with an audit trail capturing the old information, the new information, identification of the user making the correction, the date the correction was made, and the reason for change.

14.4 Laboratory data

Laboratory samples will be processed at a central laboratory selected by ALK. When the samples have been analysed and the data released, a laboratory report will be sent to the investigator. The investigator must review and sign the laboratory reports. The lab data are also imported automatically in the eCRF for investigator evaluation of outliers. At the end of the trial the blinded laboratory data will be provided electronically to data management at ALK.

[redacted]

The transfer of laboratory data to the eCRF will be described in a data transfer specification.

Documentation of receipt and quality check of laboratory and immunological data will be provided in a data management report.

14.5 Database lock

When the database has been declared to be complete and accurate by sponsor, the database will be locked and data will be unblinded. All accesses to the eCRF will be set as “read only”. CRAs and non-sponsor staffs “read only” accesses will be revoked from the eCRF, when PDF files are received at site.

If changes to trial data become necessary after database lock this must be performed according to the current ALK Standard operating procedure (SOP).

A data archive for the site subject data files (eCRF, eDiary and Laboratory data) are produced and sent to the site.

The investigator must sign and date the data archive approval form and send it back to the sponsor.

15 STATISTICAL METHODS

Statistical analyses will be carried out by ALK. All computations will be performed using SAS® version 9.4 or later version.

All analyses requiring significance testing will be two-sided at a 5% significance level, unless otherwise specified. All confidence intervals will be two-sided 95% confidence intervals. In all analyses, the null hypothesis will be one of no difference between treatment groups and the alternative hypothesis will be one of a difference. Before database lock, a separate SAP detailing the specifications given below will be prepared and agreed upon. This includes a detailed description of the total analysis set, full analysis set (FAS), safety analysis set, the per protocol (PP) analysis set and asthma analysis set (analysis sets are defined in Section **15.3**.

Numerical variables will be summarised in tables including mean, standard deviation, median, 25%-quantile, 75%-quantile, minimum and maximum.

Categorical variables will be summarised by tables displaying numbers and percentage of subjects in each category.

Any changes in the statistical methods compared to the final SAP will be documented in the ICTR. Post-hoc analyses, if any, will be clearly marked.

15.1 Estimands

A primary and secondary estimand is defined for each of the primary, key secondary and supportive secondary objectives (see Sections **2.4** - **2.6** and **15.1.2** - **15.1.4**) and a discussion of intercurrent events relevant for their definition is given in Section **15.1.1**. The main estimator and sensitivity estimators for each estimand are defined in Section **15.11.1**. Approaches for handling intercurrent events and missing data are given in Section **15.11.2**, **15.11.3** and **15.14**.

15.1.1 Intercurrent events

Intercurrent events (IE) are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address IEs when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

The IEs that have been identified as relevant is discontinuation of trial treatment due to adverse event or lack of efficacy. Prior to unblinding, potential unforeseen IEs will be specified in SAP to make sure an unbiased definition of IEs.

Due to the long duration of allergy immunotherapy clinical trials, rescue medication is dispensed to every subject for ethical reasons. The use of rescue medication is, therefore, part of the treatment policy and as such, it is not classified as an intercurrent event for this trial.

If additional unforeseen and relevant IEs occur during trial conduct, they will be included in the specification and estimation of the trial estimands. The details of their inclusion and the strategies taken to address them for each estimand will be documented in the ICTR.

15.1.2 Primary estimand

Using the framework proposed in the ICH E9(R1) addendum **(ICH 2020)**, the trial product estimand can be described by:

A. Treatment: 5-grass mix SLIT-drops, where rescue medication is taken as required.

B. Population: Subjects randomised in this trial will be adults ≥18 years of age, with a clinical history of allergic rhinoconjunctivitis (with or without asthma) as diagnosed by a physician and having had symptoms despite treatment with antihistamines or nasal steroids during the two previous grass pollen seasons

C. Variable: Average total combined score (TCS) during the 2nd PGPS

D. How to account for intercurrent events: under the hypothetical situation where all subjects had completed treatment for the planned duration (hypothetical strategy)

E. Population summary: Absolute difference in means between treatment conditions.

A hypothetical strategy will be used to address the intercurrent event of discontinuation of trial treatment. As such, if a subject discontinues trial treatment, only diary data up until the time of discontinuation will be included in the analysis. Any diary data recorded after discontinuation of trial treatment will be excluded from the analysis. Details of the handling of IEs and missing data are provided in Section **15.11.2**.

