TT-06 TRIAL PROTOCOL COVER PAGE

Official trial title	Efficacy and safety of the SQ tree sublingual immunotherapy tablet in children and adolescents (5 through 17 years of age) with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group
NCT number	NCT04878354
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Clinical trial protocol

Trial ID: TT-06

Efficacy and safety of the SQ tree sublingual immunotherapy tablet in children and adolescents (5 through 17 years of age) with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group

Sponsor: ALK-Abelló A/S
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Investigational medicinal product: SQ tree SLIT-tablet

Phase: III

Regulatory trial identifier number:
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PROTOCOL SYNOPSIS

Trial ID EudraCT no.	TT-06 2020-004372-17
Title of trial	Efficacy and safety of the SQ tree sublingual immunotherapy tablet in children and adolescents (5 through 17 years of age) with moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group
Main objectives	**Primary objective:** • To compare the efficacy of the SQ tree SLIT-tablet to placebo in the treatment of moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group in children and adolescents (5 through 17 years of age) based on the average allergic rhinoconjunctivitis daily total combined score[#] (average TCS) during the birch pollen season (BPS) [#] daily total combined score = daily symptom score + daily medication score **Key secondary objectives:** To compare the efficacy of the SQ tree SLIT-tablet to placebo based on: • The average TCS during the tree pollen season (TPS) • The average allergic rhinoconjunctivitis daily symptom score (average DSS) during the BPS and TPS • The average allergic rhinoconjunctivitis daily medication score (average DMS) during the BPS and TPS **Secondary objectives:** • To compare the safety and tolerability of the SQ tree SLIT-tablet to placebo • To compare the efficacy of the SQ tree SLIT-tablet to placebo using additional endpoints based on daily allergic rhinoconjunctivitis symptoms and rescue medication use • To compare the efficacy of the SQ tree SLIT-tablet to placebo based on assessments of quality of life • To compare the efficacy of the SQ tree SLIT-tablet to placebo based on patient treatment satisfaction • To compare the effect of the SQ tree SLIT-tablet to placebo on immunological parameters to birch, alder, hazel and oak pollen
Primary endpoint	Average TCS during the BPS
Key Secondary endpoints	• Average TCS during the TPS • Average DSS during the BPS • Average DSS during the TPS • Average DMS during the BPS • Average DMS during the TPS

Primary estimand	The absolute difference between SQ tree SLIT-tablet and placebo treatment policies based on the average TCS during the BPS, in the hypothetical situation that all subjects complete treatment for the planned duration.
Secondary estimand	The absolute difference between SQ tree SLIT-tablet and placebo treatment policies based on the average TCS during the BPS, regardless of whether subjects complete treatment for the planned duration.
Trial design	A phase III, randomised, parallel-group, double-blind, placebo-controlled, multi-regional trial in children and adolescents with AR/C (with or without asthma) induced by pollen from birch. The trial consists of 3 periods: a screening period, a treatment period, which includes pre-seasonal and co-seasonal treatment, and a follow-up period. There may be multiple cohorts recruited over consecutive seasons to complete the enrolment goal. The screening visit can take place up to approximately 6 months prior to randomisation. Eligible subjects will be randomised (1:1) to the SQ tree SLIT-tablet or placebo. The randomisation will be stratified by geographical location and by age group. Once randomised, subjects should receive at least 12 weeks pre-seasonal treatment prior to the TPS. Treatment will continue until 1 week after the end of the TPS for all subjects, corresponding to up to approximately 12 months of treatment. [redacted] Open-label rescue medication for allergic rhinoconjunctivitis will be provided during the TPS [redacted] Open-label asthma medication will be provided to subjects with asthma during the TPS [redacted] A follow-up phone visit will be conducted 1 week after the End-of-treatment visit. At least 6 in-clinic visits and 4 telephone contacts are planned for each subject. The TPS includes hazel, alder, birch and oak pollen seasons. A data monitoring committee will be established for the trial.
Main assessments	**The following data will be collected:** • Demographics • Medical history (including any allergy, urticaria, asthma, atopic dermatitis, and oral allergy syndrome) • Prior and concomitant medication • Result of IgE and skin prick testing to a panel of allergens **Efficacy assessments (eDiary during TPS):** • Allergic rhinoconjunctivitis symptoms • Allergic rhinoconjunctivitis medication use • [redacted] • [redacted]

	• [redacted] • Standardised rhinoconjunctivitis quality of life questionnaire (RQLQ(S), 12-17 years) • [redacted] • [redacted] **Other efficacy assessments during TPS:** • Paediatric rhinoconjunctivitis quality of life questionnaire (PRQLQ, <12 years) • Patient-rated global evaluation of treatment efficacy • Patient treatment satisfaction questionnaire for medication (TSQM-9) [redacted] • [redacted] • [redacted] **Immunological assessments** • Immunological and serological parameters such as IgE, IgG_4 and IgE-blocking factor (IgE-BF) and other antibody isotypes against relevant allergens as well as other serological components **Safety assessments** • Adverse events (AEs) • Vital signs, physical examination, lung function test and clinical laboratory values before treatment and at the final site visit.
Main criteria for inclusion	Subjects are eligible to be included in the trial only if all the following criteria apply: • Male or female of any race/ethnicity aged ≥4 to <18 years on the day informed consent is obtained from the parent/caregiver; the subject must be ≥5 to <18 years old at the randomisation visit • A documented[1], physician diagnosed, clinically relevant history of moderate to severe AR/C induced by birch pollen (with or without asthma) despite having received treatment with symptom-relieving medication during at least 1 previous tree pollen season for ages 4 through 6 years at screening or at least 2 previous tree pollen seasons for ages 7 through 17 years at screening • Positive skin prick test (SPT) to *Betula verrucosa* at screening[2] • Positive specific IgE[3] to Bet v at screening • Presence of 1 or more of the following Allergic Rhinitis Impact on Asthma (ARIA) quality of life items due to AR/C during the previous BPS:

[1] If medical records are not available, verbal history from subject/parent/caregiver may be elicited at the screening visit. This must be documented by the investigator in the subject study file.

[2] A positive SPT is defined in the SPT guideline. Briefly, a positive SPT is defined as a wheal size of ≥3 mm. If medication that could interfere with the SPT, according to prohibited and restricted medication table, has not been washed out, the SPT must be performed after the interfering medication has been washed out.

[3] A positive specific IgE is defined as ≥IgE Class 2; ≥0.70 kU/L

	a. Sleep disturbance b. Impairment of daily activities, leisure and/or sport c. Impairment of school or work d. Troublesome symptoms
Main criteria for exclusion	Subjects are excluded from the trial if any of the following criteria apply: • A clinically relevant history of symptomatic seasonal AR/C caused by an allergen source, other than tree pollen from the birch homologous group, with a season overlapping the TPS • A clinically relevant history of symptomatic perennial AR/C caused by an allergen source such as animal hair and dander to which the subject is exposed during the TPS • Any clinical deterioration of asthma (i.e. asthma exacerbation) that resulted in emergency treatment, hospitalisation or treatment with systemic corticosteroids within 3 months prior to randomisation • Reduced lung function at randomisation defined as forced expiratory volume in 1 second (FEV_1) <70% of predicted value. For subjects with asthma, this is assessed on subject's usual asthma medication following at least a 6-hour wash-out of SABA. This criterion does not need to be fulfilled if the subject is <7 years old, cannot perform reproducible FEV_1 manoeuvres despite coaching and is not considered as having a diagnosis of asthma • Ongoing treatment with any allergy immunotherapy product • Severe chronic oral inflammation • A diagnosis of eosinophilic oesophagitis • 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 • Immunosuppressive treatment (ATC code L04 or L01) within 3 months prior to the screening visit
Investigational medicinal products	SQ tree SLIT-tablet (dose: 12 SQ-Bet) or placebo
Duration of treatment	Each randomised subject will receive IMP daily for a maximum of approximately 13 months.
Number of subjects to be enrolled	Approximately 1000 subjects to be randomised. Approximately 45% of the subjects should be aged 5-11 years at the time of randomisation.
Number and distribution of trial sites	Estimated 75-80 sites
Statistical methods	The full analysis set (FAS) will consist of all randomised subjects, where subjects will be analysed according to the treatment to which they were randomised. Analyses for the primary estimand and the secondary estimand will be based on the FAS. For subjects discontinuing trial treatment, all diary data up to the time of discontinuation will be included in the analysis for the primary estimand. Whereas for the secondary estimand, all diary data collected (including data collected after discontinuation of trial treatment) will be included in the analysis. Subjects with missing data for the primary efficacy endpoint will be included in the analyses through a multiple imputation

	approach aligned to the respective estimand and assumptions will be assessed through sensitivity analyses. An identical statistical analysis will be used for the primary and secondary estimands, although the actual datasets used in the analyses may vary depending on the number of subjects discontinuing trial treatment and the extent of missing data. For each analysis based on the primary efficacy endpoint, 1000 multiply imputed datasets will be created, and each dataset will be analysed using the following model. The primary efficacy endpoint will be square root transformed and analysed using a linear mixed effects model assuming unequal variances in the 2 treatment groups. The model will include treatment, pollen season and age group (5-11 years, 12-17 years) as fixed effects, and geographical location as a random effect. The results will be back-transformed to the original scale and Rubin's rule will be used to combine the results obtained from the multiply imputed datasets. The p-value for the treatment effect, the absolute difference with 95% CI, and the relative difference with 95% CI will be presented. Primary and secondary estimands based on the key secondary efficacy endpoints are defined similarly for the key secondary objectives. Analyses for these estimands will be identical to those based on the respective estimand defined for the primary objective. For the primary estimand, a hierarchical testing strategy will be used for the analyses based on the primary efficacy endpoint, key secondary efficacy endpoints and quality of life endpoints to control for multiplicity and ensure a maximum overall type I error rate of 5%.
International coordinating investigator	[redacted]
Sponsor's name/address	ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark

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TABLE OF ABBREVIATIONS

AE	Adverse event
AHPS	Alder-hazel pollen season
AIT	Allergy immunotherapy
ALK	ALK-Abelló A/S
AR/C	Allergic rhinitis and/or conjunctivitis
ARIA	Allergic rhinitis and its impact on asthma
Bet v	*Betula verrucosa* (white birch)
Bet v 1	Major allergen 1 of *Betula verrucosa* (white birch)
BPS	Birch pollen season
CHMP	Committee for medicinal products for human use
CI	Confidence interval
CL	Confidence limit(s)
CRA	Clinical research associate
CRO	Clinical research organisation
CTS	Clinical trial supplies
DMC	Data monitoring committee
DMS	Daily medication score
DSS	Daily symptom score
EAACI	European Academy of Allergy and Clinical Immunology
ECC	Environmental exposure chamber
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EEC	Environmental exposure chamber
EMA	European medicines agency
EoE	Eosinophilic oesophagitis
ESI	Events of special interest
EudraCT	European Union drug regulating authorities clinical trials database
FAS	Full analysis set
FDA	Food and drug administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good clinical practice
GINA	Global initiative for asthma
[redacted]	[redacted]
IB	Investigators brochure
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
ICS	Inhaled corticosteroid
ICTR	Integrated clinical trial report
IE	Intercurrent event
IEC	Independent ethics committee
IgE	Immunoglobulin E
IgE-BF	IgE-blocking factor
IgG_4	Immunoglobulin G4
IMP	Investigational medicinal product

IRB/IEC	Institutional review board/Independent ethics committee; terms can be used interchangeably
IRT	Interactive response technology
ITT	Intention to treat
LABA	Long-acting β_2-agonist
LME model	Linear mixed effect model
LSLV	Last subject last visit
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MedDRA	Medical dictionary for regulatory activities
N	Number
OAS	Oral allergy syndrome
OC	Observed case
OPS	Oak pollen season
PDCO	Paediatric committee
PFS	Pollen food syndrome
PRQLQ	Paediatric rhinoconjunctivitis quality of life questionnaire
RQLQ(S)	Standardised rhinoconjunctivitis quality of life questionnaire
SABA	Short-acting β_2-agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SCIT	Subcutaneous allergy immunotherapy
SD	Standard deviation
SLIT	Sublingual allergy immunotherapy
SLIT-tablet	Sublingual allergy immunotherapy tablet
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPT	Skin prick test
TC	Telephone call
TCS	Total combined score (rhinoconjunctivitis symptoms and medication use)
TEAE	Treatment-emergent adverse events
TPS	Tree pollen season
TSQM©	Treatment satisfaction questionnaire for medication
UV	Unscheduled visit
V	Visit
WHO	World Health Organization

TABLE OF DEFINITIONS

Asthma	A subject must meet at least 1 of the following 4 criteria to be considered as having a diagnosis of asthma: • At least 1 episode of wheeze, cough, shortness of breath or chest tightness and a change in FEV_1 ≥12% after β_2-agonist administration • Recurrent wheeze with or without prolonged phase of forced exhalation observed at physical examination and an intake of asthma medication which resulted in a clinically relevant effect • Wheezing with or without prolonged phase of forced exhalation observed at physical examination and a change in FEV_1 ≥12% after β_2-agonist administration • Using asthma medication
Completed subject	A randomised subject is considered completed if he/she has not discontinued the trial before visit 6
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 (TC4) for the last subject in the trial globally.
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).
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 that can be used for managing randomisation, subject enrolment and trial supply management in a clinical trial.
LSLV	Last subject last visit (Follow-up phone visit TC4).
Primary completion date	According to EU regulations this is the last subject last visit. However, for ClinicalTrials.gov, the primary completion date is the date of the last data collection for the primary endpoint which is the end-of-treatment visit (visit 6) for the last subject in the trial globally.

Rescue medication	Medicinal products provided by ALK when the efficacy of the IMP is not sufficient or likely to cause an adverse event to the subject or to manage an emergency situation in relation to allergy symptoms in agreement with the EMA Definition of IMPs and use of AMPs consultation document (EMA 2016).
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 including depot formulations.
TEAE	An adverse event with start date/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 trial discontinuation date is defined as the date the investigator/sponsor decides to discontinue the subject from the trial.

PROTOCOL VERSIONS

Date	Version	Description of document	Rationale for amendment
18-Sep-2020	1.0	Protocol version 1.0 was updated due to minor inconsistencies and was never submitted to regulatory authorities or ethics committees	N/A
16-Oct-2020	2.0	Final Protocol	N/A
24-May-2022	3.0	Amendment 1: To eliminate further participation of more than one subject from the same household in the same cohort, and to add minor clarifications and correct inconsistencies. The amendment is considered non-substantial and is applicable for all countries.	To prevent unintentional swap of trial medication (IMP) within subjects from the same household.

