Clinical trial protocol

Trial ID: MT-18
A 28-day, single-armed, open-label trial to evaluate safety of the house dust mite (HDM) sublingual allergy immunotherapy (SLIT) tablet in adolescent subjects (12-17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis (AR/C) with or without asthma

Sponsor: ALK-Abelló A/S
Bøge Allé 6-8
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Investigational medicinal product: HDM SLIT-tablet

Phase: III

Regulatory trial identifier number:
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Protocol synopsis

Trial ID EudraCT no.	MT-18 2020-000446-34
Title of trial	A 28-day, single-armed, open-label trial to evaluate safety of the house dust mite (HDM) sublingual allergy immunotherapy (SLIT) tablet in adolescent subjects (12-17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis (AR/C) with or without asthma
Short title	Open-label 28-day safety trial in HDM allergic adolescents
Main objective	The primary objective is to evaluate safety and tolerability of the HDM SLIT-tablet in adolescents (12-17 years of age) with 28 days of treatment
Primary endpoint	At least one treatment-emergent adverse event (TEAE)
Key Secondary endpoints	• At least one solicited TEAE • At least one IMP-related AE • At least one treatment-emergent serious adverse event (SAE)
Trial design	A 28-day, single-armed, open-label, multi-centre trial in adolescent subjects (12-17 years of age) with HDM AR/C, with or without asthma. The trial consists of three trial periods: a screening period (up to 12 weeks), a 28-day treatment period and a 1-week follow-up period. Three in-clinic visits are planned for each subject: screening (visit 1), first dosing (visit 2), and a final visit (visit 3). In addition, a phone contact 7 days after visit 2 and a follow-up phone contact (FU-TC) approximately 7 days after visit 3 will take place. During the treatment period a subject diary will be used to capture 15 pre-specified symptoms/signs daily and associated medication taken. The diaries are to be used for evaluation by the investigator when capturing AEs at visit 3.
Main assessments	Spirometry (FEV_1), skin prick test (SPT)
Main criteria for inclusion	• Written informed consent obtained from subjects' legal representatives before any trial related procedures are performed • Male or female subjects aged ≥12 to ≤17 years on the screening day (visit 1) and at the FU-TC. • A clinical history of AR/C when exposed to HDM (diagnosed by a physician) of 1-year duration or more (with or without asthma) and with allergic rhinitis symptoms despite having received allergy pharmacotherapy during the previous year prior to screening visit (visit 1)

	• Positive skin prick test (SPT) to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* at screening (wheal size of ≥3 mm) • Lung function measured by Forced expiratory volume in 1 second (FEV_1) ≥ 70% of predicted value or according to local requirements while on subject's usual asthma medication
Main criteria for exclusion	• A subject who has previously been included in studies with the HDM SLIT-tablet, or otherwise being treated with the marketed HDM SLIT-tablet (e.g. ACARIZAX, ODACTRA) • Any SLIT or SCIT treatment with *D. pteronyssinus* or *D. farinae* reaching the maintenance dose within the last 5 years. In addition, any SLIT or SCIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months prior to visit 1 • Ongoing treatment with any allergy immunotherapy product at screening • Severe chronic oral inflammation • A diagnosis or history of eosinophilic oesophagitis • Any clinical deterioration of asthma that resulted in emergency treatment, hospitalisation or treatment with systemic corticosteroids within 3 months prior to first tablet administration (visit 2) • Female with positive urine pregnancy test, breastfeeding, pregnant or planning to become pregnant within the projected duration of the trial • Sexually active female of childbearing potential without medically accepted contraceptive method
Investigational medicinal products	The HDM SLIT-tablet is formulated as an oral lyophilisate containing standardised allergen extract from house dust mites (*D. pteronyssinus* and *D. farinae)* and the following excipients: gelatins (fish source), mannitol and sodium hydroxide. Daily dose: 12 SQ-HDM
Duration of treatment	28 days
Number of subjects to be enrolled	Approximately 250 subjects (12-17 years of age)
Number and distribution of trial sites	Estimated 20-30
Statistical methods	TEAEs will be summarised by system organ class (SOC) and preferred term (PT). The summary will include number and proportion of subjects

	with at least one TEAE, as well as number of TEAEs. For the proportion of subjects with at least one TEAE the exact 95% confidence interval will also be presented. TEAEs will also be summarised according to severity, relationship to trial product, outcome, action taken, seriousness, and number of events leading to treatment discontinuation. The summaries will be for the safety analysis set consisting of all subjects who received at least one dose of IMP.
Sponsor's name/address	ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm

Table of contents

Table of figures

Page

Table of tables

Page

List of appendices

Table of abbreviations

Abbreviation	Meaning
AA	Allergic asthma
AE	Adverse event
AIT	Allergy immunotherapy
ALT	Alanine aminotransferase
AR	Allergic rhinitis
AR/C	Allergic rhinitis/rhinoconjunctivitis
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BP	Blood pressure
BUN	Blood urea nitrogen
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical research associate
eCRF	Electronic case report form
ERS	European Respiratory Society
CRO	Clinical research organisation
DMC	Data monitoring committee
EudraCT	European Union drug regulating authorities Clinical Trials
ESIs	Events of special interest
FDA	Food and drug administration
FEV_1	Forced expiratory volume in 1 second
FU-TC	Follow-up telephone contact
GCP	Good clinical practice
GDPR	General Data Protection Regulation
HDM	House dust mite
IB	Investigators brochure
ICH	International council for harmonisation of technical requirements for registration of pharmaceuticals for human use
ICS	Inhaled corticosteroid
ICTR	Integrated clinical trial report

Abbreviation	Meaning
IEC	Independent ethics committee
IgE	Immunoglobulin E
IMP	Investigational medicinal product
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist
LSLV	Last subject last visit
MAOIs	Monoamine oxidase inhibitors
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Non-TEAE	AE, not fulfilling the definition of a TEAE
PEF	Peak expiratory flow
PT	Preferred term
SAE	Serious adverse event
SAS	Statistical analysis software; computer software for statistical programming
SCIT	Subcutaneous allergy immunotherapy
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLIT	Sublingual allergy immunotherapy
SLIT-drops	Sublingual allergy immunotherapy drops
SLIT-tablet	Sublingual allergy immunotherapy tablet
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
SPT	Skin prick test
TC	Telephone contact
TEAE	Treatment-emergent adverse events
TCRS	Total combined rhinitis score
V	Visit

Abbreviation	Meaning
WHO	World Health Organisation

Table of definitions

Anaphylaxis	The definition of anaphylaxis **(Sampson et al. 2006)** includes any one of the following 3 criteria: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus, or flushing, or swollen lips, tongue, or uvula) AND either respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia) or reduced Blood pressure (BP)* or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence) 2. Two or more of the following that occur rapidly after exposure to a likely allergen for the subject (minutes to several hours): a. Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips, tongue, or uvula) b. Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP* or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting) 3. Reduced BP after exposure to known allergen for the subject (minutes to several hours): low systolic BP* or greater than 30% decrease in systolic BP *Low systolic BP is defined as less than 90 mmHg from 11 to 17 years.
Completed subject	A subject is considered to have completed the trial if he/she has completed the treatment period (V3)
Concomitant medication	All medications being continued by a subject on entry into the trial and all medications given during the trial, except for IMP
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 contact (FU-TC) for the last subject in the trial globally
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
Last subject last visit (LSLV)	Last scheduled physical visit for any subject (V3)
Primary completion date	Date of the last data collection for the primary endpoint (ClinicalTrials.gov), which is the date of the last contact (FU-TC) for the last subject in the trial globally
Solicited AE	A pre-specified AE recorded by the investigator based on the signs/symptoms reported in the subject's diary during the 28 days of treatment

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 allergic reaction	Allergic reactions occurring after exposure to an allergen with symptoms from one or more organ system (skin, mucosal, respiratory, cardiovascular or gastrointestinal) not related to the administration site. Systemic allergic reactions can occur in different grades with the most severe reactions being anaphylaxis
Systemic corticosteroids	Oral, intramuscular, or intravenously administered corticosteroids
TEAE	TEAEs are defined as adverse events with start date 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
Subject discontinuation date	Date of subject trial discontinuation. In case of subjects lost to follow-up, the discontinuation date is defined as the date the investigator/sponsor decides to discontinue the subject

Protocol versions

Date	Version	Description of document	Rationale for amendment
06-Feb-2020	1.0	Final Protocol	N/A
08-Apr-2020	2.0	Amendment 1: Amendment to address: • risks associated with the COVID-19 pandemic • specific allergen used in the Skin Prick Test (SPT). The amendment applies to all countries. There are no changes affecting subject information and assent forms.	Amendment is done to address the EMA recommendations in the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 2 (27/03/2020). In addition, allergen for the SPT, is revised, please refer to rationale in the table below.