15.1.3 Secondary estimand

Using the framework proposed in the ICH E9(R1) addendum **(ICH 2020)**, the treatment policy estimand can be described by:

A. **Treatment:** 5-grass mix SLIT-drops, where rescue medication is taken as required.

B. **Population**: Subjects randomised in this trial will be adults ≥18 years of age, with a clinical history of allergic rhinoconjunctivitis (with or without asthma) as diagnosed by a physician and having had symptoms despite treatment with antihistamines or nasal steroids during the two previous grass pollen seasons

C. **Variable**: Average total combined score (TCS) during the 2nd PGPS

D. **How to account for intercurrent events:** regardless of whether subjects complete treatment for the planned duration (treatment policy strategy)

E. **Population summary**: Absolute difference in means between treatment conditions

A treatment policy strategy will be used to address the intercurrent event of discontinuation of trial treatment. As such, if a subject discontinues trial treatment, all available diary data will be included in the analysis, regardless of adherence to treatment. Details of the handling of IEs and missing data are provided in Section **15.11.3**.

15.1.4 Estimands for key secondary and supportive secondary endpoints

The trial product estimand and treatment policy estimand, specified for the primary objective in Sections **15.1.2** and **15.1.3** respectively, are defined similarly for each of the key secondary and supportive secondary objectives, where the relevant key secondary and supportive secondary endpoints of interest is specified in attribute C.

15.2 Sample size and power considerations

General considerations:

In this trial, primary and secondary endpoints are tested hierarchically to control the family-wise error rate at 5% level. Individual endpoint analyses are based on treatment comparisons using a 2-sided t-test on a 5% level of significance.

The power calculations were done in two steps. The initial sample size calculation was done for observed cases only. This sample size is then evaluated using the estimand framework. The power is calculated for both the primary endpoint (TCS) and the key secondary endpoint (RQLQ). It is expected that the treatment difference in RQLQ is greater than the minimal clinically important difference (MCID) (0.16).

TCS power calculation:

The estimated TCS mean, standard deviation and treatment differences during the peak season from three trials is presented in **Table 8**. The power calculation is based on a TCS treatment difference of 21% (1.64 in absolute value) and a common standard deviation of 5.5. Under these assumptions, the trial has a power of 80% with the sample size of 180 evaluable subjects. The power will be 86% for the primary estimand and 80% for the secondary estimand with the assumption that 10% out of 220 subjects will discontinue the trial, with 4.5% of subjects discontinuing due to adverse events and 1% due to lack of efficacy each year.

Table 8 Mean and standard deviation of TCS during the peak of a season.

Trial	**Placebo** μ (σ)	**Active** μ (σ)	**Difference** **Absolute (relative)**
GT-08 2006	8.44 (5.48)	5.14 (4.06)	3.3 (39%)
P05238	7.74 (6.50)	6.10 (5.09)	1.64 (21%)
P08067	5.73 (5.03)	4.56 (4.60)	1.17 (20%)
Average			**2.04**

RQLQ power evaluation:

The estimated RQLQ mean, standard deviation and treatment differences during the peak season from 3 trials raw data is presented in **Table 9**.

Table 9 Mean and standard deviation of RQLQ during the peak of a season.

Trial	**Placebo** μ (σ)	**Active** μ (σ)	**Difference** **Absolute (relative)**
GT-08 2005	1.82 (1.11)	1.37 (0.97)	0.45 (25%)

GT-08 2006	1.48 (1.05)	1.05 (0.91)	0.43 (29%)
P05238	1.73 (1.34)	1.41 (1.12)	0.33 (18%)
P08067	1.32 (1.11)	1.18 (1.08)	0.15 (11%)
Average			**0.34**

A common standard deviation of 1.15 has been assumed in the power evaluation. An expected placebo mean is 1.60 and an expected treatment difference is 0.34. With 180 evaluable subjects per treatment arm, the power of 93% is reached for testing if RQLQ treatment difference is greater than proposed MCID of 0.16. The power will be 95% for the primary and 92% secondary estimands for the sample size of 220 subjects with the same discontinuation assumptions as for TCS.