FLOW CHART

Visit ID:	**V1**	**TC1**[4]	**V2**	**V3**	**V4**	**TC2**	**TC3**	**V5**	**TC** [redacted]	**V6**	**TC4**	**UV**[5]
Name of visit	Screen-ing	Retention	Randomi-sation	Off season	Pre-TPS	Start of TPS	Pre-BPS	In season BPS	Only for cohort 1 subjects also [redacted]	End-of-treatment	Follow-up	Unsched-uled
Scheduled week	1-26 weeks prior to V2	4-12 weeks prior to V2	At least 12 weeks prior to expected start of TPS[6]	4 weeks after V2	2 weeks prior to expected start of TPS		2 weeks prior to expected start of BPS	2 weeks after expected start of BPS[7]	1 week after expected end of TPS	1 week after expected end of TPS Cohort 1 subjects also [redacted]: 1 week after expected end of [redacted][8]	1 week after V6	
Visit window				+7 days	-14 to +7 days	-4 days	+7 days	+7 days	+7 days	+7 days	+7 days	
Administrative procedures												
Informed consent[9]	X											
Inclusion/exclusion criteria	X		X									
Randomisation			X									
Demography	X											
Smoking habit	X											
Medical history	X											
Record prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
TC to ensure that subject is still interested in the trial		X										
Dispense IMP			X		X			X				(X)

[4] Only required if V1 (screening) is performed more than 12 weeks prior to randomisation.

[5] Unscheduled visits should be conducted as necessary. The evaluations/examinations listed with brackets should only be performed if deemed necessary by the investigator.

[6] Randomisation (V2) must be performed at least 12 weeks prior to expected TPS but no later than 31 October.

[7] Visit 5 can be scheduled based on the actual BPS start date.

[8] In cohort 1 subjects also [redacted] V6 is to be performed 1 week after the expected end of [redacted]. End of [redacted] can be no later than 31 August 2022.

[9] Obtain written informed consent for the trial, storage of serum samples in the ALK Research Biobank, and for pharmacogenetics testing before any other trial procedures are performed.

Visit ID:	**V1**	**TC1**[4]	**V2**	**V3**	**V4**	**TC2**	**TC3**	**V5**	**TC** [redacted]	**V6**	**TC4**	**UV**[5]
Name of visit	Screen-ing	Retention	Randomi-sation	Off season	Pre-TPS	Start of TPS	Pre-BPS	In season BPS	Only for cohort 1 subjects also [redacted]	End-of-treatment	Follow-up	Unsched-uled
Instruct the subject in use of IMP			X									(X)
Collect IMP and perform drug accountability					X			X		X		
Perform IMP compliance check				X	X			X		X		
Dispense rhinoconjunctivitis and asthma rescue medication					X			X				(X)
Collect rescue medication and perform drug accountability								X		X		
Handout eDiary					X							
Instruct in the use of the eDiary incl. training in symptom scoring					X	X	X	X	X			
Show and/or discuss trial video					X	X	X	X				
Inform that TPS is starting						X						
Clinical procedures/assessments												
Physical examination	X		X							X		(X)
Height			X							X		(X)
Weight	X		X							X		(X)
Vital signs	X									X		(X)
Lung function test[10]			X							X		(X)
SPT[11]	X		(X)									
Assess AEs	X	X	X	X	X	X	X	X	X	X	X	X
Assess symptoms of eosinophilic oesophagitis	X		X	X	X	X	X	X	X	X	X	X

[10] Measure FVC and FEV_1 while subject is on their usual asthma medication (if applicable) following at least a 6 hour washout of SABA.

[11] To be taken after a urine pregnancy test (if applicable). A positive SPT is defined in the SPT guideline. Briefly, a positive SPT is defined as a wheal size of ≥3 mm. If medication that could interfere with the SPT, according to prohibited and restricted medication table, has not been washed out, the SPT must be performed at V2 after the interfering medication has been washed out.

Visit ID:	**V1**	**TC1**[4]	**V2**	**V3**	**V4**	**TC2**	**TC3**	**V5**	**TC** [redacted]	**V6**	**TC4**	**UV**[5]
Name of visit	Screen-ing	Retention	Randomi-sation	Off season	Pre-TPS	Start of TPS	Pre-BPS	In season BPS	Only for cohort 1 subjects also [redacted]	End-of-treatment	Follow-up	Unsched-uled
Intake of IMP at clinic			X									

Visit ID:	**V1**	**TC1**[4]	**V2**	**V3**	**V4**	**TC2**	**TC3**	**V5**	**TC** [redacted]	**V6**	**TC4**	**UV**[5]
Name of visit	Screen-ing	Retention	Randomi-sation	Off season	Pre-TPS	Start of TPS	Pre-BPS	In season BPS	Only for cohort 1 subjects also [redacted]	End-of-treatment	Follow-up	Unsched-uled
All subjects (except for cohort 1 subjects with [redacted]) **Daily eDiary recording:** •AR/C symptoms •AR/C medication • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] **Weekly eDiary recording:** •RQLQ(S)[12]						X ----------X						
Cohort 1 subjects with [redacted] **Daily eDiary recording**: •AR/C symptoms •AR/C medication						X ----------X						

[12] RQLQ(S) should be performed only for subjects who were 12-17 years at the randomisation visit.

Visit ID:	**V1**	**TC1**[4]	**V2**	**V3**	**V4**	**TC2**	**TC3**	**V5**	**TC** [redacted]	**V6**	**TC4**	**UV**[5]
Name of visit	Screen-ing	Retention	Randomi-sation	Off season	Pre-TPS	Start of TPS	Pre-BPS	In season BPS	Only for cohort 1 subjects also [redacted]	End-of-treatment	Follow-up	Unsched-uled
Cohort 1 subjects with [redacted] **Daily eDiary recording:** • [redacted] **Weekly eDiary recording:** •RQLQ(S)[12]						X ----------X						
Review eDiary recordings and compliance						X----------X						
Collect eDiary										X		
PRQLQ[13]								X				
All subjects (except for cohort 1 subjects with [redacted]): •Global evaluation of treatment efficacy •TSQM-9										X		

[13] Perform PRQLQ interview, only for subjects who were 5-11 years at the randomisation visit.

Visit ID:	**V1**	**TC1**[4]	**V2**	**V3**	**V4**	**TC2**	**TC3**	**V5**	**TC** [redacted]	**V6**	**TC4**	**UV**[5]
Name of visit	Screen-ing	Retention	Randomi-sation	Off season	Pre-TPS	Start of TPS	Pre-BPS	In season BPS	Only for cohort 1 subjects also [redacted]	End-of-treatment	Follow-up	Unsched-uled
Cohort 1 subjects with [redacted]**:** •Global evaluation of treatment efficacy •TSQM-9									X			
Laboratory procedures/assessments												
Blood sample for specific IgE against *Bet v*	X											(X)
Blood and urine samples for safety laboratory assessments	X									X		(X)
Urine pregnancy test[14]	X		X	X	X			X		X		(X)
Blood sample for Immunological assessments	X				X					X		(X)
Blood sample for biobank[15]	X				X					X		(X)
Blood sample for pharmacogenetics[16]										X		(X)

[14] For female subjects of childbearing potential only, additional urine pregnancy tests should be performed during the trial, if a menstrual period is missed.
[15] Only for subjects where informed consent for biobank sampling has been obtained.
[16] Only for subjects where informed consent for pharmacogenetics sampling has been obtained.

1 INTRODUCTION

1.1 Disease background and current treatment modalities

Despite differences among countries, the incidence and prevalence of allergic rhinitis and asthma are increasing worldwide. AR/C affects between 10 to 30% of all adults and up to 40% of children (Pawankar et al. 2011). Sensitisation rates to 1 or more common allergens among school children are estimated to be 40%-50% (Pawankar et al. 2011). Tree pollen allergy is common across central and northern Europe and North America and is commonly caused by pollen from the birch and related trees, also commonly referred to as the birch homologous group (hereafter referred to as “birch group”). This group currently includes birch, alder, hornbeam, hazel, beech and oak (Lorenz et al. 2009), although more species may be included when additional data on cross-reactivity and allergen homology becomes available (Heath et al. 2015). AIT guidelines recommend treating allergic patients with AIT using a representative allergen within a homologous allergen group (Cox et al. 2011; EMEA 2008).

The trees in the birch group are characterised by having Bet v 1 homologous allergens with a high level of structural sequence identity, leading to extensive cross-reactivity at the immune response level. Thus, people who are sensitised to pollen from one of the trees often also experience symptoms in response to pollen from other members of the birch group. Sensitisation to Bet v 1 has been estimated up to 24% in adults (Burbach et al. 2009; Chan-Yeung et al. 2010), and between 14-16% in children (Schmitz et al. 2013; Stemeseder et al. 2017). The broad cross-reactivity and sequential pollen seasons of birch related allergens prolong the period of allergic symptoms for people with allergy to birch. In previous clinical trials conducted by ALK in Europe and North America with the SQ tree SLIT-tablet, more than 90% of participants with AR/C induced by birch pollen were also sensitised to alder and hazel (Biedermann et al. 2019a). Furthermore, Jantunen et al. showed that 95% of patients diagnosed with birch pollen allergy presented with allergic symptoms during the alder season (Jantunen et al. 2012). Cross-reactivity of birch pollen allergens also extends to plant food allergens, resulting in the pollen food syndrome (Biedermann et al. 2019b).

Treatment options for AR/C include allergen avoidance, symptomatic medications such as antihistamines and corticosteroids, and AIT (Bousquet et al. 2008). Avoidance of pollen is difficult to achieve in a normal daily life, and symptom-relieving medication is widely used, however it does not offer causal treatment of the allergic disease and up to 44% of patients on optimal symptom-relieving medication report poor or only partial symptom control (Valovirta et al. 2008). AIT is the only available treatment modality that can modify the natural course of the allergic disease by induction of tolerance (Bousquet et al. 2008). The use of pollen extract for AIT is well-known, both in SCIT formulations (Blumberga et al. 2011; Bousquet et al. 1998a; Lang & Hawranek 2006; Winther et al. 2000a; Winther et al. 2000b) and as SLIT-tablets or drops (Demoly et al. 2016; Durham et al. 2012).

1.2 Stage of development

The SQ tree SLIT-tablet is a once daily fast-dissolving pharmaceutical formulation (oral lyophilisate) containing standardised allergen extract of white birch (*Betula verrucosa*) for AIT of seasonal AR/C induced by pollen from birch and trees belonging to the birch homologous group.

The SQ tree SLIT-tablet is approved in 17 European countries for treatment of adults with moderate to severe AR/C induced by the pollen from the birch homologous group, while in Switzerland this approval encompasses adults and adolescents (12-17 years old). In Canada, the SQ tree SLIT-tablet is approved for treatment of adults with moderate to severe AR/C induced by pollen from birch, alder and/or hazel.

The clinical development programme for the SQ tree SLIT-tablet comprises 4 phase I-III randomised, double-blind, placebo-controlled clinical trials in Europe and North America. The clinical efficacy of the SQ tree SLIT-tablet was confirmed in a phase III in-field trial (TT-04) including both adults (≤65 years old) and a small group of adolescents (12-17 years old) in Europe. The results demonstrated a statistically significant improvement with the SQ tree SLIT-tablet treatment compared to placebo for the average TCS during the BPS, the TPS and the AHPS. The average DSS and the average DMS (both components of the total combined score) also showed statistically significant improvements compared to placebo during the BPS, TPS and AHPS. A pre-specified analysis comparing the treatment effect in the adolescent and adult populations did not show a statistically significant difference in treatment effect between the 2 age groups.

The clinical relevance of the cross-reactivity between birch and oak was demonstrated in a phase II environmental exposure chamber trial (TT-03) and was further investigated (post-hoc) in the oak pollen season in the phase III in-field trial TT-04. Significant treatment effects were seen after exposure to birch as well as oak pollen both in the environmental exposure chamber and post-hoc in the phase III clinical field trial.

The SQ tree SLIT-tablet was generally well-tolerated with a safety profile characterised by frequent but transient local allergic events in the first few days of treatment, primarily occurring in or around the mouth and throat (e.g. pruritus, irritation, sensation changes, discomfort, swellings, and pain), that were typically assessed as mild or moderate in intensity. Severe allergic reactions were uncommon. Overall, the SQ tree SLIT-tablet was well-tolerated in subjects with tree pollen allergy with no major safety concerns detected. Finally, the safety profile was generally similar across age subgroups (adolescent vs adult).

1.3 Trial rationale

The prevalence of allergy induced by birch and cross-reactive tree pollen in children and adolescents in the general population is 14-16% (Schmitz et al. 2013; Stemeseder et al. 2017). A substantial number of these children and adolescents do not reach sufficient symptom control when treated with pharmacotherapy (antihistamines/steroids) (Meltzer et al. 2009). Furthermore, most subjects with birch pollen allergy are poly-sensitised to pollen from related trees and may experience symptoms to early and/or late flowering trees in the birch homologous group. Thus, the symptom burden extends beyond the birch season and therefore this trial will evaluate symptoms and medication use during the birch pollen season and also during the alder/hazel, and oak pollen seasons.

The SQ tree SLIT-tablet has been demonstrated in adults with AR/C induced by pollen from the birch group to be efficacious in reducing the symptoms of AR/C, and has an acceptable safety and tolerability profile with few reported serious AEs (SAEs), of which none were assessed as related to the SQ tree SLIT-tablet (12 SQ-Bet). Furthermore, the TT-04 trial did not provide evidence that the efficacy and safety profile of the SQ tree SLIT-tablet differs between adults and adolescents. The SQ tree SLIT-tablet has yet to be studied in children <12 years old.

Currently, there is no approved SLIT product in Europe or North America for the treatment of allergy in children with a history of AR/C symptoms induced by pollen from the birch group and treatment in adolescents is only authorised in Switzerland.

Therefore, there is an unmet clinical need to develop a treatment that can expand the treatment options for children and adolescents suffering from AR/C induced by pollen from the birch group.

[redacted]

This trial is a part of the phase III development programme for the SQ tree SLIT-tablet. The purpose of this trial is to evaluate the efficacy and safety of the SQ tree SLIT-tablet in paediatric subjects (5 through 17 years of age) with persistent moderate to severe AR/C (with or without asthma) induced by pollen from the birch group despite being treated with symptom-relieving medication.

1.4 Benefit-risk assessments

The SQ tree SLIT-tablet provides an alternative formulation and mode of administration of immunotherapy that expands the treatment options for children suffering from AR/C induced by pollens from the birch group. The orodispersible dosage form is ideally suited for the treatment of children as it is easy to administer, and the rapid dispersion makes it difficult to spit out or aspirate (EMEA 2006).

The SQ tree SLIT-tablet is an effective treatment for adult patients for whom AIT is indicated and has an acceptable safety profile in this population. In contrast to SCIT treatments, the SQ tree SLIT-tablet does not require up- or down-titration and allows for at-home dosing after administration of the first dose in a health care setting under the supervision of a physician with experience in the treatment of allergic diseases.