Section # and name	Description of change	Brief rationale
1.4 benefit-risk assessment	A section including COVID-19 related risk in context of this trial is inserted	According to latest guidelines, Sponsor needs to address additional COVID-19 related risks to participants in the risk benefit section of the protocol.
11.13 Skin prick test	The mould allergen; *Cladosporium herbarum* is removed from SPT	The primary objective of this trial is to evaluate safety and tolerability during 28-days of treatment with HDM SLIT-tablet. From a clinical point of view the specific results of the SPT for moulds will have minimal, if any, impact on the overall trial results as well as data integrity and there is no effect on patient safety. The SPT panel will include *Alternaria alternata*, the most prevalent mould allergen

Flow chart

Trial period:	Screening	Treatment			Post-treatment	
Visit ID:	**V1**	**V2**	**TC**	**V3[1]**	**FU-TC[2]**	**UV[3]**
Visit title:	**Screening**	**Enrolment and administration of first tablet**	**Telephone contact**	**Final visit**	**Follow-up Telephone contact**	**Unscheduled Visit**
Scheduled day:		**Day 1**	**Day 8**	**Day 29[4]**	**Last day of treatment + 5-7 days**	
Scheduling window:	**Max 12 weeks prior to Day 1**		**+/- 1 day**	**+ 3 days**		
Informed consent/assent	X					
Demography	X					
Smoking habits	X					
Medical history	X					
Previous[5] and concomitant medication	X	X	X	X	X	X
Height and weight	X	X				
Vital signs	X	X		X		(X)
FEV_1[6]	X	X		X		(X)
Physical examination	X					(X)
Oropharyngeal examination		X[7]		X		(X)
Assess symptoms of eosinophilic oesophagitis	X	X	X	X	X	(X)
Urine pregnancy test, if applicable[8]	X	X		X		(X)
SPT[9]	X	(X)				
Blood and urine sampling for safety analyses	X					(X)
Assess compliance with Inclusion/exclusion criteria	X	X				

[1] If a subject discontinues prior to completing the 28-day treatment period, the assessments of V3 should be performed 5-7 days after last IMP intake.
[2] Post-trial treatment with HDM SLIT-tablets must not be initiated before FU-TC has been performed.
[3] Assessments at unscheduled visit(s) marked (X) are performed as applicable
[4] Conducted on Day 29 in order to allow for diary completion for last day of treatment (Day 28)
[5] Previous medication to be assessed only at V1 and covering at least 1 year.
[6] Measure Forced expiratory volume in 1 second (FEV_1) and calculate the % of predicted FEV_1.
[7] Oropharyngeal examinations will be done before IMP administration at V2.
[8] For female subjects of childbearing potential. Additional urine pregnancy tests should be performed during the trial, at an unscheduled visit, if a menstrual period is missed.
[9] If medication that could interfere with the skin prick test has not been washed out at visit 1, the skin prick test must be performed after the interfering medication has been washed out and before tablet administration (See **Table 5**).

Trial period:	**Screening**	**Treatment**			**Post-treatment**	
Visit ID:	**V1**	**V2**	**TC**	**V3[1]**	**FU-TC[2]**	**UV[3]**
Visit title:	**Screening**	**Enrolment and administration of first tablet**	**Telephone contact**	**Final visit**	**Follow-up Telephone contact**	**Unscheduled Visit**
Scheduled day:		**Day 1**	**Day 8**	**Day 29[4]**	**Last day of treatment + 5-7 days**	
Scheduling window:	**Max 12 weeks prior to Day 1**		**+/- 1 day**	**+ 3 days**		
Assess AEs since last visit/TC	X[10]	X[11]	X	X	X[12]	X
Provide the subject with a subject card	X					
Provide the *Local and systemic allergic reaction emergency plan* and instruct		X				
Dispense IMP and instruct in the use of IMP		X	(X)[13]			(X)[14]
Intake of IMP at clinic		X[14]				
Provide and instruct in the use of the diary		X	(X)[15]			(X)[15]
Collect and evaluate diary.				X		
Collect IMP, perform compliance check and drug accountability[16]				X		

[10] Any AE occurring during the visit from the time the informed consent/assent was signed

[11] This includes AEs related to first IMP dose: Staff must record time of onset for any event occurring or worsening 0-30 minutes post dosing.

[12] If an AE was ongoing at the previous visit or if a new AE is identified at the telephone contact the subject could be asked to return to the trial site or have an additional telephone contact for follow-up.

[13] Re-instruct in use of IMP, as applicable

[14] 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 until the oral cavity has healed.

[15] Re-instruct in use of the diary, as applicable

[16] Collect unused, partly used and empty blister packages

1 INTRODUCTION

1.1 Disease background and current treatment modalities

House dust mite (HDM) allergy is an IgE-mediated hypersensitivity reaction to allergens contained in HDM body fragments and faeces, causing symptoms of allergic rhinitis/rhinoconjunctivitis (AR/C) and/or asthma. Patients typically have symptoms year round with an increase in symptoms during the winter months (**Bousquet et al. 2001**).

House dust mite (HDM) is the most common cause of perennial allergic rhinitis with or without conjunctivitis (AR/C) worldwide. In addition, epidemiology studies suggest that HDM is the most common indoor allergen associated with asthma worldwide (**National Institutes of health 2002; Platts-Mills et al. 1991**). In the European Community respiratory health survey which included 1,132 adults with current asthma, 48% displayed a positive skin prick test result to HDM allergens (**Gruchalla et al. 2005**) but with significant regional variations. In the US general population, the prevalence of HDM sensitivity has been reported to be 28% based on the NHANES survey (**Arbes, Jr. et al. 2005**).

HDM AR/C can be treated with symptom relieving medication such as oral/ocular antihistamines or nasal steroids; however, a large proportion of the sufferers are inadequately controlled by these medications. Allergy immunotherapy (AIT) modifies the underlying immunological mechanisms responsible for allergic inflammation and represents a treatment option for HDM allergy that is complementary to pharmacotherapy (**Calderon et al. 2015**).

1.2 Stage of development

The HDM SLIT-tablet is formulated as a fast-dissolving pharmaceutical formulation (oral lyophilisate) containing standardised HDM allergen extract. Treatment involves once daily sublingual administration to provide clinical benefit in both HDM allergic rhinitis (AR) and HDM allergic asthma (AA).

To date, the HDM SLIT-tablet has been investigated in 16 randomised, double-blind, placebo-controlled trials worldwide. This includes 2 paediatric phase I trials with doses up to 12 SQ-HDM (1 in children 5-14 years of age; 1 in adolescents 12-17 years of age) and 1 paediatric phase III trial with the 6 SQ-HDM dose in children and adolescents 5-17 years of age. In addition, adolescent subjects were included in 2 adult phase III trials.

A total of 1245 paediatric subjects (<18 years) have been included in the completed clinical trials, 271 of whom were treated with the 12 SQ-HDM dose. Most paediatric subjects exposed to 12 SQ-HDM (n=265; 98%) were adolescents.

The efficacy and safety of treatment with the HDM SLIT-tablet in subjects with HDM AR have been investigated in 3 very similar phase III trials in adults/adolescents and in 1 paediatric phase III trial.

The 3 phase III trials MT-06 (**Demoly et al. 2016**), P001 (**Nolte et al. 2016**), and TO-203-3-2 (**Okubo et al. 2016**) were conducted in Europe, North America, and Japan, respectively, to demonstrate efficacy and safety in adults with HDM AR. Adolescent subjects were included in the P001 and TO-203-3-2 trials. The 3 trials had a very similar design; all 3 were randomised, parallel-group, double-blind, placebo-controlled trials assessing primary efficacy based on the average total combined rhinitis score (TCRS), calculated on daily symptom score and daily medication score,

during the last 8 weeks of approximately 1 year of daily treatment. Across trials, a consistent treatment benefit was demonstrated, with statistically significantly lower TCRS reported by subjects on active treatment compared to placebo. The HDM SLIT-tablet (6 and 12 SQ-HDM doses) was generally well tolerated with a safety profile characterised by frequent but transient local allergic events (e.g. oral pruritus, throat irritation, mouth oedema and oral paraesthesia) that were typically assessed as mild or moderate in severity. Severe systemic allergic reactions were uncommon. Across the adolescent subpopulation, no severe local swellings were reported, and no adolescent subjects were treated with adrenaline/epinephrine due to AEs.

1.3 Trial rationale

Currently, the HDM SLIT-tablet is approved for use in the adolescent population in some major regions of the world, but still lacking in some e.g. North America. Subpopulation results from the completed phase III trials (adults/adolescents) showed that treatment with the HDM SLIT-tablet in subjects with HDM AR/C with or without asthma was well tolerated and efficacious.

The purpose of this trial is to supplement the safety database supporting an application to extend the indication into the adolescent population in markets where the HDM SLIT-tablet is currently only approved for adult patients.

Endpoints have been selected based on safety data obtained in previous trials with the HDM SLIT-tablet. Safety endpoints listed will support the primary objective to evaluate the overall safety and tolerability of the HDM SLIT-tablet in the adolescent population.

Subjects will be enrolled to receive treatment with the HDM SLIT-tablet (12 SQ-HDM) for a period of 28 days. A treatment period of 28 days is chosen based on previous experience with the onset of AEs being mainly within the first few weeks of treatment with the HDM SLIT-tablet.