Conclusion:

The suggested sample size is 180 evaluable subjects per treatment arm. 220 subjects should be randomised in each arm, assuming a 10% discontinuation of subjects per year, where 1% discontinued due to lack of efficacy and 4.5% due to adverse events. In such case, the trial will have a power of at least 80% in order to detect a statistically significant difference of at least 21% with common standard deviation no larger than 5.5 for primary endpoint in observed case scenario. The trial will have a power of 86% and 80% for primary endpoint for primary and secondary estimands respectively. The trial will have a power of at least 93% to detect treatment difference greater than 0.16 in RQLQ for observed case. Similarly, 95% and 92 % for the primary and secondary estimand respectively.

15.3 Analysis data sets

The total analysis set comprises all subjects who entered the trial. This analysis set includes screening failures. The total population will be used for listing reasons for screening failures and AEs before randomisation.

The FAS is all randomised subjects in accordance with the ICH intent-to-treat (ITT) principle. Subjects will be analysed according to the treatment to which they were randomised, regardless of the treatment they actually received. This analysis set will be the primary set for all efficacy analyses. The FAS will be used for all baseline/demography tables, efficacy analysis tables, and corresponding subject listings.

The PP analysis set is all subjects in the FAS with no major protocol violations which will affect the primary endpoint. Details will be described in the SAP. The PP analysis set will be used for primary and key secondary analyses.

The safety analysis set is all randomised subject who received at least one dose of IMP. The safety analysis set will be used for all safety tables and corresponding subject listings.

Asthma analysis set includes subjects from FAS that have medical history of asthma. Asthma analysis set will be used for selected summary tables and analysis. If less than 20% of FAS will have medical history of asthma, then this analysis set will not be used.

15.4 Subject disposition

A table of subject disposition by treatment group displaying number and percentage of subjects screened, included in the FAS, included in the PP analysis set discontinued and the primary reason for discontinuation will be presented.

In addition, a Kaplan-Meier plot of time to discontinuation (all causes) will be generated.

15.5 Baseline characteristics

Demography and baseline characteristics will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25- and 75-percentiles, minimum and maximum for continuous variables, and frequency tables for categorical variables.

15.6 Extent of exposure

Extent of IMP exposure and IMP accountability will be summarised by treatment group by means of descriptive statistics.

15.7 Medical history

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) in the analysis and summarised by treatment group, system organ class (SOC) and preferred term (PT). In addition, rhinitis, conjunctivitis or rhinoconjunctivitis, atopic dermatitis and allergies (including food allergies), will be summarised separately by treatment groups.

15.8 Concomitant therapy

Prior and concomitant medication will be coded according to the World Health Organization (WHO) drug dictionary in the analysis and summarised by treatment group.

15.9 Derivation of endpoints

Average daily rhinoconjunctivitis TCS during the PGPS/EGPS is an average of available daily TCS scores during corresponding periods. Similarly, average weekly overall RQLQ score during the PGPS/EGPS is an average of available weekly RQLQ scores during corresponding periods.

The daily allergic rhinoconjunctivitis TCS is the sum of the allergic rhinoconjunctivitis DSS and the allergic rhinoconjunctivitis DMS.

The allergic rhinoconjunctivitis DSS, corresponds to a sum of 6 individual symptom scores: runny nose, nasal congestion (blocked nose), sneezing, itchy nose, itchy eyes (gritty feeling, red eyes), and watery eyes. Each symptom will be scored with the following values: no symptoms (0 points), mild symptoms (1 point), moderate symptoms (2 points), or severe symptoms (3 points). Thus, the maximum daily symptom score will be 18.

The rhinoconjunctivitis DMS will be based on use according to the need of the medications outlines in **Table 10**.

Table 10 Symptom relieving medication for rhinitis with/without conjunctivitis

Symptom-relieving medication	Score/Dose unit	Maximum Daily Score
Desloratadine tablets, 5 mg	6	6
Olopatadine eye drops, 1 mg/ml	1,5 pr. eye	6
Mometasone nasal spray, 50 µg/dose	2	8
Maximum daily rhinitis and/or conjunctivitis medication score		20

15.10 Multiplicity

The trial product estimand is the primary estimand for all endpoints. The analyses for the main estimators will be controlled for multiplicity to ensure a family wise type I error rate is no lager than 5%. The multiplicity will be controlled by employing hierarchical testing: pre-specifying the order of the hypothesis to be tested. For all 4 endpoints the null hypothesis tested is the hypothesis of equality of placebo and 5-grass mix SLIT-drops treatment group.