In the current trial, the SQ tree SLIT-tablet may show an effect on symptom relief and reduce the use of symptom-relieving medication in children as well. Thus, subjects on active treatment in the trial may receive a direct benefit of access to a new treatment that is not yet commercially available.

All subjects participating in the trial will have access to symptom-relieving medication and will receive expert medical care. Their participation will contribute to the development of the new treatment for children suffering from allergy induced by pollen from the birch group.

The SQ tree SLIT-tablet has been demonstrated to be well-tolerated and suitable for self-administration in adults. Typical adverse reactions are transient local reactions occurring within the first few days of treatment. These are expected in paediatric subjects as well. Other potential adverse reactions are class effects of AIT/SLIT and include acute worsening of asthma symptoms (exacerbation), EoE, anaphylactic reactions, and serious laryngo-pharyngeal reactions. However, these reactions are rare and are not expected to increase in the paediatric population.

Risks in this trial are manageable when the first SLIT-tablet is administered under physician supervision and with appropriate education of the subject and parent/guardian about symptoms and signs of severe allergic reactions. There is no expectation of an increased safety risk for children enrolled in this trial compared with that observed in adults in previous tree pollen trials.

This is supported by similar safety profiles in adult and paediatric subjects treated with SLIT-tablets in grass pollen and ragweed pollen trials.

Based on the efficacy/safety trials of SQ tree SLIT-tablet in adults and a small group of adolescents, in addition to the results seen for grass and ragweed SLIT-tablet in both adults and children (ages 5 to 65 years), the benefit/risk assessment for conducting this paediatric trial of SQ tree SLIT-tablet is favourable.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure and Informed Consent documents.

1.5 Considerations regarding COVID-19

Participating in this trial, including receiving treatment with AIT, is not expected to increase subjects' risk of contracting communicable diseases, including COVID-19. The risk to subjects with asthma is considered unchanged as only subjects with well controlled mild to moderate asthma are included.

The COVID-19 situation and its impact on clinical trial conduct and activities will be continuously monitored by the Sponsor to ensure safety of subjects and trial staff. Local guidance requiring the use of personal protective equipment or other measures to ensure patient safety should always be followed. If regional circumstances related to COVID-19 change, local guidance should be followed.

1.6 Ethical considerations

The population selected for this trial includes children with AR/C when exposed to birch pollen. In order to minimise the burden of the disease for subjects enrolled in the trial, and to minimise the risk related to trial activities, the following measures have been included in the trial protocol:

- Each subject will receive a supply of rescue medication to be used as needed. Subjects diagnosed with asthma will receive asthma rescue medication to be used as needed
- Each subject will be provided with a pocket-size subject card containing investigator contact information
- An independent DMC will be established for safety monitoring of the trial

A placebo group will be used as a control group in the trial because no product with a similar formulation as the IMP is available for use as an active comparator. A placebo group is considered ethically justifiable since subjects in both treatment groups will be provided with rescue medication to treat allergy symptoms during the trial. Furthermore, subjects will be medically monitored during the trial and provided with appropriate treatment, if warranted. Finally, subjects can discontinue from the trial at any time and without giving a reason, without penalty or loss of benefits to which the subject was otherwise entitled, if they find the treatment intolerable.

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.

The number of blood samples, the volumes of samples taken and the number of times each subject needs to provide blood have been reduced as much as possible. The volume of blood taken on a single day will fulfil the EMA ethical considerations guidelines (Recommendations of the

ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use 2008).

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 the local IRB/IEC and regulatory authorities (as applicable) before initiation.

2 OBJECTIVES, ESTIMANDS AND ENDPOINTS

2.1 Primary objective

To compare the efficacy of the SQ tree SLIT-tablet to placebo in the treatment of moderate to severe allergic rhinitis and/or conjunctivitis induced by pollen from birch and trees belonging to the birch homologous group in children and adolescents (5 through 17 years of age) based on the average TCS[17] during the BPS.

2.2 Key secondary objectives

To compare the efficacy of the SQ tree SLIT-tablet to placebo based on:

- The average TCS during the TPS
- The average DSS during the BPS and TPS
- The average DMS during the BPS and TPS

2.3 Secondary objectives

The additional secondary objectives are to:

- Compare the safety and tolerability of the SQ tree SLIT-tablet to placebo
- Compare the efficacy of the SQ tree SLIT-tablet to placebo using additional endpoints based on daily allergic rhinoconjunctivitis symptoms and rescue medication use
- Compare the efficacy of the SQ tree SLIT-tablet to placebo based on assessments of quality of life
- Compare the efficacy of the SQ tree SLIT-tablet to placebo based on patient treatment satisfaction
- Compare the effect of the SQ tree SLIT-tablet to placebo on immunological parameters to birch, alder, hazel and oak pollen

2.4 Exploratory objectives

The exploratory objectives are to:

- [redacted]
- [redacted]

[17] daily total combined score = daily symptom score + daily medication score

- [redacted]
- [redacted]

2.5 Primary estimand

The primary estimand is the absolute difference between the SQ tree SLIT-tablet and placebo treatment policies based on the average TCS during the BPS, in children and adolescents (5-17 years of age) with moderate to severe allergic rhinitis and/or conjunctivitis caused by pollen from birch, 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 SQ tree SLIT-tablet 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 SQ tree SLIT-tablet 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.

2.6 Secondary estimand

The secondary estimand is the absolute difference between SQ tree SLIT-tablet and placebo treatment policies based on the average TCS during the BPS, in children and adolescents (5-17 years of age) with moderate to severe allergic rhinitis and/or conjunctivitis caused by pollen from birch, 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 to the 'intention to treat' principle and provides a robust assessment of the efficacy of the SQ tree SLIT-tablet.

2.7 Estimands for key secondary objectives

The trial product estimand and treatment policy estimand, specified for the primary objective in Sections **2.5** and **2.6** respectively, are defined for each of the key secondary objectives in a similar manner.

2.8 Primary efficacy endpoint

Average TCS during the BPS.

The average TCS during the BPS is based on the allergic rhinoconjunctivitis daily symptom score and daily medication score. See Section **15.9.4** for details of the derivation of the primary endpoint.

2.9 Key secondary efficacy endpoints

- Average TCS during the TPS
- Average DSS during the BPS
- Average DSS during the TPS
- Average DMS during the BPS
- Average DMS during the TPS

2.10 Secondary efficacy endpoints

Additional secondary efficacy endpoints are:

- Average TCS, average DSS and average DMS during the alder-hazel (AHPS) and oak pollen seasons (OPS)
- Number of severe days during the BPS and TPS, where a severe day is defined by a DSS ≥6 and where ≥2 symptoms are assessed as moderate or 1 symptom is assessed as severe
- Number of well days during the BPS and TPS, where a well day is defined as no use of rescue medication and DSS ≤2
- Number of symptom-free days during the BPS and TPS, where a symptom-free day is defined as one with no symptoms and with no use of rescue medication
- Percentage of patients free of symptoms and with no use of rescue medication during the BPS and TPS
- Average TCS (EAACI scoring) during the BPS and TPS
- Average weekly overall RQLQ score during the BPS and TPS (12-17 years only)
- Overall PRQLQ score during the BPS (5-11 years only)
- Treatment satisfaction (TSQM-9) evaluations
- Patient-rated global evaluation of treatment efficacy

Immunology endpoints:

- Change from baseline in birch specific IgE and IgG_4
- Change from baseline in alder, hazel and oak specific IgE and IgG_4 (for a subgroup of randomised subjects only)
- Change from baseline in birch, alder and hazel specific IgE-BF (for a subgroup of randomised subjects only)

2.11 Safety and tolerability endpoints

Safety and tolerability endpoints are:

- Treatment-emergent adverse events (TEAEs)
- Events of special interest (ESI)
    - Systemic allergic reactions including anaphylaxis
    - Events treated with adrenaline/epinephrine
    - Severe local swelling or oedema of the mouth and/or throat
    - EoE
    - Oral allergy syndrome
    - Asthma exacerbations

- Vital signs, physical examination, lung function tests and clinical laboratory values during treatment and at the end-of-treatment visit
- Local application site reactions (defined according to a pre-specified list of MedDRA preferred terms)

2.12 Exploratory endpoints

The exploratory endpoints are:

[redacted]

3 TRIAL DESIGN

3.1 Summary of trial design

This is a phase III, randomised, parallel-group, double-blind, placebo-controlled, multi-regional trial in children (5-11 years) and adolescents (12-17 years) with AR/C, with or without asthma, induced by pollen from birch. Based on previous trials, it is anticipated that most subjects allergic to birch will also have AR/C induced by pollen from the birch group. Approximately 1000 subjects will be randomised (1:1) to receive treatment with the SQ tree SLIT-tablet or placebo. The randomisation will be stratified by geographical location and by age group (5-11 years and 12-17 years). Approximately 45% of the subjects should be aged 5-11 years at the time of randomisation.

The trial consists of 3 periods: a screening period, a treatment period, which includes pre-seasonal and co-seasonal treatment, and a follow-up period (**Figure 1**). There may be multiple cohorts recruited over consecutive seasons to complete the enrolment goal.

The screening visit can take place up to approximately 6 months prior to randomisation. Once randomised, subjects should be treated for at least 12 weeks prior to the start of the TPS. Treatment will continue until 1 week after the end of the TPS, corresponding to up to approximately 12 months of treatment.

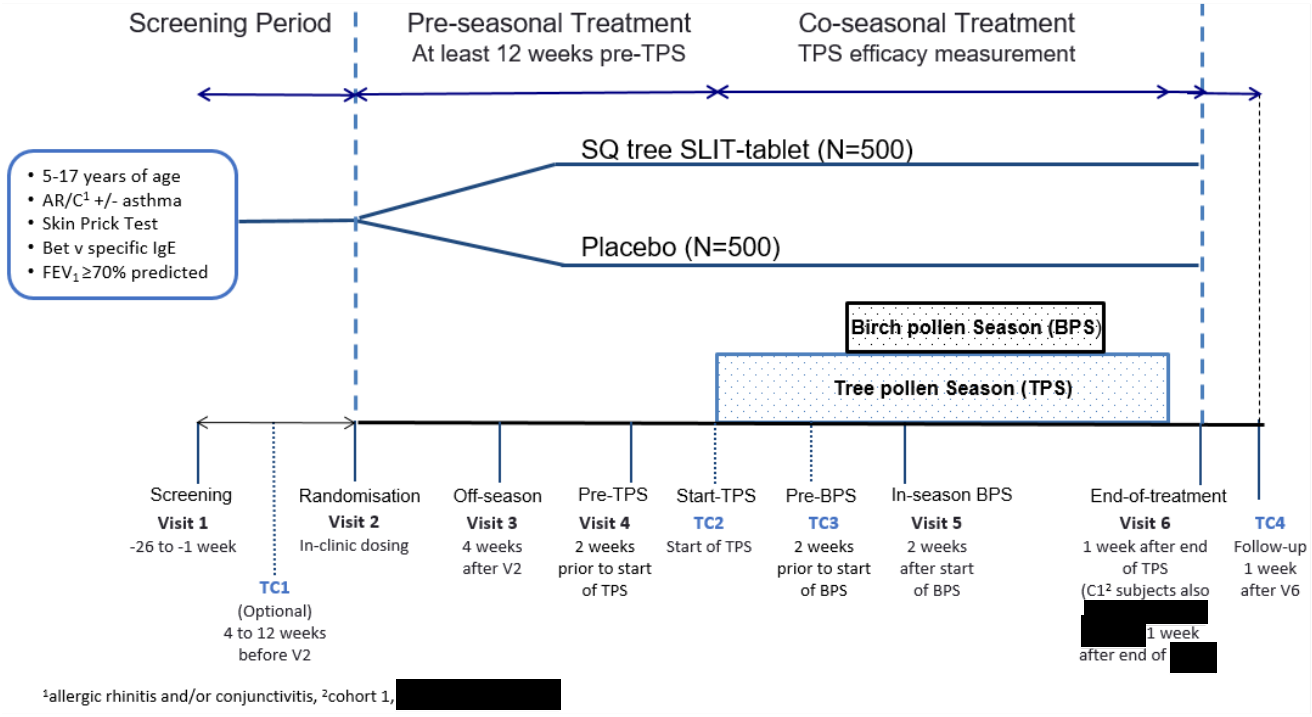
[redacted]

Open-label rescue medication for allergic rhinoconjunctivitis will be provided during the TPS [redacted] Open-label asthma medication will be provided to subjects with asthma during the TPS [redacted]

A follow-up phone visit will be conducted 1 week after the final treatment.

The expected start and stop dates of the relevant pollen seasons in each region are specified in Appendix 5. If monitoring of the daily pollen counts identifies a change to the expected start or stop date of a pollen season for any country or region, the affected site will be notified and the eDiary will be updated to allow for additional data collection. The TPS includes the hazel, alder, birch and oak pollen seasons.

Figure 1 Overall trial design



3.2 Discussion of design

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

The population selected by the eligibility criteria reflects a population that may benefit from treatment with AIT. The subjects eligible for the trial are children and adolescents with a clinical history of moderate to severe AR/C induced by birch pollen despite having received symptom-relieving medication for the past 2 BPSs prior to trial entry (only 1 past BPS for children aged 4-6 years at screening). Although a history of allergic rhinitis/rhinoconjunctivitis requiring symptomatic treatment during at least 2 consecutive seasons is recommended (EMA & PDCO 2015), 1 season was set for children below 7 years of age to facilitate enrolment of the younger children in the trial. The minimum age at screening will be 4 years (5 years at randomisation), which would require a clinical history from 2-3 years old, which is not considered feasible.

The primary endpoint is the average TCS during the BPS, which is the average of the daily sum of the DSS and DMS during the BPS. 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. Further, the primary endpoint presented as a single combined variable is believed to be consistent with current global regulatory positions on appropriate reporting of results from AIT trials. The World Allergy Organization has stated that since symptoms and symptom-relieving medication utilisation are

interdependent variables when assessing the effect of AIT, a combined score more accurately reflects efficacy (Canonica et al. 2009). EMA has also stated in their guidance on AIT that the primary endpoint for trials should be reflective of both severity of symptoms and the intake of rescue medications (EMEA 2008).

The symptom score is constructed as recommended in the EMA guideline (EMEA 2008) and is identical to the score used in previous ALK trials in the SQ tree SLIT-tablet development programme.

The medication score has been used in the previous field trials with the SQ tree SLIT-tablet (TT-02 and TT-04), in numerous clinical trials performed with grass and ragweed SLIT-tablets (Blaiss et al. 2011; Bufe et al. 2009; Creticos et al. 2013; Durham et al. 2006; Maloney et al. 2014; Nelson et al. 2011; Nolte et al. 2013), and was developed by ALK based on recognised guidelines (Canonica et al. 2007; EMEA 2008) and thorough discussions with key opinion leaders/specialists within the field of allergy. The proposed weighting of the different medications has been chosen to mirror the reduction of symptoms, i.e. the higher ability to reduce symptoms the higher maximum daily score.