The primary safety objective will be assessed based on collection of adverse events related to the 28-day treatment period. The secondary endpoints are focused on the characterisation of the frequency of pre-specified particular AEs expected to occur with the local application of the HDM SLIT-tablet (solicited AEs).

1.4 Benefit-risk assessment

Treatment with the HDM SLIT-tablet targets the underlying HDM allergy to provide clinical benefit in both HDM AR/C and HDM AA. In general, clinical efficacy is observed after 8 weeks of HDM SLIT-tablet (12 SQ-HDM) treatment. Thus, subjects in this trial may not experience clinical efficacy during the trial period. However, direct impact on subject's daily life is limited due to the short duration of the trial and limited trial related procedures. The safety profile of the HDM SLIT-tablet in the adolescent population is expected to be favourable and in line with the safety profile in the adult population, and supportive of an overall favourable benefit-risk evaluation.

The route of administration for the HDM SLIT-tablet is sublingual: This provides an advantage over subcutaneous injection, as it has a safety profile allowing for at-home administration conditioned that first intake is done during medical supervision. This results in improved convenience for patients and caters to those who have a fear of injections or who cannot set aside time off work or school for frequent doctor's visits over an extended treatment period.

The most prevalent AEs observed with the HDM SLIT-tablet include local allergic reactions in the mouth and throat (e.g. oral pruritus, throat irritation, and mouth oedema) of mild or moderate severity. There is a risk of more significant AEs, such as serious allergic reactions or larger swellings in the oral cavity. The risk of severe swellings in the oral cavity is low and across the adolescent subpopulation included in the HDM SLIT-tablet development programme, no severe local swellings compromising the airways have been reported and no adolescent subjects were treated with adrenaline/epinephrine due to AEs. A single anaphylactic reaction in an adolescent subject in the 12 SQ-HDM group was reported; the event occurred 2 days after IMP discontinuation and was assessed as unrelated to treatment (**Matsuoka et al. 2017**).

While the risk of systemic allergic reactions applies to both subcutaneous and sublingual AIT, the risk of severe systemic allergic reactions is considered minimised for the HDM SLIT-tablet, as sublingual administration has not been found to result in relevant absorption into the systemic circulation. However, few cases of serious systemic allergic reactions, including anaphylaxis have been reported post marketing and are considered a class effect of AIT. The medical supervision at first IMP intake is therefore an important precaution. In some cases, the serious systemic allergic reaction has occurred at doses subsequent to the initial dosing.

In the present trial, all subjects/legal representatives will be provided with educational information regarding symptoms of local and systemic allergic reactions and treatment, including a written local and systemic allergic reaction emergency plan. Subjects will be medically monitored during the trial and provided with appropriate treatment, if warranted. Subjects can discontinue from the trial at any time without penalty or loss of benefits to which the subject was otherwise entitled, if they find the treatment intolerable, and without giving a reason.

The population in this trial reflects subjects in whom AIT with the HDM SLIT-tablet could be a relevant choice, however due to the limited duration of the treatment in this trial, subjects cannot expect to experience direct clinical benefit from treatment during participation. However, the short duration will ensure that important safety data is collected with minimal impact on subject's daily life. Importantly, trial participation does not constitute an additional risk compared to normal treatment initiation with AIT, e.g. such as the HDM SLIT-tablet.

Participating in this trial allows subjects who are diagnosed with HDM allergy and who are candidates for SLIT-tablet AIT to enroll and experience the benefit from a thorough clinical assessment of their allergy and from starting one form of AIT in a controlled clinical trial setting. In shared decision making with their physician subjects may continue treatment with marketed drug or choose another form of AIT after the end of the trial period.

Further details about specific benefits and risks for treatment with the HDM SLIT-tablet can be found in the accompanying Investigators Brochure (IB)

1.4.1 Considerations regarding COVID-19

Regarding the pandemic of COVID-19, it is important to highlight that subjects' safety is always first priority. Participating in this trial, including receiving treatment with AIT, is not expected to increase subjects' risk of contracting communicable diseases, including COVID-19. The examinations and procedures (e.g. lung function, SPT, blood sampling) included in this trial are of minimal burden to subjects and do not include assessment outside what standard medical evaluation of allergic subjects would include. The risk to subjects with asthma is considered unchanged as only subjects

with well controlled mild to moderate asthma are included. If regional circumstances related to COVID-19 change, local guidance should be followed.

1.5 Ethical considerations

This clinical trial will follow the principles of the Helsinki Declaration 1964 and subsequent amendments and clarifications (**World Medical Association 2013**). The trial will be approved by local Independent Ethics Committees (IECs) and regulatory authorities before initiation.

The trial is an open-label trial. All participating subjects will receive active treatment. This eliminates the ethical considerations of placebo treatment, as the efficacy of the active treatment is established.

The trial will be conducted in European countries, where the HDM SLIT-tablet is already marketed and reimbursed to the adolescent population. This leaves the trial subjects with the possibility to continue treatment after trial completion.

2 OBJECTIVES AND ENDPOINTS

2.1 Objective

The objective is to evaluate safety and tolerability of the HDM SLIT-tablet in adolescents (12-17 years of age) with 28 days of treatment.

2.2 Primary endpoint

At least one treatment-emergent adverse event (TEAE)

2.3 Secondary endpoints

- At least one solicited TEAE
- At least one IMP-related adverse event (AE)
- At least one treatment-emergent serious adverse event (SAE)

2.4 Other endpoints

- At least one treatment-emergent systemic allergic reaction including anaphylaxis[17]
- At least one TEAE treated with adrenaline/epinephrine
- At least one treatment-emergent severe local swelling or oedema of the mouth and/or throat
- A TEAE of eosinophilic oesophagitis
- A TEAE leading to discontinuation
- Daily duration of recurrent TEAEs

[17] The definition of anaphylaxis according to **(Sampson et al. 2006)**, see section **12**

3 TRIAL DESIGN

3.1 Summary of trial design

This is a 28-day, single-armed, open-label, multi-centre trial in adolescent subjects (12-17 years of age) with HDM AR/C, with or without asthma.

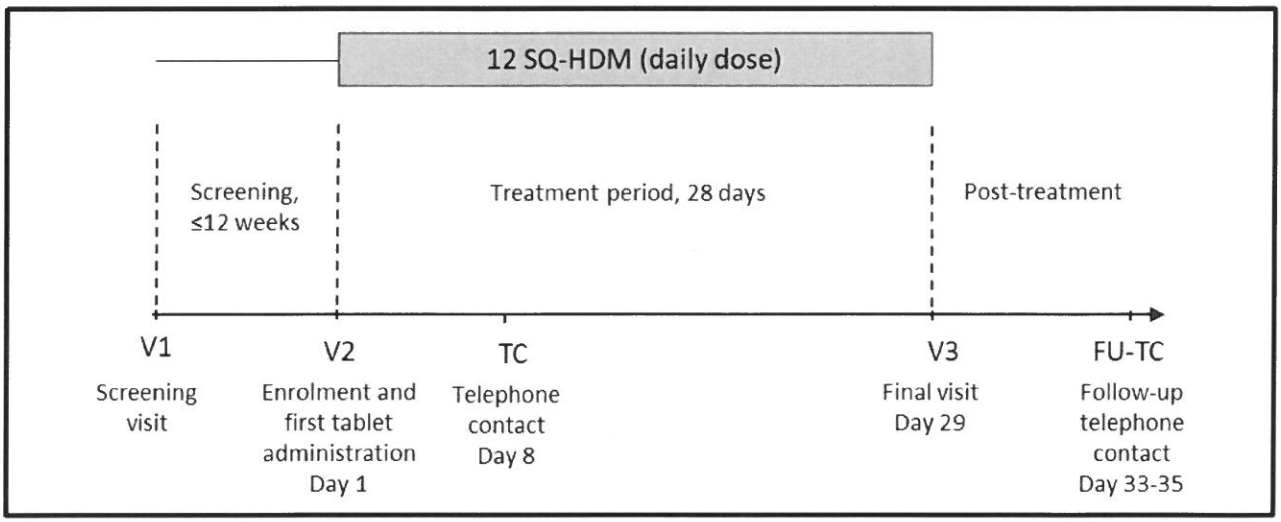
Approximately 250 subjects will be enrolled to receive daily treatment with the HDM SLIT-tablet (12 SQ-HDM).

The trial consists of three trial periods: a screening period, a 28-day open-label treatment period and a 5-7-day follow-up period (see **Figure 1**).

Each subject will participate in three in-clinic visits: screening (V1), enrolment and first tablet administration (V2), and a final visit (V3). In addition, a telephone contact 7-9 days after V2 and a follow-up telephone contact 5-7 days after intake of last IMP dose will take place.

An unscheduled visit may take place in case of technical issues with lab samples and/or need for safety follow-up.

Figure 1 Trial design



3.2 Discussion of design

This trial may be conducted throughout the year irrespective of coinciding pollen seasons, as long as the 28-day treatment period does not overlap with the relevant season for the allergen to which the individual subject is allergic. The purpose of this trial is to collect safety data in adolescents with HDM AR/C with or without asthma to supplement existing safety data in this age group.