The order of hypothesis to be tested is:

1. The primary endpoint is the average daily allergic rhinoconjunctivitis total combined score (TCS) during 2nd PGPS.
2. The overall RQLQ score during the 2nd PGPS
3. The average daily allergic rhinoconjunctivitis TCS during the 1st PGPS
4. The overall RQLQ score during the 1st PGPS

The primary endpoint is the first hypothesis in the hierarchy and will be tested on a 5% significance level. The endpoints from 2nd to 4th in hypothesis tests will be only carried out if all previously tested hypotheses are statistically significant at the 5% level.

Additional endpoints and analyses are supportive in nature and will not be controlled for multiplicity.

15.11 Efficacy analyses

The main estimator as well as sensitivity estimators will be defined in Sections **15.11.1** and **15.11.4**, handling of missing data will be defined in Sections **15.11.2** and **15.11.3**. Exploratory analyses defined in Section **15.11.5**.

15.11.1 Estimator

The main estimator and sensitivity estimator(s) for both estimands will be based on an identical method of statistical analysis (specified below), although the actual data used in each analysis may vary according to the different strategies taken for the handling of IEs and missing data. Further details of the different strategies for each estimand are provided in Sections **15.11.2** ,**15.11.3** and **15.14**.

Missing data will be imputed using the method of unrestricted random sampling with replacement. The average score will be imputed, but not the daily/weekly values. Missing data for 1st year will be imputed from observed data in 1st year and missing data for 2nd year will be imputed from the observed data in 2nd year. Thus, PGPS data will be imputed from observed PGPS data and EGPS from EGPS. Missing data for subjects with asthma will be imputed from patients with asthma

according the rules defined below and missing data for subjects without asthma will be imputed from subjects without asthma also following the rules defined below. Rubin's multiple imputation strategy with 1000 imputations will be used **(Rubin D.B 1987)**. Seed used for imputation will be 12345.

The endpoints will be analysed using Mixed Model of Repeated Measurements (MMRM) assuming unequal variances in the two treatment groups. Each endpoint (TCS, RQLQ, DMS, DSS) is modelled over two seasons (2022 and 2023) for PGPS. Similarly, each endpoint is modelled over two seasons for EGPS. The summary of response variables analysis using MMRM is presented in **Table 11**.

Table 11 Summary of MMRM response variables.

Analysis number	Endpoint in 1st year	Endpoint in 2nd year
1	2nd key secondary endpoint: TCS during 1st PGPS	Primary endpoint: TCS during 2nd PGPS
2	3rd key secondary endpoint: average weekly overall RQLQ 1st PGPS	1st key secondary endpoint: average weekly overall RQLQ 2nd PGPS
3	Supportive secondary endpoint: average weekly overall RQLQ 1st EGPS	Supportive secondary endpoint: average weekly overall RQLQ 2nd EGPS
4	Supportive secondary endpoint: TCS 1st EGPS	Supportive secondary endpoint: TCS 2nd EGPS
5	Supportive secondary endpoint: DSS 1st PGPS	Supportive secondary endpoint: DSS 2nd PGPS
6	Supportive secondary endpoint: DSS 1st EGPS	Supportive secondary endpoint: DSS 2nd EGPS
7	Supportive secondary endpoint: DMS 1st PGPS	Supportive secondary endpoint: DMS 2nd PGPS
8	Supportive secondary endpoint: DMS 1st EGPS	Supportive secondary endpoint: DMS 2nd EGPS

The relevant endpoints in 1st and 2nd years are set to be the response variables and treatment, visit, treatment/visit interaction as well as asthma indication (yes/no) are fixed effect and trial site as a random class effect. If less than 20% of subjects will have asthma indication positive, then the asthma indication will be removed from the model. The compound symmetry covariance matrix is considered. In case there will be issues with convergence, first-order autoregressive covariance matrix will be considered. Depending on the number and size of trial sites, pooling of trial sites may be considered, or trial sites may be replaced by regions or countries. This will be specified in the SAP. The summary of the results will contain p-value for the treatment effect, and both the absolute difference with 95% CI and the relative difference with 95% CI will be presented. If the assumptions underlying the MMRM are not fulfilled an appropriate transformation (e.g. the square root) of the response variables will be carried out. Results will be back-transformed and shown on

the original scale. Further details of the primary analysis, test of assumptions, and sensitivity analysis will be detailed in the SAP.