The relative treatment effect for the primary endpoint in this trial is anticipated to be at least 25% and a previous trial with the SQ tree SLIT-tablet has demonstrated a treatment effect considerably higher than this (Biedermann et al. 2019a). As such, it is expected that this trial will satisfy the requirements of EMA (point estimate of the absolute treatment effect greater than 1), FDA (point estimate of the relative treatment effect to be greater than 15% (Massie 2011)) and also meet the World Allergy Organisation task force recommendation of a clinically relevant difference of 20% (Canonica et al. 2007).

It is anticipated that pollen exposure will vary with location, therefore, the randomisation will be stratified by geographical location. To ensure a balanced target population with respect to age, randomisation will also be stratified by age group (5-11 years and 12-17 years) in accordance with EMA/PDCO recommendations (EMA & PDCO 2015).

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

Placebo has been chosen as the comparator on which to evaluate the efficacy of the SQ tree SLIT-tablet, since no well-established active comparator treatment exists. All subjects should be randomised at least 12-weeks before the anticipated start of the TPS. This is a reduction compared to the 16 weeks used in earlier trials with the SQ tree SLIT-tablet and has been introduced to reduce the trial burden on subjects. This is based on experience from other SLIT-tablet trials for pollen-induced allergies (grass, ragweed), which have shown 12 weeks pre-seasonal treatment to be sufficient to induce a clinical effect in paediatric and adult populations

[redacted]

Safety endpoints for this trial have been based on previous trials with SLIT AIT include AEs, vital signs, lung function and laboratory values.

3.3 Justification of dose

The basic principle for AIT dose selection is to use the highest tolerable and safe dose. The highest tolerable/safe and effective dose of the SQ tree SLIT-tablet has been shown to be 12 SQ-Bet in adults. The TT-04 trial did not provide evidence that the efficacy and safety profile of the SQ tree SLIT-tablet differs between adults and adolescents. Further, practice guidelines do not recommend dose adjustment in children as allergens act on the immune system and are neither systemically absorbed nor metabolized by the liver and kidneys. This has also been demonstrated for grass and ragweed SLIT-tablets, where the same dose is used regardless of age.

Therefore, the 12 SQ-Bet dose of the SQ tree SLIT-tablet approved for use in adults will also be used in children in this trial.

3.4 End of trial definition

The end of the trial is defined as the date of the last follow-up phone visit (TC4) for the last subject in the trial.

4 TRIAL POPULATION

Subjects randomised will be children and adolescents 5 through 17 years of age with moderate to severe birch pollen AR/C, with or without asthma, despite use of symptom-relieving medication. Approximately 45% of the subjects will be 5 through 11 years of age at the time of randomisation. No more than one subject from the same household can be enrolled in the same cohort. Subjects from the same household can be enrolled in separate cohorts.

4.1 Inclusion criteria

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

I1. Written informed consent obtained from parents/caregivers before any trial related procedures are performed. Consent or assent from the subject must be obtained according to national requirements.

I2. Male or female of any race/ethnicity aged ≥4 to <18 years on the day informed consent is obtained from the parent/caregiver. The subject must be ≥5 to <18 years old at the randomisation visit

I3. A female subject of child-bearing potential[18] must have a negative pregnancy test and be willing to practise appropriate[19] contraceptive methods until the follow-up TC

[18] Females are considered of child-bearing potential after their first menstrual period

[19] For the purpose of this protocol the following contraceptive methods are considered appropriate: oral contraceptives, trans dermal 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.

I4. A documented,[20] physician diagnosed, clinically relevant history of moderate to severe AR/C induced by birch pollen (with or without asthma) despite having received treatment with symptom-relieving medication during at least 1 previous tree pollen season for ages 4 through 6 years at screening or at least 2 previous tree pollen seasons for ages 7 through 17 years at screening

I5. Positive skin prick test (SPT) to *Betula verrucosa* at screening[21]

I6. Positive specific IgE[22] to Bet v at screening

I7. Presence of one or more of the following Allergic Rhinitis Impact on Asthma (ARIA) quality of life items due to AR/C during the previous BPS:
   a. Sleep disturbance
   b. Impairment of daily activities, leisure and/or sport
   c. Impairment of school or work
   d. Troublesome symptoms

I8. Subject must be willing and able to comply with trial protocol

4.2 Exclusion criteria

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

E1. Previously randomised in this trial.

E2. Is participating or planning to participate in any other interventional clinical trial during the duration of this trial

E3. A clinically relevant history of symptomatic seasonal AR/C caused by an allergen source, other than tree pollen from the birch homologous group, with a season overlapping the TPS

E4. A clinically relevant history of symptomatic perennial AR/C caused by an allergen source such as animal hair and dander to which the subject is exposed during the TPS.

E5. Asthma requiring high daily doses[23] of inhaled corticosteroids within 3 months prior to the randomisation visit

E6. Any clinical deterioration of asthma (i.e. asthma exacerbation) that resulted in emergency treatment, hospitalisation or treatment with systemic corticosteroids within 3 months prior to randomisation

[20] If medical records are not available, verbal history from subject/parent/caregiver may be elicited at the Screening Visit and can be used to fulfil this criterion if documented in the subject study file by the investigator.

[21] A positive SPT is defined in the SPT guideline. Briefly, a positive SPT is defined as a wheal size of ≥3 mm. If medication that could interfere with the SPT, according to prohibited and restricted medication table, has not been washed out, the SPT must be performed after the interfering medication has been washed out.

[22] A positive specific IgE is defined as ≥IgE Class 2; ≥0.70 kU/L

[23] For acceptable/prohibited ICS doses see **Table 4** (for children) or **Table 5** (for adolescents)

E7. Reduced lung function at randomisation defined as FEV_1 <70% of predicted value. For asthmatic subjects this is assessed on subject's usual asthma medication following at least a 6-hour wash-out of SABA.
This criterion does not need to be fulfilled if the subject is <7 years old, cannot perform reproducible FEV_1 manoeuvres despite coaching and is not considered as having a diagnosis of asthma.

E8. SLIT treatment with pollen allergen extracts from birch and trees belonging to the birch homologous group for more than 1 month within the last 5 years. In addition, any SLIT treatment with birch pollen or a cross-reactive/homologous tree pollen allergen extracts within the previous 12 months.

E9. SCIT treatment with pollen allergen extracts from birch and trees belonging to the birch homologous group reaching the maintenance dose within the last 5 years. In addition, any SCIT treatment with birch pollen or a cross-reactive/homologous tree pollen allergen extracts within the previous 12 months.

E10. Ongoing treatment with any allergy immunotherapy product

E11. Severe chronic oral inflammation

E12. 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)

E13. A diagnosis of EoE

E14. A history of chronic urticaria (>6 weeks) and/or chronic angioedema (>6 weeks) within the last 2 years prior to screening that in the opinion of the investigator may constitute and increased safety concern

E15. 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

E16. 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

E17. Active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance

E18. Immunosuppressive treatment (ATC code L04 or L01) within 90 days prior to the screening visit

E19. Treatment with medications with potential impact on efficacy endpoints. For example:
- Treatment with anti-IgE drugs within 130 days/5 half-lives of the drug (which ever longest) prior to randomisation
- Treatment with antidepressant within 14 days prior to randomisation
- Treatment with antipsychotic medications with antihistaminic effect within 7 days prior to randomisation

E20. Treatment with an investigational drug within 30 days/5 half-lives of the drug (which ever longest) prior to screening

E21. 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

E22. Female who is pregnant or breast-feeding

E23. Has a direct or indirect business or personal relationship with trial staff or sponsor who is directly involved with the conduct of the trial

E24. A history of alcohol or drug abuse

4.3 Screening 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.

A minimal set of screen failure information will be recorded to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

4.3.1 Re-screening

Re-screening is NOT allowed if the subject has failed one of the inclusion or exclusion criteria, however, the following exceptions applies: a subject is allowed to be re-screened once if failing inclusion criterion I2. Re-screening is allowed once for a subject who met all inclusion and exclusion criteria but were not able to meet the closing data of randomisation in that cohort. A re-screened subject is required to sign a new ICF, and a new subject ID number will be allocated.

Resampling of central laboratory samples is not allowed for any failed inclusion or exclusion criteria. Only in cases when laboratory samples are lost or haemolysed, resampling is allowed. Subjects with evidence of current, clinically significant, intercurrent illness (e.g., significant cold or flu) at screening may be rescheduled for a new screening visit on resolution of their illness.

5 DISCONTINUATION OF IMP TREATMENT AND SUBJECT WITHDRAWAL

5.1 Criteria for discontinuation from IMP treatment

All efforts should be made to keep the subject on IMP treatment. However, the subject has the right to discontinue IMP treatment at any time without prejudice or may be discontinued from IMP treatment at the discretion of the investigator due to safety concerns.

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 have a confirmed diagnosis of EoE
- 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
- Simultaneous or previous participation (within 30 days or 5 half-lives of the product, whichever is longer, before randomisation) in other clinical trials of an approved or non-approved IMP
- If treatment is unblinded for the subject or investigator

If found required by ALK after discussion with the investigator, subjects may be discontinued from IMP treatment as a result of a protocol deviation.

Subjects that discontinue IMP treatment should be encouraged to continue to participate in the trial and to continue with all scheduled visits/site contacts and complete all assessments and the patient eDiary according to the protocol. Subjects must be educated about the continued scientific importance of their data, even if they discontinue trial product.

5.2 Subject withdrawal from the trial

The subject and/or the subject's parent/caregiver will be advised in the informed consent form that he/she has the right to withdraw from the trial at any time without prejudice.

If a subject withdraws consent, the investigator must ask the subject if he/she is willing, as soon as possible, to have assessments performed according to visit 6.

Although a subject is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the 'End of study' form in the eCRF and in the subject's medical records.

Final drug accountability must be performed even if the subject is not able to come to the site.

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 by the time of the subject's last scheduled visit (V6). 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.

Efforts to regain contact should continue until the end of the subject's last scheduled site visit (V6).

5.4 Replacement of subjects

Subjects who withdraw consent or discontinue IMP treatment 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 in the eCRF at the screening visit.

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 randomisation will be administered centrally via IRT and will be stratified based on geographical location and age group.

The randomisation codes will only be made available for data analysis 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 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 (or another treating physician) in a medical emergency 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.

The emergency unblinding will be performed via 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. Unblinding may also be done by the Qualified person responsible for pharmacovigilance.

The IRT will notify the CRA and the sponsor's safety department immediately after the randomisation code is broken. The subject must be discontinued from IMP treatment after randomisation code breaking.

It may also be necessary to unblind an individual subject's treatment by the sponsor's 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). 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 must be given a subject card at screening 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 an emergency.

7 RESTRICTED AND PROHIBITED CONCOMITANT MEDICATION

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.

The medication listed in **Table 1** is restricted or prohibited unless it is provided by ALK. All listed medications interfere with safety assessments or rhinoconjunctivitis [redacted] assessments.

Table 1 Restricted and prohibited concomitant medications

Drug	Time window
An investigational drug other than the IMP	≤30 days/5 half-lives of the drug (whichever longest) before visit 1 and until TC4
Antihistamine, unless provided by the sponsor • Oral, intravenous, nasal or ocular • Long-acting (astemizole)	 • From visit 4 and until visit 6 • ≤90 days before visit 4 and until visit 6
Antidepressant medications[24]: • Antidepressant medication with antihistaminic effect (e.g. doxepin, mianserine) • Tricyclic antidepressants (e.g. amitriptyline, clomipramine) • Monoamine oxidase inhibitors (MAOIs)	≤14 days before visit 2 and until TC4
Antipsychotic medications with antihistaminic effects (e.g. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)	≤7 days before visit 2 and until TC4
Biologic asthma 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/5 half-lives of the drug (whichever longest) prior to visit 2 and until TC4
Glucocorticosteroids -unless provided by the sponsor (see section 8.2) -does not include inhaled corticosteroids (ICS), however a subject must have been on a stable regimen (daily dose unchanged) of ICS for at least 4 weeks before randomisation (visit 2) • topical (nasal or ocular) • with systemic effect[25] - any oral tablets (oral corticosteroid use is allowed in cases of asthma exacerbation) - any parenteral formulations (intravenous, intra-articular or intramuscular) or depot formulations regardless of treatment days and dose	 • topical: from 30 days before visit 4 and until visit 6 • oral: from 60 days before visit 4 and until visit 6 • parenteral or depot: from 90 days before visit 4 and until visit 6
Systemic immunosuppressive treatments (ATC code L04, L01) other than glucocorticosteroids	≤90 days before visit 1 and until TC4
Immunotherapy with any other allergen(s)	From visit 1 and until TC4
Inhaled, topical or oral nedocromil or cromolyn sodium	≤14 days before visit 4 and until TC4

[24]Tricyclic antidepressants and MAOIs may potentiate the effect of adrenaline/epinephrine
[25]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)

Drug	Time window
Long-acting β_2-agonist (LABA) monotherapy (low and medium dose ICS/LABA in combination are allowed).	From 30 days before visit 4 and until TC4
Leukotriene receptor antagonists (e.g. montelukast, zafirlukast)	From visit 1 and until TC4. If treatment has begun at least 30 days prior to visit 1 dose can be kept unchanged during trial.
Nasal or ocular decongestants	≤7 days before visit 4 and until TC4
SABA, unless provided as rescue medication in the trial	From visit 4 and until visit 6

8 TRIAL PRODUCTS

8.1 IMP

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

Please refer to **Table 2** for details regarding IMP.

Table 2 IMP details

	Active treatment	Placebo
IMP name:	SQ tree SLIT-tablet	Placebo
Active ingredients:	*Betula verrucosa*, allergen extract	N/A
Dosage form:	Oral lyophilisate	Oral lyophilisate
Excipients:	Gelatine (fish source), mannitol and sodium hydroxide	Gelatine (fish source), mannitol and sodium hydroxide
Route of administration:	Sublingual	Sublingual
Dose/strength:	12 SQ-Bet	-
Dosing instruction:	1 oral lyophilisate daily preferably in the morning.	1 oral lyophilisate daily preferably in the morning.

IMP dispensing

The treatment will start at visit 2 (the randomisation visit) where the IMP will be dispensed. Hereafter, the IMP will be dispensed at visit 4 (pre-TPS visit) and visit 5 (in season BPS visit).

8.2 Rescue medication

During the trial, subjects may experience allergy symptoms that require additional treatment. Medication to treat rhinoconjunctivitis or asthma symptoms (only for subjects with asthma) will be provided by the sponsor and can be used in addition to the IMP to which the subjects have been randomised. All medication should be used in accordance with the product's labelling (e.g. SmPC).