An open-label trial design is expected to reduce the time of trial conduct since recruitment of the relevant trial population, adolescents (12-17 years of age) with HDM AR/C, is likely to be less challenging as all subjects will receive active treatment.

The single-armed, open-label design also eliminates the ethical considerations of placebo treatment since the efficacy of the active treatment is established. The trial will be conducted in countries in which the HDM SLIT-tablet is authorised for use in the adolescent age group, thereby all subjects will have the opportunity of continuing treatment after trial completion.

To ensure an unbiased selection of subjects and reporting of AEs, if any, subjects must be naïve to treatment with the HDM SLIT-tablet.

A treatment period of 28 days is chosen based on previous experience with the onset of AEs in the HDM SLIT-tablet development programme. Subjects who develop IMP-related AEs generally experience these, if any, within the first few days of treatment, with few new IMP-related AEs occurring beyond the first weeks of treatment. In addition, the proposed treatment duration of 28 days will allow for solicitation of pre-specified AEs identified as events of special interest (ESIs) of SLIT-tablets. In previous trials with this product, few AEs have occurred after end of treatment, and in follow-up periods of up to 14 days, the majority of events have occurred in the first few days, hence, as the safety profile of the HDM SLIT-tablet is well established a follow-up period of 5-7 days is chosen after last day of treatment.

It is expected that the proportion of reported AEs will be higher in this trial compared to previous trials due to the open-label design and active solicitation.

3.3 Justification of dose

The active dosage chosen in the trial is 12 SQ-HDM, which is the approved dose for adults in the United States, Canada, Europe, Australia, New Zealand, Russia, and Southeast Asia, and for adolescents (12-17 years) in Europe, Australia, Russia and Southeast Asia. The selected dose for this trial, is based on phase I safety data in children, as well as the being the appropriate dose established in adults as the dose providing the highest efficacy with the fastest onset of effect and with a safety profile that supports daily at-home administration (**Demoly et al. 2016; Nolte et al. 2015; Virchow et al. 2016**). This dose (12 SQ-HDM) is intended to constitute the relevant dose for all populations ≥5 years of age, in accordance with the general practice for AIT (**Alvarez-Cuesta et al. 2006**).

3.4 End of trial definition

A subject is considered to have completed the trial if he/she has completed the treatment period (V3).

The overall end of the trial is defined as the date of last contact (FU-TC) for the last subject in the trial globally.

4 TRIAL POPULATION

Approximately 250 adolescent subjects (12-17 years of age) with HDM allergic rhinitis/rhinoconjunctivitis (AR/C) with or without asthma who meet all inclusion criteria and none of the exclusion criteria will be selected to participate in the trial.

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 subjects' legal representatives before any trial related procedures are performed[18]

I2. Male or female subjects aged ≥12 to ≤17 years on the screening day (visit 1) and at the FU-TC.

I3. A clinical history of allergic rhinitis/rhinoconjunctivitis (AR/C) when exposed to HDM (diagnosed by a physician) of 1-year duration or more (with or without asthma) and with allergic rhinitis (AR) symptoms despite having received allergy pharmacotherapy during the previous year prior to screening visit (visit 1)[19]

I4. Positive skin prick test (SPT) to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* at screening (wheal size of ≥3 mm)[20]

I5. Lung function measured by Forced expiratory volume in 1 second (FEV_1) ≥ 70% of predicted value[21] or according to local requirements while on subject's usual asthma medication

I6. The subject must be willing and able to comply with trial protocol and adhere to IMP treatment

4.2 Exclusion criteria

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

E1. A clinically relevant history of symptomatic perennial AR/C caused by a perennial allergen source, such as animal hair and dander and/or mould to which the subject is exposed during the 28-day treatment period

E2. A clinically relevant history of symptomatic seasonal AR/C caused by an allergen to which the subject is exposed, and which could potentially overlap with the 28-day treatment period

E3. A subject who has previously been included in studies with the HDM SLIT-tablet, or otherwise being treated with the marketed HDM SLIT-tablet (e.g. ACARIZAX, ODACTRA)

E4. Any SLIT or SCIT treatment with *D. pteronyssinus* or *D. farinae* reaching the maintenance dose within the last 5 years. In addition, any SLIT or SCIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months prior to visit 1

E5. Ongoing treatment with any allergy immunotherapy (AIT) product at screening

[18] Assent from the subject must be obtained according to national requirements.

[19] The investigator should do everything possible to obtain medical records with documentation for HDM allergic rhinitis. If medical records are not available, verbal history from subject/legal representative can be used to fulfil this criterion and this must be documented in the medical records by the investigator

[20] If medication that could interfere with the SPT, according to **Table 5**, has not been washed out and the positive control is <3 mm, the SPT must be performed/repeated after the interfering medication has been washed out and before enrolment

[21] Lung function will be measured according to the ATS/ERS spirometry recommendations (**Reddel et al. 2009**). The subjects will be included based on spirometry values measured at the site and reported by the site according to the site's pre-programmed spirometric reference equations. The reference equations and values used should be documented on every pulmonary function report.

E6. Severe chronic oral inflammation

E7. A diagnosis or history of eosinophilic oesophagitis

E8. Systemic immunosuppressive treatment within 3 months prior to screening

E9. Any clinical deterioration of asthma that resulted in emergency treatment, hospitalisation or treatment with systemic corticosteroids within 3 months prior to first tablet administration (visit 2)

E10. Any clinically relevant chronic disease, including malignancy, that in the opinion of the investigator would interfere with the trial evaluations or the safety of the subject

E11. A history of chronic urticaria (> 6 weeks) and/or chronic angioedema (> 6 weeks) within the last 2 years prior to screening visit that in the opinion of the investigator may constitute an increased safety concern

E12. 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

E13. Active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance

E14. Treatment with an investigational drug within 30 days or 5 half-lives of the drug (whichever is the longest) prior to screening visit

E15. Known history of allergy, hypersensitivity or intolerance to any of the excipients or active substances of the IMP (except for *D. pteronyssinus* and/or *D. farinae*)

E16. Female with positive urine pregnancy test, breastfeeding, pregnant or planning to become pregnant within the projected duration of the trial

E17. Sexually active female of childbearing potential without medically accepted contraceptive method[22]

E18. A business or personal relationship with trial staff or sponsor who is directly involved with the conduct of the trial

E19. Previously been enrolled into this trial, is participating in this trial at another investigational site or is participating or planning to participate in any other clinical trial during the duration of this trial

E20. A history or current evidence of any condition, treatment, laboratory values out of range or other circumstance that in the opinion of the investigator are clinically relevant and might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial

[22] 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; intrauterine device (IUD), intrauterine system (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.

E21. Has a condition or requires treatment that may increase the risk of the subject developing severe adverse reactions after adrenaline/epinephrine administration

E22. Treatment with restricted and prohibited concomitant and previous medication listed in **Table 1**.

4.3 Screening failures

Screening 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 assigned to study intervention. A minimal set of screen failure information is required 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 on end of trial form, eligibility criteria, and any non-serious and serious adverse event (SAE) (if applicable).

4.3.1 Rescreening

Screen failures may be rescreened for one of the following reasons:

- if the reason for screening failure is of an administrative character
- if the subject fails to meet the inclusion criterion I3 with regards to the length of HDM allergy history being less than the required one year that may resolve by rescreening later
- if the subject meets exclusion criterion E2 with regards to symptomatic seasonal AR/C that could potentially overlap with the 28-day treatment period, and that may resolve by rescreening later
- in case of technical issues with laboratory samples (e.g. haemolysed or lost).
- issues with prohibited medication/previous medication that may resolve by rescreening later
- in case of oral surgery, including dental extraction and shedding of a deciduous tooth, to allow healing of the oral cavity
- temporary inflammatory conditions in the oral cavity
- upper airway viral infection or other temporary infections

Rescreened subjects will be assigned a new subject number and the subject's legal representative is required to sign a new ICF. Rescreening of an individual subject is allowed only once.

5 SUBJECT DISCONTINUATION

5.1 Discontinuation from IMP treatment and trial

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

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

- If a subject becomes pregnant

- The subject experiences severe or persistent symptoms of oesophagitis or have a confirmed diagnosis of eosinophilic oesophagitis
- The subject's asthma becomes difficult to control
- If, in the investigator's opinion, continuation with IMP treatment would be detrimental to the subject's well-being
- If subject is lost to follow-up
- If IMP is interrupted for more than 7 days in a row
- If informed consent/assent is withdrawn

In case a subject discontinues from the trial, the discontinuation page in the eCRF should be completed. If a subject discontinues prior to completing the 28-day treatment period, a follow-up visit should be performed 5-7 days after last IMP intake. Assessments should be done according to V3. On the discontinuation page the investigator should record the date of the discontinuation from the trial, the person initiating the discontinuation, and the primary reason for discontinuation. If an AE is involved in a discontinuation, this must be recorded as the primary reason. In all cases, the primary reason for discontinuation must be recorded in the eCRF and in the subject's medical records.