15.11.2 Handling of intercurrent events and missing data for the trial product estimand

For the trial product estimand, diary data occurring after discontinuation of trial treatment will be excluded from the derivation of the primary endpoint (see Section **15.1.2**). Subjects for whom the primary endpoint is missing (because of either missing diary data or the exclusion of diary data due to discontinuation of trial treatment) will be included in the analysis through multiple imputation under the hypothetical situation where subjects continued to take trial treatment as planned. Multiple imputation for subjects missing the primary endpoint will be conducted as follows:

- For subjects that discontinue trial treatment due to lack of efficacy, multiple imputation of the missing endpoint will be from the placebo group. This assumes that had the subject continued to take trial treatment, they would have experienced similar efficacy to subjects in the placebo arm. Data is assumed to be missing not at random (MNAR).
- For subjects that discontinue trial treatment due to treatment-related AEs, multiple imputation of the missing endpoint will be from their own treatment group. This assumes that the level of efficacy that would have been experienced by the subject if they had continued to take trial treatment is unrelated to the occurrence of the AE and, if they had continued to take trial treatment, they would have experienced similar efficacy to subjects in their own treatment group. Data is assumed to be missing at random (MAR).
- For subjects that discontinue trial treatment due to any other non-treatment related reason, multiple imputation of the missing endpoint will be from their own treatment group. This assumes that the level of efficacy that would have been experienced by the subject had they continued to take trial treatment is not related to their discontinuation of trial treatment. Data is assumed to be MAR.

The sensitivity estimator for the trial product estimand will use the multiple imputation policy described above for the main estimator except that:

- For subjects that discontinue trial treatment due to treatment-related AEs, multiple imputation of the missing endpoint will be from the placebo group. This assumes subjects reporting treatment-related AEs would have been experienced a level of efficacy similar to subjects in the placebo group if they had continued to take trial treatment. Data is assumed to be MNAR.

Further sensitivity estimator(s) for the trial product estimand may also be considered and will be detailed in the SAP.

15.11.3 Handling of intercurrent events and missing data for the treatment policy estimand

For subjects discontinuing trial treatment, all diary data (including data collected after discontinuation of trial treatment) will be included in the derivation of the primary endpoint (see Section **15.1.3**). Subjects for whom the primary endpoint is missing will be included in the analysis through multiple imputation as follows:

- For subjects discontinuing trial treatment due to treatment-related AEs or lack of efficacy, multiple imputation of the missing endpoint will be from the placebo group. This assumes that missing data following treatment-related discontinuation of trial treatment is MNAR and that subjects no longer taking active treatment for these reasons would have shown similar efficacy to subjects receiving placebo.

- For subjects discontinuing trial treatment due to non-treatment related reasons, multiple imputation of the missing endpoint will be their own treatment group. This assumes that the missing data are MAR.

The sensitivity estimator for the treatment policy estimand will use multiple imputation from the placebo group for all subjects that discontinue trial treatment regardless of the reason for discontinuation. Further sensitivity estimator(s) for the treatment policy estimand may also be considered and will be detailed in the SAP.

15.11.4 Estimators for estimands defined for key secondary efficacy objectives

The key secondary and supportive secondary endpoints will be analysed identically to the primary endpoint using the definitions of the trial product estimand and treatment policy estimand (see Sections **2.4** and 2.5) and the main and sensitivity estimators described in Section **15.11.1**.

15.11.5 Exploratory analysis

[redacted]

15.12 Safety analyses

15.12.1 Evaluation of AEs

AEs will be summarised by treatment group, MedDRA SOC and PT displaying number of subjects in treatment group, number and percentage of subjects having the event as well as number of events. Furthermore, the AEs will be summarised according to severity, relationship, outcome and seriousness.

The analyses will be described further in the SAP.

15.12.2 Evaluation of other safety parameters

Laboratory assessments, vital signs, physical examination and FEV_1 will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 25- and 75-percentiles, minimum and maximum for continuous variables, and frequency tables for categorical variables.

The analyses will be described further in the SAP.

15.13 Interim analyses

No interim analysis is planned.

15.14 Handling of missing data

Efficacy endpoints which are an average of daily diary entries over a defined pollen season period will be derived provided there is at least one relevant diary entry for that endpoint in the given pollen season period. Subjects with missing data for an endpoint will be included in the analysis of that endpoint through multiple imputation (see Sections **15.11.2**, **15.11.3** and **15.11.4**). Detailed specification of sensitivity analyses to address the assumptions underlying the main estimators of each estimand will be provided in the SAP.