8.2.1 Rhinoconjunctivitis rescue medication

For the treatment of allergic rhinoconjunctivitis symptoms, the subject will be provided with:

- Oral antihistamine tablets (Loratadine tablets 10 mg) or oral antihistamine solution (Desloratadine oral solution 0.5 mg/mL)
- Olopatadine eye drops, 1 mg/mL
- Mometasone furoate nasal spray, 50 µg/dose

The dosing instructions for these medications are provided in **Table 3**.

Rescue medication for allergic rhinoconjunctivitis will be provided by the sponsor before the start of the TPS as pre-defined, open-labelled medication and can be used as needed, in addition to the IMP to which the subjects have been randomised. An adequate initial supply of each of these rescue medications will be dispensed to the subject at visit 4 but must not be used before the investigator has informed the subject that the TPS has started (TC2). The subjects must be instructed to start with antihistamine tablets and/or eye drops and continue with nasal corticosteroids only if antihistamine tablets and/or eye drops cannot alleviate the symptoms. The medication is to be used according to investigators instructions (and according to the package insert/leaflet for the individual medications).

Table 3 Schedule for rhinoconjunctivitis rescue medication

Rhinoconjunctivitis rescue medication	Subject dosage instructions
Rhinitis	
Loratadine, 10 mg	5-12 years old and >30 kg: 1 tablet once daily as needed
	>12 years old: 1 tablet once daily as needed
Desloratadine, 0.5 mg/mL	5 years old: 2.5 mL solution once daily as needed
	6-11 years old: 5.0 mL solution once daily as needed
	≥12 years old: 10 mL solution once daily as needed
Mometasone, 50 µg/dose	5-11 years old: 1 puff in each nostril once daily as needed
	≥12 years old: 2 puffs in each nostril once daily as needed
Conjunctivitis	
Olopatadine eye drops, 1 mg/mL	1 drop in the affected eye(s) twice daily, morning and evening as needed

8.2.2 Asthma rescue medication

SABA (i.e. salbutamol inhaler, 100 mcg/puff) will be provided to subjects with asthma at visit 4 and at subsequent visits as necessary. The salbutamol inhaler should be used when necessary according to the label.

Other medications for asthma will not be provided or reimbursed. Subjects who are taking low or medium daily dose ICS alone or in combination with LABA for asthma management will be allowed

to continue with the same medications during the trial. A subject must have been on a stable regimen (daily dose unchanged) for at least 4 weeks before randomisation (visit 2). Low and medium daily doses of ICS are defined in **Table 4** and **Table 5**.

If a subject requires additional asthma medications, the subject should follow recommendations regarding medication adjustments provided by his/her physician. Medication use should be recorded in the eCRF.

Table 4 Definition of low, medium and high dose ICS for subjects aged 5-11 years as defined by the modified GINA Guideline

Inhaled corticosteroid	Low daily dose (micrograms (µg))	Medium daily dose (micrograms (µg))	High daily dose (micrograms (µg))
Beclomethasone dipropionate (pMDI, standard particle, HFA)	100 – 200	>200 – 400	>400
Beclomethasone dipropionate (pMDI, extrafine particle*, HFA)	50 – 100	>100 – 200	>200
Budesonide (DPI)	100 – 200	>200 – 400	>400
Budesonide (nebules)	250 – 500	>500 – 1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80 –160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50 – 100	>100 – 200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50 – 100	>100 – 200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100	200	>200

DPI: dry powder inhaler; HFA: hydrofluoroalkaline propellant; ICS: inhaled corticosteroid; n.a.: not applicable; pMDI: pressurised metered dose inhaler (non-cholofluorocarbon formulations).
* See product information.

Note: Dose delivery by method or modality other than those noted above must be equivalent
Source: modified from GINA (GINA Executive Committee 2020)

Table 5 Definition of low, medium and high dose ICS for subjects aged 12 years and above, as defined by the modified GINA Guideline

Inhaled corticosteroid	Low daily dose (micrograms (µg))	Medium daily dose (micrograms (µg))	High daily dose (micrograms (µg))
Beclomethasone dipropionate (pMDI, standard particle, HFA)	200 – 500	>500 – 1000	>1000
Beclomethasone dipropionate (pMDI, extrafine particle*, HFA)	100 – 200	>200 – 400	>400
Budesonide (DPI)	200 – 400	>400 – 800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80 – 160	>160 – 320	>320
Fluticasone furoate (DPI)	100	100	200
Fluticasone propionate (DPI)	100 – 250	>250 – 500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100 – 250	>250 – 500	>500
Mometasone furoate (DPI)	200	200	400
Mometasone furoate (pDMI, standard particle, HFA)	200 - 400	200 – 400	>400

DPI: dry powder inhaler; HFA: hydrofluoroalkaline propellant; ICS: inhaled corticosteroid; n.a.: not applicable; pMDI: pressurised metered dose inhaler (non-cholofluorocarbon formulations).
* See product information.
Note: Dose delivery by method or modality other than those noted above must be equivalent
Source: modified from GINA (GINA Executive Committee 2020)

8.3 Packaging and labelling

The IMP will be supplied in blister cards containing 10 tablets. The blister cards will be packed in specific boxes containing a sufficient number of tablets to cover the treatment period 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 and identified by a unique medication number per pack.

Rescue medication supplied by the sponsor will be supplied with labels and patient information leaflets in local language.

Packaging and labelling will be outsourced (See Appendix 3).

In exceptional circumstances where ALK is not able to provide rescue medication, it may be provided locally by ALK or by the trial site and reimbursed by sponsor.

8.4 Handling and storage

The trial products provided by ALK (IMP, rescue medication and SPT materials) 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. IMP and rescue medication 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 all trial products must be monitored by the site staff for adherence to label specifications and reviewed by the CRA during monitoring visits.

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.

The site must maintain records of:

- Inventory at the site
- Dispensing to each subject
- Return by each subject to site
- Return 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 residual and unused IMPs and all empty packaging to the site at every drug accountability visit. Compliance will be assessed by SLIT-tablet 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 dosing regimen.

Drug accountability for rescue medication will be performed on a pack level.

After LSLV at site, the investigator will return all unused and partly used IMP and rescue medication and a copy of the completed drug accountability form to the CRA or to the sponsor 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 IMP should be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue, where it will disperse. Swallowing should be avoided for approximately 1 minute. Wash hands after handling the tablet.

Food and beverages should not be taken for the following 5 minutes after intake of IMP. The daily dose of IMP is 1 SLIT-tablet, which should preferably be taken in the morning.

9.2 Precautions in relation to first dosing

First intake of IMP should be at the clinic with a subsequent 30 minute observation period.

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

The subject/parent/caregiver will be provided with educational information regarding symptoms of anaphylaxis and treatment.

In the event of symptoms or treatment of anaphylaxis, the subject/parent/caregiver must immediately call the local emergency number and the 24-hour investigational site emergency number indicated 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 1 working day of first becoming aware of symptoms or treatment of anaphylaxis. The symptoms and/or circumstances that triggered symptoms or treatment of anaphylaxis must be clearly recorded on the eCRF.

9.4 Temporary interruption of treatment

Treatment may be temporarily interrupted for the following reasons:

- In case of oral surgery, including dental extraction, or shedding of a deciduous tooth, to allow healing of the oral cavity
- Inflammatory conditions in the oral cavity
- Upper airway viral infection in subjects with asthma
- Other reasons if deemed necessary by the investigator

Interruptions should be kept to a minimum, but 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 previously experienced AEs if the subject should re-initiate treatment again at the clinic.

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 ALK.

10 VISIT SCHEDULE

The assessments that should be performed at each visit are described in **Table 6**. The assessments are listed in the chronological order in which they should preferably be performed:

Table 6 Visit schedule

Visit ID	Assessments to be performed at the visit
Visit 1 (screening)	Visit window: 1 to 26 weeks prior to randomisation visit 2
	• Obtain written informed consent for the trial before any other assessment is performed • Obtain written informed consent for collection and storage of serum samples in the ALK Research Biobank and for pharmacogenetic testing, if applicable, before any other assessments are performed • Assess compliance with inclusion and exclusion criteria • Obtain demographic data (sex, month and year of birth, race and ethnicity) • Record smoking habits • Record medical history • Record use of relevant prior and concomitant medications • Perform physical examination • Measure weight • Measure vital signs • Perform urine pregnancy test (if appropriate) No data is available for SPT in pregnant subjects, therefore **for female subjects of child-bearing potential, perform the urine pregnancy test before SPT** • Perform SPT and evaluate results (to be performed at visit 2, if wash-out of concomitant medication is required) • Assess AEs • Assess symptoms of eosinophilic oesophagitis • Collect blood and urine sampling for safety laboratory assessments • Collect blood sampling for specific IgE against Bet v and immunological assessments • If the specific consent has been obtained, collect the biobank blood sample • Schedule the date for the retention visit TC1 and/or visit 2 and complete this in the eCRF

TC1 (Retention)	Visit window: 4 to 12 weeks prior to visit 2. Only required if screening is more than 12 weeks prior to randomisation
	• Confirm subject's continued interest in trial participation • Assess AEs occurring since the last visit • Record concomitant medication • Reconfirm date for visit 2
Visit 2 (Randomisation and first IMP administration)	Visit window: 1 to 26 weeks after screening visit 1
	• Re-assess compliance with inclusion and exclusion criteria • Randomise the subject • Record concomitant medication • Perform physical examination • Measure height and weight • Lung function: - All subjects who are 7 years of age or older must perform the lung function test related to Exclusion criterion 7. - Subjects who are less than 7 years of age may not have to perform the lung function test depending on the following: ▪ Does the subject have asthma? • If yes, the lung function test needs to be performed • If no, can the subject produce reproducible FEV1 results if they are coached on how to do this? ○ If yes, the lung function test needs to be performed ○ If no, then the subject is exempt from performing the lung function test and the attempt to perform the lung function test is to be recorded in the subject journal • Perform urine pregnancy test, if applicable • For subjects requiring wash-out of concomitant medication as per visit 1, SPT should be performed and results evaluated • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis • Dispense IMP to the subject • Instruct the subject in how to use the IMP • First intake of IMP at the clinic. The first dose will be administered at the clinic with a subsequent 30 minutes observation period • Schedule the date for visit 3
	Visit window: 4 weeks after V2 (+ 7 days)

Visit 3 **(Off season)**	• Record changes to concomitant medication • Perform IMP compliance check (see Section **8.5**) • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis • Perform urine pregnancy test, if applicable • Schedule the date for visit 4
Visit 4 (Pre-TPS)	Visit window: 2 weeks prior to the expected start of TPS specified for the country/region (-14 to +7 days)
	• Record changes to concomitant medication • Dispense IMP to the subject • Collect used IMP, perform drug accountability and the compliance check (see Section **8.5**) • Dispense rhinoconjunctivitis [redacted], if applicable • Issue and instruct the subject/parent/caregiver in the use of the eDiary including training in symptom scoring • Show and discuss the trial video • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis • Perform urine pregnancy test, if applicable • Collect blood sample for immunological assessments • If the specific consent has been obtained, collect the biobank blood sample • Schedule the date for TC2 and visit 5
TC2 **(Start of TPS)**	Visit window: Expected start of TPS (-4 days)
	• Record changes to concomitant medication • Inform subjects that TPS has started and eDiary recording should begin • Re-instruct in the use of the eDiary including training in symptom scoring as needed • Remind the subject to watch the trial video as needed • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis
TC3 **(Pre-BPS)**	Visit window: 2 weeks prior to the expected start of BPS (+ 7 days)
	• Record changes to concomitant medication • Re-instruct in the use of the eDiary including training in symptom scoring as needed • Remind the subject to watch the trial video as needed • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis
Visit 5 **(In season BPS)**	Visit window: 2 weeks after the expected start of the BPS (+ 7 days)
	• Record changes to concomitant medication • Dispense IMP to the subject • Collect used IMP, perform drug accountability and the compliance check (see Section 8.5) • Dispense rhinoconjunctivitis [redacted], if applicable

	• Collect rescue medication, as applicable, and perform drug accountability • Review eDiary recordings and check eDiary compliance • Re-instruct in the use of the eDiary including training in symptom scoring as needed • Remind the subject to watch the trial video as needed • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis • Perform PRQLQ interview for children 5 through 11 years of age at randomisation • Perform urine pregnancy test, if applicable • [redacted]
TC [redacted] (Cohort 1 subjects with [redacted]	Visit window: 1 week after the expected end of TPS specified for the country/region (+ 7 days)
	• Perform the interview for global evaluation of treatment efficacy • Perform the interview for the TSQM-9 • Record changes to concomitant medication • Review eDiary recordings and check eDiary compliance • Re-instruct in the use of the eDiary including training in symptom scoring as needed • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis • Schedule the date for visit 6
Visit 6 (End-of-treatment)	Visit window: 1 week after the expected end of TPS specified for the country/region (+ 7 days)
	Important: for subjects in cohort 1 with [redacted], visit 6 should take place 1 week (+ 7 days) after expected end of [redacted]
	• Record changes to concomitant medication • Collect used IMP, perform drug accountability and the compliance check (see Section **8.5**) • Collect rescue medication, as applicable, and perform drug accountability • Perform physical examination • Measure height and weight • Measure vital signs • Perform lung function test • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis • Collect the eDiary • Perform the interview for global evaluation of treatment efficacy (subjects with [redacted] from cohort 1 will complete this during the TC [redacted] • Perform the interview for the TSQM-9 (subjects with [redacted] from cohort 1 will complete this during the TC [redacted]) • Collect blood and urine sampling for safety laboratory assessments • Perform urine pregnancy test (if appropriate) • Collect blood sampling for immunological assessments • If the specific consent has been obtained, collect the biobank blood sample • If the specific consent has been obtained, collect the pharmacogenetic blood sample for analysis

	• Schedule the date for a telephone follow-up contact (TC4)
Follow-up phone visit (TC4)	Visit window: 1 week (+ 7 days) after visit 6
	• Record changes to concomitant medication • Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis

11 TRIAL PROCEDURES

This section outlines the trial procedures that will be performed during the trial. For further details on the specific timing, please refer to the visit schedule in Section **10**.

The tasks listed below must be performed by a physician with experience in paediatric research:

- Obtainment of informed consent
- Evaluation of inclusion and exclusion criteria
- Physical examination
- Assessment of AEs/SAEs
- Assessment of lung function (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 questioned, 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, incl. any period for wash-out of concomitant medication.

For minors, the legal written informed consent must be obtained from the legal parent(s)/ guardian in accordance with national/local regulations. If the minor can understand the risks and benefits of the trial, he/she should also be informed and, if capable, provide written assent. Subjects turning 18 years (or according to local requirement) during the trial must sign the adult informed consent form.

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

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 parent(s)/ guardian and 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 parent(s)/ guardian and subject must sign and date the informed consent/ assent forms 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 parent(s)/ guardian and 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 **11.16**). Participation in the trial does not depend on giving consent to donating blood samples for biobank storage.