5.2 Lost to follow-up

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

Data obtained until discontinuation will be used for statistical analyses.

5.3 Replacement of subjects

Subjects who discontinue 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 and a 3-digit site number, which in combination ensures a unique subject identification (e.g. 101-50001) that will be used throughout the trial period.

The subject number will be generated when the subjects' data are entered in the eCRF.

6.2 Randomisation

This trial is an open-label trial, so randomisation will not be performed.

6.3 Treatment blinding/unblinding

This trial is an open-label trial. All subjects will receive active treatment.

6.4 Subject card

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

7 RESTRICTED AND PROHIBITED CONCOMITANT MEDICATION AFTER ENROLMENT

Restricted and prohibited concomitant medications are listed in **Table 1**. For medications that could possibly interfere with SPT performed at screening, please refer to **Table 5**.

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

The medication listed in **Table 1** is restricted or prohibited.

Table 1 Restricted and prohibited prior and concomitant medications

Product	Time window	Reason
An investigational product other than the IMP	≤ 30 days or 5 half-lives of the product (which ever longest) before visit 2 and until FU-TC	Possible interaction between IMPs. Protect subject's safety. Interferes with safety evaluations
Anti-IgE treatment, e.g. omalizumab	< 130 days or 5 half-lives of the product (which ever longest) prior to visit 2 and until FU-TC	Interferes with safety evaluations

Product	Time window	Reason
Antihistamine, routine use and preventive use to treat anticipated adverse events:		
- Oral, intravenous, nasal or ocular	From visit 2 and until FU-TC	Interferes with safety evaluation
- Long-acting (astemizole)	≤ 90 days before visit 2 and until FU-TC	Interferes with safety evaluation
(antihistamines Pro re nata (when necessary) are permitted for treatment of acute allergic symptoms, see section **11.5**)		
Antidepressant medications:		
- Antidepressant medication with antihistaminic effect (e.g. doxepin, mianserine)	≤ 14 days before visit 2 and until FU-TC	Interferes with safety evaluation
- Tricyclic antidepressants (e.g. amitriptyline, clomipramine)		Interferes with safety evaluation
-Monoamine oxidase inhibitors (MAOIs)		Tricyclic antidepressants and MAOIs may potentiate the effect of adrenaline/epinephrine
Antipsychotic medications with antihistaminic effects (e.g. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)	≤ 7 days before visit 2 and until FU-TC	Interferes with safety evaluation
Systemic glucocorticosteroids	≤ 90 days before visit 2 and until FU-TC	Interferes with safety evaluation
High daily dose of inhaled corticosteroids (ICS)	1 months before visit 2	Interferes with safety evaluation

Product	Time window	Reason
Immunosuppressive treatment (ATC code L04 or L01) (e.g. dupilumab, mepolizumab, reslizumab, lebrikizumab)	≤ 130 days or 5 half-lives (which ever longest) before visit 1 and until FU-TC	Interferes with safety evaluation
Inhaled, topical or oral nedocromil or cromolyn sodium	≤ 14 days before visit 2 and until FU-TC	Interferes with safety evaluation
Leukotriene receptor antagonist (LTRA) (e.g. montelukast, zafirlukast)	From visit 1 and until FU-TC. Unless treatment has started prior to subject entering the trial, in which case it should remain unchanged throughout the trial.	Interferes with safety evaluation
Pizotifene	≤ 7 days before visit 1 and until FU-TC	Interferes with safety evaluation
Beta 1 blockers	≤ 7 days before visit 2 and until FU-TC	Interferes with safety evaluation Beta blockers may reduce the effect of adrenaline/epinephrine

8 TRIAL PRODUCTS

8.1 IMP

The IMP provided in the trial is HDM SLIT-tablet. The IMP is manufactured and provided by ALK.

Please refer to the Trial Supplies Catalogue provided by ALK for details regarding IMP.

IMP name:	Active treatment: HDM SLIT-tablet
Active ingredients:	Standardised allergen extract from the HDMs *D. pteronyssinus* and *D. farinae*
Dosage form:	Oral lyophilisate (SLIT-tablet)
Excipients:	Gelatine (fish source), mannitol and sodium hydroxide
Route of administration:	Sublingual
Dose/strength:	12 SQ-HDM

IMP dispensing

The treatment will start at V2 (enrolment and first tablet administration). The first dose will be administered under medical supervision, and the subject will be observed for at least 30 minutes after the tablet intake.

8.2 Packaging and labelling

The IMP will be supplied in blister cards containing 10 tablets each. The blister cards will be packed in boxes containing a sufficient number of tablets to cover the treatment period.

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

Packaging and labelling will be outsourced by ALK.

8.3 Handling and storage

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

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

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

Storage temperature should be monitored according to the storage requirements defined in the Trial Supplies Catalogue using a calibrated, stationary and continuously recording system. As a minimum a calibrated min/max thermometer is required.

8.4 IMP accountability

The investigator or appropriate delegated staff must maintain records of the IMP 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 received from ALK.

All IMP 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 the final visit. Compliance will be assessed by SLIT-tablet counts.

At the final visit, the investigator must return a copy of the completed drug accountability form to the ALK-appointed CRA or to the ALK address provided. The investigator must not destroy any IMP without written agreement with ALK.

8.5 Reporting of technical complaints

Any technical complaint related to the trial products provided by ALK (IMP or 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.

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

Prior to IMP intake, an oropharyngeal examination should be performed.

First intake of IMP must be at the clinic with a subsequent observation period for at least 30 minutes.

For subjects with severe oral inflammation (e.g. oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction, or following tooth loss, V2 (including initiation of IMP treatment) should be postponed allowing healing of the oral cavity.

For asthmatic 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.

9.3 Treatment of severe allergic reactions/anaphylaxis

If, following exposure to an allergen, multiple organ systems are adversely affected, anaphylaxis is a likely event/diagnosis. Symptoms that may be present during anaphylaxis include flushing, apprehension, syncope, tachycardia, thread or unobtainable pulse associated with a fall in BP, vomiting, diarrhoea and abdominal cramps, wheezing, dyspnoea due to laryngeal spasm, lower airway obstruction, pruritus, rashes (such as urticaria), or angioedema. At V2, the subject and legal representative will be provided verbal and written information, in the form of a local and systemic allergic reaction emergency plan, on how to identify any potential local and systemic allergic reactions including symptoms/signs of anaphylaxis, upper airway obstruction and what actions to take, including phone numbers to call in case of emergency.

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

circumstances that triggered symptoms of anaphylaxis and/or the use of self-injectable adrenaline/epinephrine must be clearly recorded on the eCRF.

9.4 Temporary interruption of treatment

Treatment may be interrupted for up to 7 days due to any of the following reasons:

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

Interruptions should be kept to a minimum. If IMP is interrupted for more than 7 consecutive days, the subject should be discontinued.

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

In **Table 2**, the assessments that should be performed at each visit are described.

Table 2 Visit schedule

Visit ID	Assessments to be performed at the visit
Visit 1 (screening)	• Obtain written informed consent/assent, for the trial before any other assessments are performed • Record demographic data (sex, age, month and year of birth, race, ethnic origin, childbearing potential[23]) and body measurements (height and weight) • Record smoking habits • Record medical history (incl. rhinitis/rhinoconjunctivitis and asthma medical history) • Record use of relevant previous medications • Record use of any concomitant medication • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 • Perform physical examination • Assess symptoms of eosinophilic oesophagitis • Urine pregnancy test (if applicable) • Perform SPT [24] • Collect blood and urine for safety laboratory assessments

[23] Only year of birth in countries which do not allow the month to be collected, and ethnic origin only if allowed according to local regulation

[24] If medication that could interfere with the skin prick test, according to **Table 5** has not been washed out and the positive control is <3 mm the skin prick test must be performed after the interfering medication has been washed out and before enrolment

Visit ID	Assessments to be performed at the visit
	• Assess compliance with inclusion and exclusion criteria, and register the subject in the eCRF accordingly • Assess AEs occurring after informed consent/assent • Provide the subject with a subject card • Schedule date for visit 2 (and remaining visits/contacts, if possible)
Visit 2 (Enrolment and first tablet administration)	• Record any change to concomitant medication • Record body measurements (height and weight) • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 • Urine pregnancy test (if applicable) • SPT, if not possible at visit 1 due to necessary washout of concomitant medication • Perform oropharyngeal examination pre-dosing • Assess symptoms of eosinophilic oesophagitis • Assess AEs occurring since the last visit[25] • Reassess compliance with inclusion and exclusion criteria • Provide and instruct the subject in completion of the diary • Provide the subject and their legal representative with the *Local and systemic allergic reaction emergency plan* and instruct in signs, symptoms and management of the potential reactions • Instruct the subject on how to use the IMP • Dispense IMP to the subject, and monitor the subject 30 min post-dosing • Schedule dates for telephone contact and visit 3
TC (Telephone contact)	• Assess AEs occurring since the last visit • Assess symptoms of eosinophilic oesophagitis • Record changes to concomitant medication • Follow-up on how to use the IMP and how to fill in the Diary
Visit 3 (Final)	• Collect unused, partly used and empty blister packages • Perform drug accountability • Check IMP compliance • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 • Urine pregnancy test (if applicable) • Perform oropharyngeal examination • Assess symptoms of eosinophilic oesophagitis • Record changes to concomitant medication, including medications reported in the diary • Assess AEs, including collect and evaluate diary • Schedule date for a telephone follow-up contact 5-7 days later
FU-TC	• Assess AEs occurring since the last visit. If an AE was ongoing at the previous visit or if a new AE is identified at the telephone contact the subject could be asked to return to the trial site. • Assess symptoms of eosinophilic oesophagitis

[25]This includes AEs related to first IMP dose: Staff must record time of onset for any event occurring or worsening 0-30 minutes post dosing.