Imputation of missing daily diary data is not considered for the main estimators of the trial product and treatment policy estimands. Occasional missing diary values are assumed to be missing completely at random (MCAR) and are therefore not a source of bias in the derivation of the endpoints. Investigation of patterns of extended periods of missing daily diary data and potential sensitivity analyses, however, will be considered in the SAP although appropriate imputation of missing daily diary values is a complex problem. Diary entries over the course of a pollen season are highly specific to the subject completing the diary; they are a function of the local pollen exposure in the immediate environment of the subject and that individual subject's tolerance to allergic rhinoconjunctivitis symptoms and subsequent rescue medication usage. Imputation of missing daily data could easily introduce daily data inconsistent with a subject's individual profile and subsequent bias in the derivation of the endpoints.

16 QUALITY ASSURANCE AND CONTROL

16.1 Monitoring

Regular monitoring visits will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. In accordance with

SOPs, the CRAs will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

16.2 Source data and access to source documents

Prior to start of recording of data from subjects, the investigator, with the aid of the CRA, will prepare a source data location agreement to document where the first recording of data is done.

As a minimum requirement, the following data must be source data-verifiable in source documentation other than the CRF:

- Subject's date of birth
- Confirmation of participation in the trial (trial ID, subject number/randomisation number, diagnosis)
- Date of informed consents
- Confirmation of subject eligibility (in/exclusion criteria)
- Concomitant diseases and medication
- Relevant medical history (incl. specific allergy and asthma history and date of diagnosis)
- Any AEs and SAEs should be described in detail
- Date and number of each trial visit including signature and/or initials of persons conducting the trial visit
- Date and information of any relevant telephone contact with the subject and signature and/or initials of persons conducting or receiving the call
- IMP dispensed/returned
- Subject discontinuation from the trial including reason

Documentation of FEV_1, SPT and lab results must be kept in the subject's medical record, evaluated, signed and dated by an investigator at the trial site. Documentation on thermo-sensitive paper must be copied and signed by the investigator. The copy signed by the investigator should be kept together with the original in the subject's medical record.

The following data could be recorded directly on the eCRF and is then considered to be source data (if acceptable by national legislation and hospital routine):

- Demography and body measurements
- Vital signs
- Physical examination
- Smoking habits

The investigator must give the CRA direct access to examine, analyse and verify any medical records or reports to procedures, source documentation, data records and reports used, referenced or created as part of the conduct of this trial (e.g. relevant hospital or medical records), to confirm consistency with CRF entries.

The CRA will examine the electronic medical record system and decide one of the following options for source data verification:

- Option 1
  If an audit trail is available, the CRA may choose either to perform source data verification through a direct comparison of the eCRF and the electronic medical record or may choose to work according to option 2

- Option 2
  If no audit trail is available, relevant source data from electronic medical records should be printed out by the investigator or delegate preferably at the day of the monitoring visit. The investigator or delegate must sign and date the printout to confirm that the print and the electronic source data are identical. The CRA must verify the original source data at least once during the trial.

Either option will be agreed with the investigator prior to trial start.

All documents must be stored safely under confidential conditions. On all trial-specific documents, other than the signed consent, the subject will be referred to by the subject ID number or randomisation number. If ALK becomes aware of the identity of a subject, ALK is bound to keep this information confidential and to take immediate actions to delete any information received that identifies the subject.

16.3 Investigator site file – and other trial documentation

The investigator must maintain source documents for each subject in the trial in accordance with local legislation.

The investigator must retain the investigator site file for at least 25 years.

No trial related documentation may be destroyed by the investigator without prior written agreement with ALK. The investigator agrees to adhere to the document retention procedures by signing the protocol.

Should the investigator choose to transfer the trial documents to another physician or institution, ALK must be notified.

16.4 Protocol compliance

The instructions in the protocol must be followed. If deviations occur, the investigator must inform the CRA, and the implications of the deviation must be reviewed and discussed. Deviations must be documented (or included in CRF data). In addition, deviations must be accompanied by a description of the deviation, the relevant dates and the action taken. Deviation reports and supporting documentation must be kept in the investigator's file and in the ALK trial master file.

If a deviation that is likely to affect to a significant degree the safety and rights of a subjects or the reliability and robustness of the data generated in the clinical trial (serious breach) has occurred, the investigator should inform ALK/CRO within 24-hours.