When the subject/parent/guardian is asked to consent/assent to the participation in the trial, children with a body weight over 19 kg will be asked specifically if they will donate a blood sample (5 mL each) 3 times during the trial. The answer to this question will be recorded on the consent form for retention of blood samples for future research, as well as in the eCRF. If specific consent is not provided, the samples must not be drawn.

11.3 Consent for collection of blood samples for pharmacogenetic testing

Storage of a DNA/RNA sample for pharmacogenetic testing is planned for this trial (see Section **11.16**). Participation in the trial does not depend on giving consent to donating pharmacogenetic samples.

When the subject/parent/guardian is asked to consent/assent to the participation in the trial, children with a body weight over 19 kg will be asked specifically if they can accept sampling for storage of a DNA and RNA sample for pharmacogenetic testing. The answer to this question will be recorded on the consent form for retention of samples for future pharmacogenetic testing, as well as in the eCRF. If specific consent is not provided, the samples must not be drawn.

11.4 Demographics

The following data will be recorded:

- Month and year of birth
- Age
- Race and ethnicity
- Sex

11.5 Height and weight

The subject's height without shoes will be recorded.

The subject's weight will be recorded.

11.6 Medical history

The relevant medical history, including diseases present at trial entry and any allergy, urticaria, asthma, atopic dermatitis and OAS, 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. Those subjects suspected of having a history of asthma must meet at least one of the following 4 criteria to be considered as having a diagnosis of asthma (and documented as such in the eCRF):

- At least one episode of wheeze, cough, shortness of breath or chest tightness and a change in FEV_1 ≥12% after β_2-agonist administration
- Recurrent wheeze with or without prolonged phase of forced exhalation observed at physical examination and an intake of asthma medication which resulted in a clinically relevant effect
- Wheezing with or without prolonged phase of forced exhalation observed at physical examination and a change in FEV_1 ≥12% after β_2-agonist administration
- Using asthma medication

The OAS history should include a description of food triggers and symptoms.

11.7 Smoking habits

Information on exposure to tobacco smoke (active and passive) will be collected.

11.8 Prior and concomitant medication

The subjects' use of concomitant medication including allergy and asthma medication must be recorded. Relevant prior medication should also be recorded. This includes allergy and asthma pharmacotherapy taken for the past 2 years. Other prior 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.

At each visit and phone 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.

11.9 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 visit 6, which meet the definition of an AE, must be recorded on an AE page in the eCRF.

11.10 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 (exception: a subject who does not have asthma and who is <7 years of age and cannot perform a reproducible lung function test despite coaching from site staff, will not be required to perform the lung function test. The attempts to perform the test and coach the subject must be documented). Lung function measurements will be performed with a spirometer available at the clinic. FVC and FEV_1 should be recorded from a series of at least 3 valid measurements. The lung function measurement with the highest recorded FEV1 is to 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). Values of FVC, FVC percent predicted, FEV_1 and FEV_1 percent predicted reported by the site will use the site's pre-programmed spirometric reference equations. The reference equations and resulting values of predicted FVC and predicted FEV_1 should be documented on every lung function report. For subjects with asthma, a 6-hour wash-out of SABA will be required before measurement of lung function.

11.11 Physical examination

The physical examination should be performed by a physician and should be based on the body systems described in **Table 7**.

Table 7 Physical examination

Body system	Minimum examinations to be completed
General appearance	Nutritional status, consciousness, skin colours, temperature and developmental status (in children)
Head (ears, eyes, nose and throat)	Ears - Inspection of auricles and external canal (otoscopy is not required)
Oral inspection	Inspection of lips, mucosa and tongue
Respiratory	•Assessment of respiratory effort, including respiratory rate and use of accessory respiratory muscles •Palpation and percussion of chest •Auscultation/stethoscopy of lungs
Heart	It is up to the investigators discretion to evaluate whether a physical examination of the heart is necessary based on auscultation/stethoscopy of the heart. A full physical examination will not be performed

Abdomen	A physical examination will not be performed. It is up to the investigators discretion to evaluate whether a physical examination of the abdomen is necessary based on questions regarding pain, tenderness and swelling
Urogenital	A physical examination will not be performed. It is up to the investigators discretion to evaluate whether a physical examination of the genitourinary system is necessary based on questions regarding sores, lesions, pain, frequency or pattern change, incontinence, infections etc. For females, questions regarding birth control, menstrual regularity, menopause etc. must be asked
Musculoskeletal and neurological	It is up to the investigators discretion to evaluate whether a physical examination is necessary*. Based on questions regarding pain, tenderness and swelling of joints and/or musculature, sores lesions, disturbance of sensation and examination and observations of gait, station and agility at displacements the musculoskeletal/neurological systems are assessed as normal/abnormal
Lymph nodes	A physical examination will not be performed. It is up to the investigators discretion to evaluate whether a physical examination of the lymph nodes is necessary based on the questions regarding pain, tenderness and swelling
Skin	Inspection and palpation of skin and subcutaneous tissue
Other abnormality	If applicable

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.

11.12 Pregnancy test

For female subjects of child-bearing potential, a urine pregnancy test will be performed at all site 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.

11.13 Skin prick test

Skin prick testing will be performed to confirm hypersensitivity to Bet v extract. 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 8**.

All skin prick testing supplies will be provided by the Sponsor or designee.

Some medications may affect the outcome of the SPT and should be washed out before performing the SPT (see **Table 9**).

Table 8 Skin prick test

Country	Allergen
All Countries	HDM - *Dermatophagoides pteronyssinus* HDM - *Dermatophagoides farinae* Cat - *Felis domesticus* Dog - *Canis familiaris* Mould - *Alternaria alternata** Grass – *Phleum pratense* Weed – *Ambrosia artemisiifolia* Weed – *Artemisia vulgaris* Tree – *Betula verrucosa* Positive control – Histamine Negative control – Saline

*Not applicable in Germany

Table 9 Medications with a possible interference with SPT

Drug[26]	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	
• Local application of ultra-high and high potency[27] (on 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

11.14 Blood and urine sampling

The following types of blood samples will be drawn during the trial (**Table 10**), totalling an approximate blood volume of 18 mL (if the subject consents to the pharmacogenetic and biomarker samples, the total blood volume will be approximately 35.5 mL).

Table 10 Blood samples drawn by visit

Visit	V1	V4	V6
Purpose	**Approximate blood volume (mL)**		
Safety / Haematology	2		2
Screening / IgE	5		5
Safety / Blood chemistry			
Immunology		4	
Long-term storage - Biobank (optional)	(5)	(5)	(5)
Long-term storage - DNA (optional)			(2.5)
Total (mL)	**7 mL (12 mL)**	**4 mL (9 mL)**	**7 mL (14.5 mL)**

[26] If medication that could interfere with the SPT, according to **Table 9**, has not been washed out, the SPT must be performed after the interfering medication has been washed out.

[27] Augmented betamethasone dipropionate 0.05%; clobetasol propionate 0.05%; diflorasone diacetate 0.05%; fluocinonide 0.1%; flurandrenolide 4 mcg per m^2; halobetasol propionate 0.05%; amcinonide 0.1%; betamethasone dipropionate 0.05%; desoximetasone; halcinonide 0.1%

The following urine samples will be drawn:

Purpose	Volume	Number of urine samples during the trial
Safety/Urinalysis	10 mL	2
Pregnancy tests	NA	At each visit (if applicable)

11.15 Laboratory assessments

All safety laboratory assessments and screening IgE will be performed centrally at one or more certified laboratories, except for urine dipsticks, which will be handled on site.

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

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

In case of lost or haemolysed samples, the subject may be requested to have an additional blood sample drawn to enable analyses and ensure results.

The following analyses will be conducted:

Haematology - Automated differential

Erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelets, leukocytes, and differential count (including absolute and relative amount of neutrophils, eosinophils, basophils, lymphocytes, and monocytes).

Blood chemistry

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

Urinalysis

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

IgE for inclusion criteria

To assess the inclusion criteria, blood samples will be drawn at the screening visit (visit 1) for determination of specific IgE against Bet v.

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.

Immunology

To assess the immunological response of the treatment, blood samples will be drawn for determination of antigen-specific antibodies e.g. IgE, IgG_4 and IgE-BF) and other immunological parameters at visit 1, 4 and 6. Immunological parameters to birch will be assessed for all randomised subjects. Immunological parameters to alder, hazel and oak will only be assessed for a stratified random subset sample of subjects in each treatment group for cohort 1. The subset sample will be stratified by age group.

11.16 Long-term storage of samples

The blood samples for storage in the biobank and for pharmacogenetic analysis are for research purposes only and will not be used for the generation of any trial endpoints. As such, no biomarker or pharmacogenetic endpoints will be reported in the ICTR.

Blood sample for storage in Biobank

These blood samples will only be drawn if the subject consents to long-term storage of blood samples.

If long-term storage is accepted, a 5.0 mL blood sample will be drawn at visits 1, 4 and 6, where blood sampling is already planned. The subject will consequently only donate extra blood, no additional venepuncture 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, which today are 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 children and adults with allergies. The surrogate markers may be antibody levels, cytokine profiles, cell surface markers, specific set of proteins or metabolites, 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.

Blood sample for pharmacogenetics

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

If pharmacogenetic sampling is accepted, a 2.5 mL blood sample will be drawn at visit 6 where blood sampling is already planned. The subject will consequently only donate extra blood, no

additional venepuncture is required.

DNA/RNA material will be extracted from the blood sample. The DNA/RNA material will be used to investigate various genetic causes for how subjects may respond to the treatment. Studies may include analyses for identifying, e.g. genomic markers of atopic diseases, efficacy of allergy treatment, AEs, or other genomic markers relevant for the atopic disease and treatment of allergy. Pharmacogenetic results may be compared to pharmacodynamic results or clinical outcomes. Any significant pharmacogenetic relationships to outcome will require validation in future clinical trials.

Since 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 pharmacogenetic 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 genotyping 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.

11.17 Subject and parent/caregiver reported outcomes

To minimise the burden to the subjects, a number of outcomes will be reported by the subjects using an eDiary rather than at site visits.

11.17.1 eDiary assessments

During the trial, the subject and/or their parent/caregiver will complete an eDiary.
Children <12 years must fill in the eDiary together with a parent/caregiver and the same person should assist the child for the duration of the trial.

The eDiary is a hand-held electronic device that will be issued to the subjects at visit 4. Subjects/parents/caregivers will be instructed by the investigator in how to fill in the eDiary. In addition, a training video describing use of the eDiary and symptom scoring will be available to subjects/parents/caregivers during the trial.

The following items should be answered in the eDiary on a daily basis during the TPS period:

- Rhinoconjunctivitis symptoms (see Section **11.18**)
- Use of symptom-relieving rescue medication for treatment of rhinoconjunctivitis (see Section **11.19**)
- [redacted]

The following questionnaire should be answered in the eDiary on a weekly basis during the TPS period:

- RQLQ(S) (for all subjects aged 12-17 years of age at randomisation)

[redacted]

- [redacted]
- [redacted]

11.17.2 Assessments entered in the eCRF

11.17.2.1 Paediatric quality of life questionnaire

The quality of life in children (5 through 11 years of age) will be assessed by an interviewer using the standardised PRQLQ (Juniper et al. 1998) at visit 5. The PRQLQ and details on the scoring principles are described in Appendix 4.

11.17.2.2 Treatment satisfaction evaluation

Treatment satisfaction will be evaluated using the 9-item treatment satisfaction questionnaire for medication (TSQM-9).

This evaluation will be performed at V6 for most subjects. For those subjects in cohort 1 with [redacted] this evaluation will be performed during a TC approximately 1 week after the TPS.

11.17.2.3 Patient-rated global evaluation of treatment efficacy

Subjects will be asked the following question regarding their perception of the efficacy of the treatment they received during the birch/tree pollen season: “Compared to your rhinitis and/or conjunctivitis symptoms in the previous birch/tree pollen season, how have you felt overall in this birch/tree pollen season?”

Subjects will respond to the question using a 5-point scale (much better, better, the same, worse, much worse).

This evaluation in the eCRF will be performed at V6 for most subjects. For those subjects in cohort 1 with [redacted], this evaluation will be performed during a TC approximately 1 week after the TPS.

11.18 Assessment of rhinoconjunctivitis [redacted]

During the diary completion period, subjects will record their daily rhinoconjunctivitis [redacted] symptoms in an eDiary, with assistance from their parent/caregiver as appropriate. Symptoms should be recorded in the eDiary each evening.

A total of 10 allergic symptoms, 6 rhinoconjunctivitis symptoms [redacted] will be assessed on a scale from no symptoms to severe symptoms.

Subjects will be instructed by the investigator or delegated staff on how to record their symptoms in the eDiary using the definitions in **Table 11**. In addition, a training video describing use of the eDiary and symptom scoring will be available to subjects/parents/caregivers during the trial.

Details of the derivation of the daily rhinoconjunctivitis symptom score [redacted] are provided in Sections **15.9.1** [redacted]

Table 11 Subject's symptom scoring

Scored by subject	Definition of score
No symptoms	No sign/symptom evident
Mild symptoms	Symptom clearly present, but minimal awareness; easily tolerated
Moderate symptoms	Definite awareness of symptom that is bothersome but tolerable
Severe symptoms	Symptoms that are hard to tolerate; causes interference with activities of daily living and/or sleeping

The [redacted] symptoms are classified [redacted] as follows:

Rhinoconjunctivitis symptoms:

- Runny nose
- Blocked nose
- Sneezing
- Itchy nose
- Gritty feeling/red/itchy eyes
- Watery eyes

[redacted]

11.19 Assessment of use of rescue medication

Rhinoconjunctivitis rescue medication

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.
Subject/parents/caregiver will be instructed by the investigator or delegated staff on how to record their use of rhinoconjunctivitis rescue medication daily in the eDiary. Usage of rescue medication should be recorded in the eDiary each evening during the diary completion period. If appropriate, subjects may receive assistance from their caregiver when completing the eDiary.

Details of the derivation of the DMS are provided in Section **15.9.2**.

Asthma (SABA) medication

Subjects with asthma are provided with open-label asthma rescue medication to be used as needed for treatment of their asthma symptoms not controlled by the IMP. [redacted]

[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 is 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

12.1.1 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.

12.1.2 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)

12.1.3 Events of special interest

Selected AEs (non-serious or serious) 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 on a separate eCRF form. ESIs for this trial are:

- Systemic allergic reactions including anaphylaxis
- Events treated with adrenaline/epinephrine
- Severe local swelling or oedema of the mouth and/or throat
- Oral allergy syndrome
- EoE
- Severe asthma exacerbations and clinically relevant asthma exacerbations

12.1.4 Significant laboratory event

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

12.1.5 Medication errors, including overdose, abuse and misuse of the IMP

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.