Visit ID	Assessments to be performed at the visit
	• Record changes to concomitant medication • Post-trial treatment with HDM SLIT-tablets may be initiated in line with the SmPC

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 flow chart and the visit schedule in section **10**.

The tasks listed below must be performed by a physician.

- Obtainment of informed consent
- Evaluation of inclusion and exclusion criteria
- Physical examination
- Assessment of AEs/SAEs
- Assessment of FEV_1 and laboratory results

Evaluation of the completed diary, 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 is needed, the subject must be asked, and a conclusion made in the subject's source documents. Care must be taken not to bias the subject.

11.1 Informed consent

All legal representatives 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 washout of concomitant medication.

If the minor can understand the risks and benefits of the trial, he/she should also be informed. Assent should be obtained according to national requirements.

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

The investigator must explain the nature of the trial, its purpose, the assessments involved, the expected duration, the potential risks and benefits involved and any discomfort it may. Information to the legal representative and 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 and assent form to document this.

The legal representative and subject must be given sufficient time to consider the trial before deciding whether to participate. Each subject and the legal representative 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/assent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The legal representative/subject must sign and date the informed consent form/assent form before entering the trial (i.e. before any trial related activity). The investigator must give a copy of the signed informed consent/assent to the legal representative/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 and the Competent authorities. The legal representative and the subject must be informed in a timely manner about the updated subject information sheet and written informed consent and assent must be obtained.

11.2 Demographics

The following data will be recorded:

- Month[26] and year of birth
- Age
- Race and ethnic[27] origin
- Sex
- Childbearing potential

11.3 Smoking habits

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

11.4 Medical history

The relevant medical history, incl. diseases present at trial entry must be recorded in the eCRF. This includes a detailed allergy history including recording of the subject's history of rhinitis, conjunctivitis, asthma, atopic dermatitis and food allergy.

11.5 Concomitant and previous medication

The subjects' use of concomitant medication including AR/C and asthma medication must be recorded. Relevant previous medication must also be recorded. This includes previous allergy and asthma pharmacotherapy taken for the past year. Other previous medication taken by the subject should also be recorded if considered relevant by the investigator. Standard information about the medication will be collected including name of medication, indication, dose, administration route and treatment period.

Concomitant medication 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. Antihistamines should not be used to pre-treat for potential adverse events related to the IMP but can be used to treat acute symptoms of allergic rhinoconjunctivitis, or to relieve symptoms from AEs. As such, antihistamine cannot be part of

[26] Only year of birth in countries which do not allow the month to be collected

[27] Ethnic origin only collected if allowed according to local regulation

subject's routine treatment as prophylactic treatment during this trial, as this would interfere with the overall purpose of this trial. Rescue medication will not be provided as part of the study.

Subjects with asthma are allowed to continue their regular asthma controller therapy as long as this is not violating exclusion criteria (section **4.2**) or prohibited medication (section **7**). Additional treatment for asthma exacerbations is allowed. This asthma medication should be captured in eCRF as concomitant medication.

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

11.6 Height and weight

The subject's height (without shoes) and weight will be recorded at V1 and V2, as listed in the flow chart.

11.7 Vital signs

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

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

11.8 Lung function

The assessment of the lung function will include measurements of forced vital capacity (FVC), and FVC percent predicted, FEV_1 and FEV_1 percent predicted, for all subjects. Lung function measurements will be performed with a spirometer available at the clinic. FVC and the derived FEV_1 is measured as 3 valid measurements and the highest value will be entered in the eCRF.

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

11.9 Physical examination

The physical examination should be performed by a physician or designee (in accordance with local practice) and should be based on the following body systems:

Table 3 Physical examination

Organ system	Minimum examinations to be completed
General appearance	As applicable
Skin	Inspection of skin
Head	Ears - Inspection of auricles and external canal (otoscopy is not required) Eyes - Inspection of conjunctivae and eyelids Nose - Inspection of nasal mucosa (nasal endoscopy is optional) Oral cavity - oropharyngeal inspection of lips, tongue, tonsils and uvula will be performed for signs of mouth irritation, oedema, and any other abnormalities. When performed at visit 2, it will take place before IMP administration.
Lymph nodes	Examination of lymph nodes (cervical, axillary, and inguinal lymph nodes)
Respiratory	Auscultation/stethoscopy of lungs
Heart	Auscultation/stethoscopy of the heart.
Abdomen	As applicable
Urogenital	
Musculoskeletal and neurological	
Other abnormality	

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

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

11.10 Oropharyngeal examination

At the oropharyngeal examination, the oral cavity and oropharynx, if possible, will be inspected for signs of mouth irritation, oedema, and any other abnormalities. Abnormal findings at visit 2 prior to first IMP administration should be recorded on the medical history. Abnormal or worsening of abnormal findings after first IMP dose are considered to be AEs.

Oropharyngeal examinations will take place before first IMP administration (V2). In case of any findings, dosing may need to be postponed, see section **9.2**. Oropharyngeal examinations performed at V3 may be completed at any time during the visit.

11.11 Eosinophilic oesophagitis

At each visit to the clinic, subjects/parents/caregivers will be asked whether any of the following are present or have occurred since the last clinic visit:

- food impaction requiring medical intervention

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

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

11.12 Pregnancy test

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

The urine pregnancy tests will be performed by dip-sticks at the trial site. If a pregnancy is confirmed the subject must be discontinued, please also refer to section **12.3.7** for reporting of pregnancy.

11.13 Skin prick test

SPT must be performed according to the procedure provided by ALK.

No data are available for SPT in pregnant subjects, therefore the urine pregnancy test must be performed before SPT.

Subjects enrolled in the trial will be tested for:

Table 4 Skin prick test

Country	Allergen
All Countries	Positive control Negative control HDM – *Dermatophagoides pteronyssinus* HDM – *Dermatophagoides farinae* Cat – *Felis domesticus* Dog – *Canis familiaris* Mould – *Alternaria alternata* Grass – *Phleum pratense* Mugwort – *Artemisia vulgaris* Birch – *Betula verrucosa*

Some medication may affect the outcome of the SPT and should be washed out before performing the SPT. Concerned medications are listed below:

Table 5 Medications with a possible interference with skin prick test

Drug	Recommended washout period prior to performing SPT
Antihistamine • Oral, intravenous or topical (skin) • Long-acting (astemizole)	 3 days 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[28] • Local application of ultra high and high potency[29] (on the skin area used for SPT) • Oral • Short-acting parenteral • Long-acting parenteral (intra-articular or intramuscular)	 21 days 30 days 30 days 90 days
Pizotifene	7 days

11.14 Blood and urine sampling

The following blood samples will be drawn during the trial, adding to an approximate total blood volume of 5 ml:

Purpose	Approximate volume	Number of samples
Safety / Haematology	2 ml	1
Safety / Blood chemistry	2.5 ml	1
Approximate total volume	4,5 ml	

In case of technical issues with sampling and/or unscheduled visits additional samples may be drawn.

The following urine samples will be collected:

[28] Treatment with systemic prednisolone with daily doses below 20 mg should not be discontinued (**Des Roches et al. 1996**). Estimated equipotent doses 20 mg Prednisolone = 20 mg Prednisone = 100 mg Hydrocortisone (iv. or per oral) = 16 mg Methylprednisolone = 3 mg Dexamethasone

[29] Augmented betamethasone dipropionate 0.05%; clobetasol propionate 0.05%; diflorasone diacetate 0.05%; fluocinonide 0.1%; flurandrenolide 4 mcg per m2; halobetasol propionate 0.05%; amcinonide 0.1%; betamethasone dipropionate 0.05%; desoximetasone; halcinonide 0.1%

Purpose	Volume	Samples during the trial.
Safety/Urinalysis	10 ml	1
Pregnancy tests	N/A	At each visit (if applicable)

11.15 Laboratory assessments

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

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

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

The following laboratory variables will be measured:

Haematology

Erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelets, leukocytes, 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 and calcium.

Urinalysis:

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

11.16 Solicited signs/symptoms

In order to aid the AE and concomitant medication reporting, subjects will be given a paper diary to fill in daily (See Appendix 4). The diary will be used by the subject to help remember details and dates, when discussing AEs and concomitant medication with the investigator at the telephone contact and at visit 3 (and unscheduled visits, if applicable).