16.5 Audit

ALK may conduct audit(s) of clinical research activities in accordance with internal SOPs to evaluate compliance with GCP and international and local guidelines and regulations.

The investigator must be available during the audit and give the auditors direct and unlimited access to source documentation and data, records and reports used, referenced or created as part of the performance of this trial.

17 ETHICS AND REGULATORY PROCEDURES

17.1 Statement of compliance

This trial must be carried out in compliance with the protocol, which is designed to ensure adherence to the Declaration of Helsinki and the principles of GCP, as described in:

- The Declaration of Helsinki (1964, and its amendments and subsequent clarifications) ICH Harmonised Tripartite Guidelines for GCP, 1996 **(ICH 1996)**
- EU Directive 2001/20/EC of the European Parliament and of the Council on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. 2001 **(The European parliament 2001)**
  - European Commission. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of manufacturing or importation of such products. 2005 **(European Commission 2005)**

17.2 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information, data and materials whether in oral, written, graphic, electronic or other form provided by ALK or a third party acting on behalf of or at the instruction of ALK in strict confidentiality.

Trial documents provided by ALK (protocol, IB, CRFs and other material) should be stored appropriately to ensure their confidentiality. The information provided by ALK to the investigator may not be disclosed to others except as expressly authorised by this protocol or the clinical trial agreement or with the prior written consent of ALK.

The investigator may disclose confidential information to employees of the investigator, hospital authorities and IECs/IRBs on a need-to-know basis and only if the aforementioned parties are bound or obligated by provisions of confidentiality no less strict than imposed upon the investigator under this protocol or the clinical trial agreement. Further, the investigator may disclose confidential information set out in the protocol to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

Any data, results, reports, findings, discoveries and any other information developed or collected during this trial shall be regarded as ALK's confidential information until published.

Financial disclosure from the investigators will be obtained before the trial.

17.3 Subject confidentiality

The trial staff should ensure that the subject’s anonymity is maintained. The subjects will be identified by a subject ID number in the CRF and any electronic database owned by ALK. All documents will be stored securely and only accessible by trial staff and authorised personnel.

17.4 Data protection

All data will be handled and stored according to GDPR (The European parliament 2016).

Investigator

By signing this protocol, the investigator recognises that certain personal identifying information with respect to the investigator and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- Name, address, telephone number and email address
- Hospital or clinic address and telephone number
- Curriculum vitae or other summary of qualifications and credentials
- Financial disclosure information
- Other professional documentation

Consistent with the purposes described above, this information may be transmitted to ALK, affiliates and ALK representative, in the investigator's country and other countries, including countries that do not have laws protecting such information. In these cases, ALK will take appropriate measures to protect data and ensure that the transfer of data will have an adequate level of data protection. ALK will rely on valid standard contract clauses signed with third parties.

Additionally, the investigator's name and business contact information may be included when reporting certain SAEs to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multi-site trial, in order to facilitate contact between investigators, ALK may share an investigator's name and contact information with other participating investigators upon request.

Subjects

Subjects will be assigned a unique identifier, a subject number. Any subject records or datasets that are transferred to ALK will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. This way the subject data will go through a pseudonymisation process, which means that the data cannot be attributed to a specific subject without the use of additional information.

The subject and any biological material obtained from the subject will be identified by subject number, visit number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects as required by local, regional and national requirements.

The subject must be informed that his/her personal trial related data will be used by ALK in accordance with local data protection law. The disclosure of the data must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by ALK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Transfer of data

If data are transferred to or accessed by third countries, that is, countries outside EU/EEA countries, the data will be protected to have an adequate level of data protection principles.

Description of arrangements

To ensure the safekeeping of clinical trial data ALK has Standard Operating Procedures that defines how data shall be managed including handling of security data breaches. When data is

managed by external parties, written agreements are in place to ensure that the data is handled according to ALK's instructions/standards.

17.5 IEC/IRB/regulatory authorities

Before initiation of this trial, the protocol, the proposed informed consent form and other information to subjects as well as other documents required, must be reviewed by a properly constituted IEC/IRB and provided to the national (and local, if applicable) regulatory authority.

A signed and dated statement that the protocol and the subject information sheet/informed consent form and any other information to the subjects have been approved by the IEC/IRB and the regulatory authority must be obtained before trial initiation.