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 sequelae meet an SAE criterion, the AE must be reported as an SAE
- 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

At each contact with the trial site, the subject must be asked about AEs in an objective manner such as “Have you experienced any problems since the last contact?"

AEs must be recorded on the AE form in the eCRF. One single AE form must be used per AE from start to resolution. For SAEs and ESIs, specific SAE and ESI data fields in the eCRF must also be filled in.

In case of concomitant medication for treatment of the AE, the concomitant medication form must be filled in.

If the same type of AE reoccurs 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, approximate daily duration in minutes and the description. Once the AE no longer reoccurs, 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).

12.3.1 Events of special interest

ESIs must be recorded via the eCRF. For each of the 6 pre-defined ESIs, investigator must fill out a specific eCRF ESI form with additional questions, in order to ensure that all relevant data is captured. EoE symptoms will be assessed at each visit according to Section **12.3.1.1**.

12.3.1.1 Eosinophilic Oesophagitis

During the trial, subjects will be monitored for emerging symptoms of EoE at the scheduled visits. At each contact with a subject, the investigator should assess if any of the following has occurred since the last contact:

- 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 presents with any of the above, or there is any clinical suspicion of eosinophilic oesophagitis, the investigator should refer the subject to a gastroenterologist for evaluation.

12.3.2 Reporting of AEs

The investigator must report all SAE information (initial as well as follow-up) to ALK within 24 hours after obtaining knowledge of the SAE information.

SAEs must be recorded via the eCRF. The initial eCRF SAE report must contain as much information as possible including relevant eCRF pages (e.g. medical history, concomitant medication). 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 must be reported by email to ALK.

Email address:	[redacted]
Emergency phone:	[redacted]

ESIs 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 email. Please state the trial ID (TT-06) 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.

The assessment of listedness for SAEs is performed by ALK according to the current version of the Investigators Brochure section 6.

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

12.3.3 Follow-up on AEs and SAEs

SAEs must be followed up until the outcome of the event is “recovered”, “recovered with sequelae” or “fatal” 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.

Ongoing SAEs can be closed at the subject’s last follow-up telephone contact with the term “not recovered” for chronic diseases (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 last follow-up telephone contact.

12.3.4 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 and not on drug accountability procedures. 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.

12.3.5 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 eCRF. Significant laboratory events found at the following visits, and which meet the definition of an AE, must be recorded on an AE form in the eCRF.

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

The following constellation of laboratory values should, by definition, be considered an AE and reported accordingly:

- An elevated AST or ALT (≥3 times the normal upper limit) and an elevated total bilirubin (≥2 times the normal upper limit), at the same time an alkaline phosphatase is not >2 times the normal upper limit (Hy’s law) as determined by protocol-specified laboratory testing or unscheduled laboratory testing

The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying aetiology.

12.3.6 Reporting of pregnancies

The investigator must report information on pregnancy and pregnancy follow-up information within 14 calendar days of obtaining the information, using the pregnancy form. For further information see Section **12.6**.

12.3.7 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 telephone 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 telephone 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 and SAEs.

12.5 DMC

A DMC will be established. The DMC will consist of external clinical experts within the area of allergy.

The DMC will convene at pre-specified intervals in accordance with a written procedure to evaluate safety data and perform ongoing safety evaluation (i.e. AE, SAE, ESI and laboratory data). Based on the review of safety data, the DMC will make recommendations suggesting appropriate actions in case of safety issues.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the sponsor; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC.

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 must be obtained.

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 2 years of age) and suspected to be related to intra-uterine exposure to the IMP should be reported to ALK.

13 EARLY TERMINATION OF TRIAL

ALK reserves the right to terminate the trial due to safety concerns and/or recommendation by the DMC.

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.

14 DATA HANDLING

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, March 2020 or higher).

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 23.0 or higher).

14.2 eDiary

Diary data should be entered daily by the adolescent subject or by the child subject's parent/caregiver together with the subject, and the same person should assist the child for the duration of the trial. This data will be transferred to the vendor database daily. 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 daily diary compliance to be greater than or equal to 80% and for the weekly RQLQ compliance to be greater than or equal to 80%.

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

Once all electronic diary data has been collected, the diary database will be closed and transferred from the vendor to ALK. 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 periodical review by the sponsor. Findings during the review of the eDiary data must be evaluated by the investigator. Any corrections to the data can only be approved by the

investigator after confirmation by the adolescent subject or by subject's parent/caregiver. Documentation of the data transfer from the electronic diary 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 system. 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

The safety and screening IgE laboratory samples processed by a central laboratory selected by ALK. When the samples are analysed and the data released, a laboratory report will be sent to the investigator and the data will be transferred electronically to the eCRF. The investigator must review the laboratory data in the eCRF. Results out of reference range must be classified as non-significant/significant in the eCRF by the investigator.

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

Immunological data will be analysed by ALK. Data will be provided electronically after database lock to data management.

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

14.5 Pollen data

Pollen data from relevant pollen stations will be provided to ALK regularly during the trial by a professional provider (see Appendix 3).

14.6 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 by site.

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

A data archive for the site subject data files (eCRF, eDiary and Laboratory data) is 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 computation will be performed using SAS® version 9.4, or a later version if applicable at the time of reporting.

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.

Numerical variables will be summarised in tables including mean, standard deviation, median, 5%-quantile, 25%-quantile, 75%-quantile, 95%-quantile, minimum and maximum.

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

Before database lock, a separate statistical analysis plan (SAP) detailing the specifications given below will be prepared and agreed upon.

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 indicated.

15.1 Estimands

A primary and secondary estimand is defined for each of the primary and key secondary objectives (see Sections **2.5**-**2.7** 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 given in Sections **15.12.1** and **15.12.4**. Approaches for handling intercurrent events and missing data are given in Section **15.12.2**, **15.12.3** and **15.15**.

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 IE that has been identified as relevant is discontinuation of trial treatment.

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, the trial product estimand can be described by:

A. **Treatment:** SQ tree SLIT-tablet or placebo, with rescue medication taken as required
B. **Population**: Children and adolescents (5-17 years of age) with moderate to severe AR/C caused by pollen from birch
C. **Variable**: Average TCS during the BPS
D. **How to account for intercurrent events:** under the hypothetical situation where all subjects have completed treatment for the planned duration (hypothetical strategy)
E. **Population summary**: Absolute difference between treatment policies

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 **15.12.2**.

15.1.3 Secondary estimand

The treatment policy estimand can similarly be described by:

A. **Treatment:** SQ tree SLIT-tablet or placebo, with rescue medication taken as required
B. **Population**: children and adolescents (5-17 years of age) with moderate to severe AR/C caused by pollen from birch
C. **Variable**: Average TCS during the BPS
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 between treatment policies

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 **15.12.3**.

15.1.4 Estimands for key secondary objectives

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 objectives, where the relevant key secondary endpoint of interest is specified in attribute C.

15.2 Sample size and power considerations

Sample size calculations are based on the primary endpoint, the average TCS during the BPS, which will be square root transformed prior to analysis in order to better approximate the normal distribution. Based on previous ALK SLIT-tablet studies in both adult and paediatric populations, it is assumed that the mean of the square root transformed average TCS during the BPS in the placebo group is 2.5 with corresponding common standard deviation of 1.4 in both placebo and active groups.

Analyses for the primary and secondary estimands will include all randomised subjects and use different multiple imputation strategies to account for missing data. For the purposes of sample size estimation, it is assumed that 5% of observations in the active arm are imputed from the placebo arm. A true relative treatment effect of 25% is assumed, which corresponds to an effective relative treatment effect of 23.75% after placebo imputation.

For a range of sample sizes and a 1:1 randomisation ratio between active and placebo groups, 1000 trial datasets were simulated under the above assumptions and each trial was analysed using a linear model with a fixed term for treatment. For each choice of sample size, the probability of the trial fulfilling the regulatory requirements of both the EMA and FDA for the primary endpoint was assessed over all the simulated trials.

The following regulatory requirements were considered:

1. Statistical significance of the absolute treatment effect (EMA)
2. Point estimate of the absolute treatment effect greater than 1 (EMA)
3. Point estimate of the relative treatment effect greater than 15% (FDA)
4. Lower limit of the 95% CI for the relative treatment effect greater than 10% (FDA)

Based on the results of the simulation study, 500 randomised subjects per arm (1000 subjects in total) was chosen to provide at least 85% power to satisfy regulatory requirements 1, 2 and 3 for the analyses based on all randomised subjects (assuming 5% imputation of placebo in the active arm for missing data). Assuming 10% of the 1000 randomised subjects do not have any diary data during the BPS, the power for an observed case (OC) analysis to meet the requirements is also presented.

Table 12 Power to meet regulatory criteria for FAS and Observed Case Analyses

	Statistical significance of absolute treatment effect	Point estimate of absolute treatment effect >1	Point estimate of relative treatment effect >15%	Lower limit of 95% CI for relative treatment effect >10%
FAS analysis[1,3] n=500[2] per arm	95.0%	88.3%	92.8%	60.2%
OC analysis[1,4] n=450[2] per arm[3]	94.7%	89.9%	93.9%	62.2%

[1] FAS analysis includes all randomised subjects, OC analysis includes all randomised subjects with diary data in the BPS
[2] n=number of subjects included in the analysis
[3] Assumptions: placebo mean=2.5, SD=1.4 (active & placebo), true relative treatment effect=25%, 5% of active arm imputed from placebo
[4] Assumptions: placebo mean=2.5, SD=1.4 (active and placebo), true relative treatment effect=25%, no MI, 10% of 1000 randomised subjects excluded due to missing data

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 failure and AEs before randomisation.

The FAS is defined as 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 tables, and corresponding subject listings.

The safety analysis set is defined as all randomised subject who received at least one dose of IMP. Subjects will be analysed according to the treatment they actually received, regardless of the treatment to which they were randomised. The safety analysis set will be used for all safety tables and corresponding subject listings.

15.4 Subject disposition

A table of subject disposition by treatment group displaying number and percentage of subjects screened, included in the FAS, discontinued from trial and the primary reason for discontinuation from trial 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

The extent of IMP exposure will be assessed based on tablet counts, where the number of tablets taken is the difference between the number of tablets dispensed and the number of tablets returned/lost. Lost tablets will be accounted for if explicitly recorded in the eCRF. Treatment duration (days) will be calculated from the date of randomisation up until (and including) the date of last IMP intake. Compliance (%) will be assessed as the number of tablets taken divided by the number of treatment days multiplied by 100.

The number of tablets taken, treatment duration (days) and treatment compliance (%) will be summarised by treatment group.

15.7 Medical history

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarised by treatment group, system organ class (SOC) and preferred term (PT).

15.8 Concomitant therapy

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

15.9 Derivation of endpoints

15.9.1 Allergic rhinoconjunctivitis daily symptom score (DSS)

The allergic rhinoconjunctivitis daily symptom score (DSS) is derived as the sum of the 6 allergic rhinoconjunctivitis symptom scores (see **Table 11**) using the following numerical scores: no symptoms =0, mild symptoms =1, moderate symptoms =2 and severe symptoms =3). The DSS takes values between 0 (no symptoms) and 18 (severe symptoms for all 6 allergic rhinoconjunctivitis symptoms assessed).

15.9.2 Allergic rhinoconjunctivitis daily medication score

The allergic rhinoconjunctivitis daily medication score (DMS) is derived using the scoring system in **Table 13** and takes values between 0 and 20 (maximum allowable daily rescue medication used).

Table 13 Scoring for allergic rhinoconjunctivitis rescue medication usage

Rescue medication	Dosage	Score/ Dose unit	Max daily score
Loratadine, 10 mg Or Desloratadine, oral solution 0.5 mg/mL	6-12 years old and >30 kg: 1 tablet once daily as needed	6 per tablet	6
	>12 years old: 1 tablet once daily as needed		
	5 years old: 2.5 mL solution once daily as needed	6 per 2.5mL	
	6-11 years old: 5.0 mL solution once daily as needed	6 per 5 mL	
	≥12 years old: 10 mL solution once daily as needed	6 per 10 mL	
Olopatadine eye drops, 1 mg/mL	1 drop in the affected eye(s) twice daily, morning and evening as needed	1.5 pr. drop	6
Mometasone nasal spray, 50 µg/dose	5-11 years old: 1 puff in each nostril once daily as needed (max 2 puffs)	4 per puff	8
	≥12 years old: 2 puffs in each nostril once daily as needed (max 4 puffs)	2 per puff	
Maximum allergic rhinoconjunctivitis daily medication score (DMS)			20

15.9.3 Allergic rhinoconjunctivitis daily total combined score (daily TCS)

The allergic rhinoconjunctivitis daily total combined score is the sum of the daily symptom and medication scores (that is, daily TCS=DSS+DMS) and takes values between 0 and 38.

15.9.4 Average allergic rhinoconjunctivitis daily total combined score (average TCS)

The average TCS during a given pollen season is the mean of all non-missing daily TCS over all days in the selected pollen season. Average TCS will be derived for the BPS, TPS, AHPS, OPS [redacted] The definitions of the pollen seasons are provided in Section **15.10**.

15.9.5 Average allergic rhinoconjunctivitis daily symptom score (average DSS) and average allergic rhinoconjunctivitis daily medication score (average DMS)

The average DSS (average DMS) during a given pollen season is the mean of all non-missing DSS (DMS) over all days in the selected pollen season. Average DSS and average DMS will be derived for the BPS, TPS, AHPS, OPS [redacted]

[redacted]

15.9.7 Severe, well and symptom-free days during the BPS and TPS

A severe day is defined as one with a DSS ≥6 and either at least 2 moderate or 1 severe allergic rhinoconjunctivitis symptom(s). A well day is defined as one with no use of allergic rhinoconjunctivitis rescue medication and a DSS ≤2. A symptom-free day is defined as one with no allergic rhinoconjunctivitis symptoms and with no use of rescue medication (i.e. daily TCS=0). The number of severe days, well days and symptom-free days will be calculated during the BPS and TPS.

15.9.8 Average TCS (EAACI scoring)

The average TCS will also be derived using the system proposed in an EAACI position paper on the standardisation of clinical outcomes (Pfaar et al. 2014). The rhinoconjunctivitis daily medication score with EAACI scoring (DMSEAACI) takes values 0, 1 or 2 (see **Table 14**). The allergic rhinoconjunctivitis daily total combined score with EAACI scoring is the sum of the DSS/6 and the DMSEAACI and takes a range of (non-integer) values between 0 and 5. The average TCS (EAACI scoring) is the mean of the daily non-missing values of the allergic rhinoconjunctivitis daily TCS with EAACI scoring. The average TCS (EAACI scoring) will be derived in the BPS and TPS.