The diary will be used to capture 15 pre-specified symptoms/signs, identified as potential local side effects of sublingual immunotherapy (**Passalacqua et al. 2013**):

- Food tastes different
- Mouth ulcer/sore in the mouth[30]

[30] A mouth ulcer is a discrete, painful lesion affecting the lining of the mouth where the mucosa is eroded

- Swelling of uvula/back of the mouth
- Itching in the mouth
- Itching in the ear
- Swelling of the lips
- Swelling of the tongue
- Tongue pain
- Tongue ulcer/sore on the tongue[31]
- Throat irritation/tickle
- Throat swelling
- Stomach pain
- Nausea (feel like throwing up)
- Vomiting
- Diarrhoea

If the subject answers "yes" to any of the symptoms, listed in the diary, the subject must also fill in whether any medication was used to treat this symptom and what type of medication.

Subjects and their legal representative will be trained by the investigator or designee at V2 on the proper method to complete the diary. In addition, the subject will be instructed to report other symptoms, that are not part of the diary list, to the investigator. The reported symptoms will be discussed with the subjects and after medical evaluation by the investigator be reported as AEs on the AE form in the eCRF. The evaluation of the solicited signs/symptoms must be documented in the medical records.

When evaluating the diary together with the subject at V3 the investigator should identify use of medication reported on the diary and fill each use of medication into the eCRF linked to the relevant AE.

If any AEs are reported on several consecutive days, the investigator should mark the AE as "recurrent" and inquire about the approximate duration each day of these recurring AEs and enter this information into the eCRF (see section **12.3**).

12 SAFETY

Information about AEs, whether reported by the subject, discovered by the investigator by reviewing diary records, detected through physical examination 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.

[31] A tongue ulcer is a discrete, painful lesion affecting an area on the tongue, where the mucosa is eroded

Any AE occurring from the time the informed consent was signed by the subject and until the FU-TC 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. TEAEs are defined as adverse events with start date on or after the time of first IMP administration and no later than 7 days after last IMP administration.

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. a 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.

Events of special interest

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

- Systemic allergic reactions including anaphylaxis[32]
- Events treated with adrenaline/epinephrine
- Severe local swelling of the mouth and/or throat
- Eosinophilic oesophagitis

See Appendix 5 for definitions and aggregated preferred terms used to identify ESIs.

[32] The definition of anaphylaxis **(Sampson et al. 2006)** includes any 1 of the following 3 criteria:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus, or flushing, or swollen lips, tongue, or uvula) AND either respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) or reduced BP* or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for the subject (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips, tongue, or uvula)
   b. Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP* or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for the subject (minutes to several hours): low systolic BP* or greater than 30% decrease in systolic BP

*Low systolic BP is defined as less than 90 mmHg from 11 to 17 years.

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

The definition of an AE also covers medication errors and uses of the IMP outside what is foreseen in the protocol, including misuse and abuse of the product. If doses higher than the recommended dose are taken, whether intentionally or unintentionally, the risk of AEs may increase. This includes the risk of anaphylaxis or severe local reactions.

- 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

See Appendix 5 for definitions and aggregated preferred terms used to identify medication errors, abuse and misuse of the IMP.

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 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 qualify as a SAE, the AE must be reported as such
- Not recovered: The condition has not returned to baseline, however, symptoms may have improved
- Fatal: Event that results in death
- Unknown: The outcome is unknown. This term should only be used when no other definition is possible e.g. the subject is lost to follow-up

12.3 Collection, recording and reporting of AEs

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. One single AE form must be used per AE from start to resolution. For SAEs, the SAE form 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 occurs more than 1 day in a row with the same pattern and severity (e.g. itching in the mouth for 5-10 minutes after intake of IMP) it is considered a recurrent AE. The AE form should be filled in with the start date and the description. Once the AE does no longer reoccur after IMP intake, the AE form should be completed with a stop date and the event should be marked as recurrent in the eCRF. If the AE then re-appears on a subsequent day or if the AEs changes in severity, a new AE form should be filled in. For recurrent events, the investigator should ask the patient about approximate daily duration and record this in the eCRF.

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).

The AE start time of AEs that occur on V2 will be recorded in source documents and entered into the eCRF.

12.3.1 Solicited AEs

The diary (See Appendix 4) will be used by the subject to help remember details and dates, when discussing AEs and concomitant medication with the investigator at the visits.

The diary lists 15 specific signs/symptoms, identified as local side effects of sublingual immunotherapy (**Passalacqua et al. 2013**). These local side effects will be collected on a daily basis by the subject during the 28 days of treatment (section **11.16**).

See Appendix 5 for preferred terms used (PT) to identify solicited AEs.

12.3.2 Eosinophilic Oesophagitis

During the trial, subjects will be monitored for emerging symptoms of eosinophilic oesophagitis at the scheduled visits as described in section **11.11**.

12.3.3 Reporting of AEs

The investigator must report all SAE and ESI information (initial as well as follow-up) to ALK within 24 hours after obtaining knowledge of the information. SAEs and ESIs will automatically be sent to ALK via the eCRF system. In case the eCRF system is unavailable during the 24-hour reporting timeline, SAEs and ESIs (including relevant data e.g. demography, medical history, concomitant medication) must be reported by email to ALK. For the ESI of adrenaline/epinephrine administration, the symptoms and/or circumstances that triggered the use of adrenaline/epinephrine must be clearly recorded as AEs in the eCRF.

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 (MT-18) and the site and subject ID on all documents.

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

Email address:	clinical-safety-hq@alk.net
Emergency phone:	+45 20 81 77 24

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

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

12.3.4 Follow-up on AEs and SAEs

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

Ongoing SAEs can be closed at the FU-TC 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 FU-TC.

12.3.5 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 5 calendar days of obtaining the information. Reporting of overdoses must be based on actual IMP exposure as reported by the subject 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.

12.3.6 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.

12.3.7 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**.

12.3.8 Reporting of SAE and pregnancies after last subject contact (FU-TC)

SAEs that in the opinion of the investigator are related to IMP that are brought to the attention of the investigator after the last subject contact (FU-TC) 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 subject contact (FU-TC) 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 Data monitoring committee (DMC)

In this trial there will not be a DMC as it is an open-label trial, and the product is already marketed for adolescents in Europe where the trial will be conducted.

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 the trial.

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

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.

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

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

1. IMP-related death of an individual
2. IMP-related anaphylactic shock in at least 2 subjects[33] defined as:

   Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus, or flushing, swollen lips, tongue, or uvula) AND medically confirmed reduced BP with associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
   Low systolic BP for children is defined as less than 70 mmHg + (2 x age) from 1 to 10 years, and less than 90 mmHg for 11 to 17 years of age.

IMP intake may only be resumed after the information has been presented to regulatory authorities, and regulatory authorities concur with continued IMP intake. In case of complete premature IMP discontinuation, participating investigators/subjects/legal representative, the IEC, and the relevant regulatory authorities will be promptly informed.

[33] The criterion for 2 events is based on prior trial experience where it has been observed that events of severe anaphylactic reactions unrelated to IMP may occur in allergic subjects even with a temporal relationship to tablet administration.

14 DATA HANDLING

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

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

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 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 Clinical research associate (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, version WHO DDE C3 March 1, 2017 or higher).

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

The writing access to the eCRF will be revoked for all site staff prior to database lock, but the reading access will not be revoked until the investigator have received all subject PDF files.

14.2 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.

14.3 Laboratory data

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

14.4 Database lock

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

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

A data archive for the site subject data files are produced and sent to the site.

The investigators 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 the statistical analysis system (SAS), SAS® version 9.4 or later.

Any changes in the statistical methods compared to what is described in the protocol will be documented in the ICTR. Post-hoc analyses, if any, will be clearly marked.

Summary tables for numerical variables will display the descriptive statistics mean, SD, median, 5%-quantile, 25%-quantile, 75%-quantile, 95%-quantile, minimum and maximum.

Summary tables for categorical variables will be frequency tables displaying numbers and percentages.

15.1 Sample size and power considerations

Approximately 250 subjects will be included in the study.

The study will supplement the safety database supporting an application for extension of the indication into the adolescent population in markets where the HDM SLIT-tablet is currently only approved for use in adults. Therefore, the number of subjects has been chosen so that in total, at the time of submission, approximately 500 adolescent subjects have been exposed to the HDM SLIT-tablet (12 SQ-HDM dose) in clinical trials.

The rationale for doing this, is to be able to exclude a 1% or higher proportion of subjects experiencing an AE for rare events, when the observed proportion is 0.2%. The argumentation is as follows: no events of severe systemic allergic reactions or severe local swellings have been reported in the 265 adolescent subjects exposed to 12 SQ-HDM in clinical trials, indicating that the risk in adolescents is no higher than that observed in adults. If 1 event were to occur in this study, it will correspond to an overall proportion of 0.2%, and the upper limit of the two-sided 90% confidence interval for the proportion will then be 0.95%, i.e. it can be concluded that the true proportion with 90% confidence will be lower than 0.95%, or in other words a true proportion of 1% is excluded with 90% confidence.