17.6 Inspections

An IEC/IRB or a national or international regulatory authority may also wish to conduct an inspection (during the trial or after its completion). If an inspection is requested by a regulatory authority, the investigator must inform ALK of the request immediately. The investigator or ALK should agree (in accordance with the prevailing law) with the inspectors that ALK shall have the right to be present at any inspection or investigation. The investigator or ALK should agree with the inspector that ALK may conduct and control applicable action arising from the inspections at ALK's expense.

The investigator must be available during the inspection and give the inspectors direct and unlimited access to source documentation and data, records and reports used, referenced or created as part of performance of this trial.

17.7 Protocol amendment and other changes in trial conduct

Substantial changes to this protocol require a protocol amendment that must be signed off by ALK and the investigator(s) and be approved by IEC/IRB and/or regulatory authorities as applicable before implementation.

The requirements for approval of the substantial changes should in no way prevent any immediate action from being taken by the investigator or by ALK in the interest of preserving the safety of all subjects included in the trial.

Amendments not considered substantial such as administrative changes will only be submitted to the regulatory authorities once another substantial amendment must be submitted or together with the end of trial notification unless national legislation requires otherwise.

18 REPORTING AND PUBLICATION

18.1 Integrated clinical trial report

Data will be reported in a clinical trial report in compliance with the requirements of the current version of ICH E3: Structure and Content of Clinical Trial Report, ICH GCP Guidelines and ALK SOPs.

The national coordinating investigator(s) will review and sign the clinical trial report.

18.2 Publication of results

ALK retains exclusive ownership of all data, results, reports, findings, discoveries and any other information developed or collected during this trial and ALK shall have the exclusive right to use all such information for any purpose, including, but not limited to, use of the results and data either in the form of CRF (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the regulatory authorities of any country.

By signing the investigator agreement, the investigator agrees that the results of this trial may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

It is envisaged that the findings of this trial, including sub-analysis, and if relevant the epidemiology of the screened population and the selection process, will, in due time and by mutual agreement, be published in international journals, theses and/or presented at scientific meetings or symposia. All presentations and publications must be reviewed by ALK prior to public presentation or submission. For multi-site trials, it is mandatory that the primary publication is based on data from all trial sites, analysed as stipulated in the protocol and in the SAP.

Authorship is based on the International Committee of the Medical Journal Editors “Uniform Requirements” (Vancouver Declaration). Invitation to author publications will be at the discretion of ALK. All authors of publications need to fulfil all four criteria stated in the Vancouver guidelines/ICMJE criteria: 1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; 2) drafting the work or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Failure to meet all 4 ICMJE criteria will result in removal as author. Other significant contributions to the publication will be acknowledged in accordance with journal or other relevant specific guidelines.

If the number of authors is restricted, selection will be based on accountability for the conduct and reporting of the trial.

Investigators participating in multi-site trials agree not to present data gathered from one trial site or a group of trial sites before the primary publication has been accepted for publication unless formally agreed by all other investigators and ALK.

ALK shall be provided with copies of any proposed publication or presentation at least 60 days in advance of the submission of such proposed publication or presentation to a journal, editor, or other third party. ALK has the right to review and comment on any such publication or presentation within 60 days of receipt but cannot prevent publications of findings. The investigator agrees that all reasonable comments made by ALK will be incorporated into the publication. Furthermore, the investigator agrees that the investigator shall, at ALK's request exclude or delete any confidential information, except trial results generated hereunder, from the proposed publication or presentation.

Furthermore, results of the trial will be posted in the EU Clinical Trials Registry no later than 12 months after LSLV. No individual de-identified subject data will be shared. Results of the trial, together with the protocol and SAP, will be posted at ClinicalTrials.gov together with the final protocol and SAP no later than 12 months after the primary completion date. No individual de-identified subject data will be shared.

If results are not disclosed on external websites in accordance with international and national regulations, a justification must be given.

19 FINANCE AND INSURANCE

ALK subscribes to an insurance policy covering, in its terms and provisions, it is legal liability for injuries caused to participating subjects and arising out of these trial assessments performed strictly in accordance with this protocol as well as with applicable law and professional standards.

The compensation to the investigators for work performed under this protocol will be set out in separate clinical trial agreements with the investigators.

20 TRIAL ORGANISATION

The title, name, address and contact details of investigators and clinical research organisations (CROs) and e.g. subcontractors for project management, monitoring, central laboratory, etc. are listed in Appendix 3: Trial organisation.

21 REFERENCE LIST

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