Table 14 EAACI scoring for allergic rhinoconjunctivitis rescue medication usage

Rescue medication	Dosage	EAACI component score if medication is used (0 otherwise)
Loratadine, 10 mg Or Desloratadine, oral solution 0.5 mg/mL	6-12 years old and >30 kg: 1 tablet once daily as needed	1
	>12 years old: 1 tablet once daily as needed	
	5 years old: 2.5 mL solution once daily as needed	
	6-11 years old: 5.0 mL solution once daily as needed	
	≥12 years old: 10 mL solution once daily as needed	
Olopatadine eye drops, 1 mg/mL	1 drop in the affected eye(s) twice daily, morning and evening as needed	1
Mometasone nasal spray, 50 µg/dose	5-11 years old: 1 puff in each nostril once daily as needed (max 2 puffs)	2
	≥12 years old: 2 puffs in each nostril once daily as needed (max 4 puffs)	
Maximum allergic rhinoconjunctivitis daily medication score (DMSEAACI)		2
DMSEAACI is defined as the greatest of the EAACI components for each rescue medication type i.e. DMSEAACI can takes values of 0, 1, or 2. Note that in DMSEAACI can take a value of 3 if a subject uses “Oral corticosteroids with/without INS, with/without H1A” (Pfaar et al. 2014). This is not relevant for this trial as oral corticosteroids are not supplied as rescue medication.		

15.9.9 Rhinoconjunctivitis quality of life (RQLQ(S)) scores

The RQLQ(S) consists of 28 items covering 7 domains (activities, sleep, no-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, emotional). Each item is scored on a 7-point (0-6) scale, where lower scores indicate better quality of life and all items within each domain are weighted equally. The domain scores are derived as the mean of all item scores within each domain. The overall RQLQ score is the mean of the 28 item scores.

The RQLQ(S) is completed weekly in the eDiary by subjects aged 12-17 years at randomisation.

15.9.10 Paediatric rhinoconjunctivitis quality of life (PRQLQ) scores

The PRQLQ consists of 23 items covering 5 domains (nasal symptoms, eye symptoms, practical problems, activity limitation and other symptoms). Each item is scored on a 7-point (0-6) scale, where lower scores indicate better quality of life and all items within each domain are weighted equally. The domain scores are derived as the mean of all item scores within each domain. The overall PRQLQ score is the mean of the 23 item scores.

The PRQLQ is completed once during the BPS by subjects aged 5-11 years at randomisation.

15.9.11 Treatment satisfaction (TSQM) evaluation scores

The TSQM-9 consists of 9 items covering 3 domains (Effectiveness, Convenience, Global satisfaction). Items are scored on either a 5-point (1-5) scale or 7-point (1-7) scale, where higher scores indicate greater treatment satisfaction. For each domain, item scores are summed and normalised to a 0-100 scale, where 0 is the worst possible level of satisfaction and 100 is the best possible level of satisfaction.

15.9.12 Patient-rated global evaluation of treatment efficacy

Subjects will be asked the following question regarding their perception of the efficacy of the treatment they received *during* the birch/tree pollen season: “Compared to your rhinitis and/or conjunctivitis symptoms in the previous birch/tree pollen season, how have you felt overall in this birch/tree pollen season?”

Subjects will respond to the question using the 5-point scale: much better, better, the same, worse, much worse.

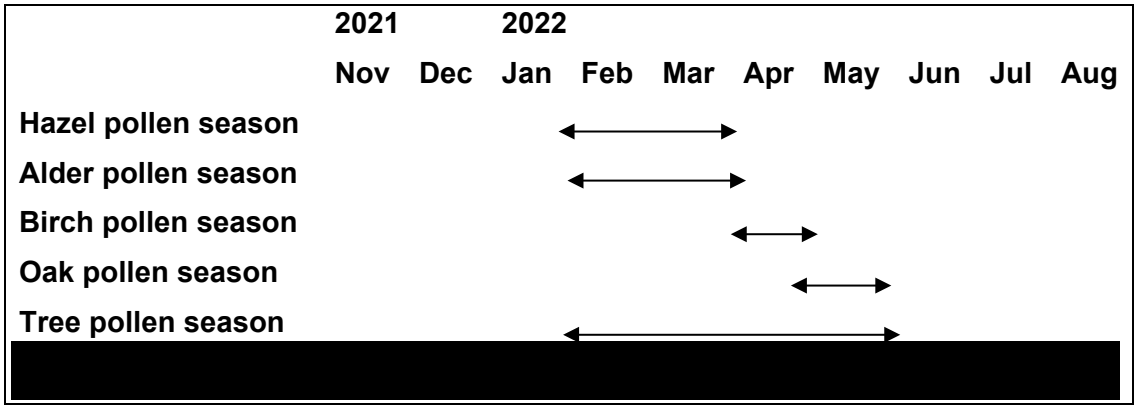
15.9.13 Lung function

Measurements of FVC, FVC percent predicted, FEV_1 and FEV_1 percent predicted will be recorded by the trial sites. The formulae used for calculating predicted FVC and predicted FEV_1 can vary slightly depending on the spirometer used at each site. Therefore, for reporting purposes, FVC percent predicted and FEV_1 percent predicted will be recalculated using values of predicted FVC and predicted FEV_1 calculated from the Quanjer equations (Quanjer et al. 1995). This is to ensure a standard approach to the derivation of the endpoints. The Quanjer formulae for predicted FVC and FEV_1 are a function of age, height and race.

15.10 Definition of pollen seasons

The different pollen seasons will vary across the selected pollen regions in both intensity and duration. Hypothetical pollen seasons in 2022 for an arbitrary location are shown in **Table 15**.

Table 15 Hypothetical pollen seasons in the Northern European region



For each pollen, start and stop dates will be defined for the respective pollen season based on actual daily pollen counts. Before defining the start and stop dates for the pollen seasons, days where the pollen counts are missing (after the first occurrence of pollen) will be replaced by applying the last observation carried forward method.

In addition, a visual inspection of the pollen plots (pollen grains/m^3 versus time) for all species will be made to validate the pollen counts in the season based on the criteria described below. This procedure can identify long periods with low pollen counts within the season e.g. due to rain or measurement errors and may lead to corrections of the start and stop dates.

Pollen seasons (i.e. start and stop dates) will be derived for the relevant pollens during the trial. The final pollen seasons will be defined prior to database lock and further specified in the SAP.

15.10.1 Birch pollen season definition

For each pollen region, the BPS is defined for each year as follows:

Start date: The start date of the BPS is defined as the first day of 3 consecutive days with birch pollen count larger than or equal to 30 grains/m^3

Stop date: The stop date of the BPS is defined as the last day in the last occurrence of 3 consecutive days with birch pollen count larger than or equal to 30 grains/m^3

15.10.2 Alder, hazel and oak pollen season definition

For each pollen region, the hazel, alder and oak pollen seasons is defined in each year as follows:

Start date: The start date of the pollen season is defined as the first day of 3 consecutive days with pollen count larger than or equal to 10 grains/m^3

Stop date: The stop date of the pollen season is defined as the last day in the last occurrence of 3 consecutive days with pollen count larger than or equal to 10 grains/m^3

Based on experience from trial TT-04, it is anticipated that there will be a high degree of overlap between the alder and hazel seasons. As such, a combined alder-hazel season is defined for each pollen region as follows:

Start date: The start date of the alder-hazel pollen season is the earliest of the alder season start date and hazel season start date

Stop date: The stop date of the alder-hazel pollen season is the latest of the alder season stop date and the hazel season stop date

15.10.3 Tree pollen season definition

For each pollen region, the TPS is defined as all days included in any of the hazel, alder, birch and oak pollen seasons. The TPS is not necessarily a continuous period.

[redacted]

15.11 Multiplicity

For the trial product estimands based on the primary efficacy endpoint and the key secondary efficacy endpoints, the analyses for the main estimators will be controlled for multiplicity to ensure a maximum overall type I error rate of 5% in the hypothesis testing of these endpoints. The control for multiplicity will be performed through hierarchical testing, using a pre-specified order of hypothesis to be tested. For each endpoint, the null hypothesis to be tested is the hypothesis of no difference between placebo and active SQ tree SLIT-tablet.

The order of the hypotheses to be tested is:

1. The primary efficacy analysis of average TCS during BPS
2. The key secondary efficacy analysis of average TCS during TPS
3. The key secondary efficacy analysis of average DSS during BPS
4. The key secondary efficacy analysis of average DSS during TPS
5. The key secondary efficacy analysis of average DMS during BPS
6. The key secondary efficacy analysis of average DMS during TPS

The first hypothesis in the hierarchy will be tested at a 5% significance level. Testing will proceed to the second hypothesis only if the first test is statistically significant ($p<0.05$). Similarly, testing will proceed to the next level of the hierarchy, only if the previous comparison is statistically significant at the 5% level. If a test is not statistically significant ($p >0.05$) then no further testing within the

hierarchy will be conducted. Thus, the 2nd, 3rd, 4th, 5th and 6th hypothesis tests in the hierarchy will only be conducted if all previously tested hypotheses are statistically significant at the 5% level.

Furthermore, analysis of the quality of life endpoints will be included as the final steps in the testing hierarchy, where the order of the hypotheses to be tested is:

7. The secondary efficacy analysis of average weekly overall RQLQ score during the BPS
8. The secondary efficacy analysis of average weekly overall RQLQ score during the TPS
9. The secondary efficacy analysis of overall PRQLQ score during the BPS

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

15.12 Efficacy analyses

15.12.1 Main estimator, sensitivity estimator(s) and statistical analysis for the trial product and treatment policy estimands

The main estimator and sensitivity estimator(s) for both estimands will be the absolute treatment difference.

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 **15.12.2**, **15.12.3** and **15.12.4**.

Analyses will be based on all randomised subjects. Subjects for whom the efficacy endpoint is missing will be included in the analysis through multiple imputation, where missing data will be imputed from the same age group according to the approaches specified in Sections **15.12.2**-**15.12.4**. Imputation will use the method of unrestricted random sampling with replacement (seed=7127) and 1000 multiply imputed datasets will be created. For each dataset, the efficacy endpoint will be square root transformed to better approximate the normal distribution and analysed using a linear mixed effects model assuming unequal variances in the 2 treatment groups. The model will include treatment, pollen season and age group (5-11 years, 12-17 years) as fixed effects and geographical location as a random effect. The results will be back-transformed to the original scale and Rubin's rule will be used to combine the results obtained from the multiply imputed datasets. Adjusted means for each treatment group, the absolute treatment difference with 95% CI, the relative treatment difference with 95% CI and the p-value for the treatment effect will be presented.

15.12.2 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 **15.9.3** and Section **15.15**). 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.

15.12.3 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 **15.9.3** and Section **15.15**). 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.

15.12.4 Estimators for estimands defined for key secondary efficacy objectives

The key secondary endpoints, average TCS during the TPS, average DSS during the BPS/TPS and average DMS during the BPS/TPS will be analysed identically to the primary endpoint using the definitions of the trial product estimand and treatment policy estimand (see Section **2.7**) and the main and sensitivity estimators described in Sections **15.12.2** and **15.12.3**.

15.12.5 Supportive analyses

For the primary and key secondary efficacy endpoints, an observed case analysis based on all subjects with at least one diary entry in the relevant pollen season will be performed as a supportive analysis. This analysis will allow comparison of results both to previous studies where the primary efficacy analyses were based on observed cases and also to acknowledged criteria for clinical success, which were established based on observed case analyses.

15.12.6 Secondary efficacy analyses

The following secondary endpoints will be analysed identically to the primary endpoint using the estimators of the trial product and treatment policy estimands: average TCS, average DSS and average DMS during the AHPS and OPS, average TCS (EAACI scoring) [redacted]

Proportion of severe days, proportion of well days, proportion of symptom-free days and patient-rated global evaluation of treatment efficacy (categorised as improvement versus no improvement) will be analysed with a logistic regression model with treatment, pollen season and age group as fixed effects and pollen station (or region) as random effects.

Average weekly overall RQLQ scores during the BPS and TPS, overall PRQLQ scores during the BPS and TSQM-9 domain scores will be analysed with a linear mixed model.

Change from baseline in immunological endpoints will be analysed with a repeated measures linear mixed model.

15.12.7 Exploratory efficacy analyses

[redacted]

15.13 Safety analyses

15.13.1 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 to IMP, outcome and seriousness.

AEs identified as local administration site reactions, by comparison against a pre-defined list of MedDRA PTs, will be summarised separately.

Further details will be provided in the SAP.

15.13.2 Evaluation of other safety parameters

Laboratory assessments, physical examination assessments, lung function tests and vital signs will be summarised by treatment group displaying number of subjects, mean, standard deviation, median, 5-, 25-, 75- and 95-percentiles, minimum and maximum for continuous variables, and frequency tables for categorical variables.

Further details will be provided in the SAP.

15.14 Interim analyses

No interim analysis is planned.

15.15 Handling of missing data and sensitivity analyses

Efficacy endpoints which are an average of daily diary entries over a defined pollen season will be derived provided there is at least one relevant diary entry for that endpoint in the given pollen season. Subjects with missing data for an endpoint will be included in the analysis of that endpoint through multiple imputation (see Sections **15.12.2**, **15.12.3** and **15.12.4**). 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 written standard operating procedures (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 in the eCRF:

- Subject's month and year of birth
- Confirmation of participation in the trial (trial ID, subject number/randomisation number, diagnosis)
- Date of informed consent and assent for adolescent subjects where this is relevant
- 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 laboratory 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 in 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 eCRF 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 or according to local legislation.

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 eCRF 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 and the CRO within 24-hours.

In cases related to COVID-19 where protocol procedures are not carried out as intended, a comment should be entered in the eCRF with the prefix 'COVID-19'. In addition, a COVID-19 protocol deviation must be reported as for all deviations caused by the coronavirus outbreak.

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) (World Medical Association 2013)
- 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)
- FDA regulations relating to GCP and clinical trials, (FDA 2018)
- GDPR (Regulation (EU) 2016/679) (The European parliament 2016)

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, eCRFs 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 eCRF 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.

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.

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 be pseudonymised, 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 SOPs that define 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 amendments 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 Clinical trial report

Data will be reported in an ICTR 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 international coordinating investigator will review and sign the ICTR.

18.2 Publication and disclosure 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 eCRF (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).

If the number of authors is restricted, selection will be based on the degree to which individuals can be held accountable 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.

ALK will review the presentations and publications for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), verify that the confidential information is not being inadvertently divulged, and/or provide any relevant supplementary information. Upon ALK's request, the investigator shall delay a publication or presentation for 6 months from ALK's

receipt of the publication or presentation to permit ALK to file a patent application or take other steps as necessary to protect the confidential information (including trial results of ALK).

Results of the trial will be posted in the EU Clinical Trials Registry no later than 6 months after LSLV. No individual de-identified subject data will be shared.

Results of the trial, in accordance with the protocol and SAP, will be posted at ClinicalTrials.gov 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, 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 vendors, including CROs and subcontractors for e.g. project management, monitoring and central laboratory, are listed in Appendix 3.

21 REFERENCE LIST

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