15.2 Analysis data sets

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

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

15.3 Subject disposition

A table of subject disposition displaying number and percentage of subjects screened, enrolled, included in the safety analysis set, discontinued and the primary reason for discontinuation will be presented.

15.4 Baseline characteristics

Demographic variables (including age, sex, race, ethnic origin, country/region, weight, height, and body mass index [BMI]) will be summarised.

Baseline characteristics (including baseline asthma status, inhaled corticosteroid use, duration of HDM AR/C, and HDM wheal size from SPT), primary and secondary diagnoses, and prior and concomitant therapies will be summarised.

15.5 Extent of exposure

The duration of treatment for each subject will be evaluated by calculating the number of days on IMP treatment. The range and mean for days on IMP treatment will be calculated for the safety analysis set population

For each subject, percent compliance with IMP will be calculated using the following formula:

$$\text{Percent compliance} = \frac{\text{number of days on IMP treatment}}{\text{number of expected days on IMP treatment}} \text{ X } 100\%$$

A day within the trial will be considered an "on IMP treatment" day, if the subject takes the required medication as instructed. When a subject takes less than or more than the required medication on a day, that day is not considered an "on IMP treatment" day.

For subjects who are followed for the entire trial period, the "Number of expected days on IMP treatment" is the number of days from the first scheduled treatment day to the last scheduled treatment day. For subjects who discontinue from the trial, the "Number of expected days on IMP treatment" is the number of days from the first scheduled treatment day to the last dose day.

Exposure, defined as number of expected days on IMP treatment, and percent compliance will be summarised.

15.6 Medical history

Medical history will be summarised.

15.7 Concomitant therapy

Concomitant medication and illness will be summarised.

15.8 Safety analyses

The evaluation of safety results will be based on TEAEs. TEAEs are defined as adverse events with start date on or after the time of first IMP administration and no later than 7 days after last IMP administration.

No statistical hypothesis testing will be performed.

All adverse events occurring in the trial including non-TEAEs will be listed.

15.8.1 Evaluation of AEs

Below is the list of the safety endpoints in the trial:

Primary endpoint	At least one TEAE
Secondary endpoint	At least one solicited TEAE
Secondary endpoint	At least one IMP-related AE
Secondary endpoint	At least one treatment-emergent serious adverse events (SAE)
Other	At least one treatment-emergent systemic allergic reaction including anaphylaxis
Other	At least one TEAE treated with adrenaline/epinephrine
Other	At least one treatment-emergent severe local swelling or oedema of the mouth and/or throat
Other	A TEAE of eosinophilic oesophagitis
Other	A TEAE leading to discontinuation
Other	Daily duration of recurrent TEAEs

The different types of AEs (TEAEs, solicited TEAEs, IMP-related AEs, treatment-emergent SAEs, treatment-emergent systemic allergic reactions including anaphylaxis, TEAEs treated with adrenaline/epinephrine, treatment-emergent severe local swellings or oedemas of the mouth and/or throat, TEAEs of eosinophilic oesophagitis, and TEAE leading to discontinuation) in the above table will be summarised by system organ class (SOC) and preferred term (PT).

Summaries will include number and proportion of subjects having the event, as well as number of events. For the proportion of subjects with at least one events the exact 95% confidence interval will also be presented.

The different types of AEs mentioned in the above table will generally also be summarised according to severity, relationship to trial product, outcome, action taken, seriousness, and number of events leading to treatment discontinuation. However, in case of few events of the specific type, these details will be listed instead.

Duration of recurrent TEAEs will be summarised according to PT.

Most frequent AEs defined as those occurring in more than 2% of subjects will be summarised according to SOC and PT. Duration of most frequent AEs, as well as time to onset of most frequent AEs, will be summarised according to SOC and PT.

15.8.2 Evaluation of other safety parameters

Vital signs, physical examination assessments, and laboratory assessments will be summarised by visit.

The pulmonary function test parameters (FEV_1, FVC, percentage predicted FEV_1 and percentage predicted FVC) will be summarised by visit.

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

16.2 Source data and access to source documents

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

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

- Subject's month[34] and year of birth
- Confirmation of participation in the trial (trial ID, subject number, diagnosis)
- Date of informed consent/assent
- Confirmation of subject eligibility (in-/exclusion criteria)
- Concomitant diseases and medication
- Relevant medical history (incl. specific allergy and asthma history and date of diagnosis)
- Relevant previous medication (incl. medication for allergy and asthma)
- 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

[34] For countries where it is allowed

- Subject discontinuation from the trial including reason

Documentation of assessments made during the trial, e.g. 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 on 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
- 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. 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 in accordance with 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 or 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 the Clinical research organisation (CRO) within 24-hours.

16.5 Audit

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

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

17 ETHICS AND REGULATORY PROCEDURES

17.1 Statement of compliance

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

- The Declaration of Helsinki (1964, and its amendments and subsequent clarifications) (**World Medical Association 2013**)
- ICH Harmonised Tripartite Guidelines for GCP, 1996 (**ICH 1996**) including amendments
- 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 (**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)

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

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

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

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

17.3 Subject confidentiality

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

17.4 Data protection

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

Investigator

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

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

Consistent with the purposes described above, this information may be transmitted to ALK, affiliates and ALK representative, in the investigator's country and other countries, including countries that do not have laws protecting such information.

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 go through a pseudonymisation process, which means that the data cannot be attributed to a specific subject without the use of additional information.

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

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

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

Transfer of data

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

Description of arrangements

To ensure the safekeeping of clinical trial data ALK has standard operating procedures that 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/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 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 and the regulatory authority must be obtained before trial initiation.

17.6 Inspections

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

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

17.7 Protocol amendment and other changes in trial conduct

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

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

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

18 REPORTING AND PUBLICATION

18.1 Integrated clinical trial report

Data will be reported in 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 signatory investigator will review and sign the ICTR.

18.2 Publication of results

ALK retains exclusive ownership of all data, results, reports, findings, discoveries and any other information developed or collected during this trial and ALK shall have the exclusive right to use all such information for any purpose, including, but not limited to, use of the results and data either in the form of 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. It is mandatory that the primary publication is based on data from all trial sites, analysed as stipulated in the protocol.

Authorship is based on the International Committee of the Medical Journal Editors "Uniform Requirements" (Vancouver Declaration).

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

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 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 (EudraCT) no later than 6 months after the trial is completed (the date of last contact (FU-TC) for the last subject in the trial globally), in accordance with relevant international and national regulations regarding public disclosure of clinical trials. No individual de-identified subject data will be shared.

Results of the trial, together with the final protocol will be posted at ClinicalTrials.gov no later than 12 months after the final completion date (the date of last contact (FU-TC) for the last subject in the trial globally). No individual de-identified subject data will be shared.

19 FINANCE AND INSURANCE

ALK subscribes to an insurance policy covering, in its terms and provisions, ALK's 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

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.
Ref Type: Report

Alvarez-Cuesta,E., Bousquet,J., Canonica,G.W., Durham,S.R., Malling,H.J. & Valovirta,E. 2006. Standards for practical allergen-specific immunotherapy. Allergy, 61 Suppl 82, 1-20.

Arbes,S.J., Jr., Gergen,P.J., Elliott,L. & Zeldin,D.C. 2005. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. J Allergy Clin Immunol, 116, 377-383.

Bousquet,J., Van Cauwenberge,P., Khaltaev,N., Aria Workshop Group & World Health Organization 2001. Allergic rhinitis and its impact on asthma. J. Allergy Clin. Immunol., 108, S147-S334.

Calderon,M.A., Kleine-Tebbe,J., Linneberg,A., de,B.F., Hernandez Fernandez de,R.D., Virchow,J.C. & Demoly,P. 2015. House Dust Mite Respiratory Allergy: An Overview of Current Therapeutic Strategies. J Allergy Clin Immunol Pract., 3, 843-855.

Demoly,P., Emminger,W., Rehm,D., Backer,V., Tommerup,L. & Kleine-Tebbe,J. 2016. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet:

Results from a randomized double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol, 137, 444-451.

Des Roches,A., Paradis,L., Bougeard,Y.H., Godard,P., Bousquet,J. & Chanez,P. 1996. Long-term oral corticosteroid therapy does not alter the results of immediate-type allergy skin prick tests. J Allergy Clin Immunol, 98, 522-527.

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.
Ref Type: Report

Gruchalla,R.S., Pongracic,J., Plaut,M., Evans,R., III, Visness,C.M., Walter,M., Crain,E.F., Kattan,M., Morgan,W.J., Steinbach,S., Stout,J., Malindzak,G., Smartt,E. & Mitchell,H. 2005. Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. J Allergy Clin Immunol, 115, 478-485.

ICH . ICH Harmonised Tripartite Guideline Topic E6 (R1): Guideline for Good Clinical Practice. 1996.
Ref Type: Report

Matsuoka,T., Bernstein,D.I., Masuyama,K., Nolte,H., Okamiya,K., Seitzberg,D. & Nelson,H.S. 2017. Pooled efficacy and safety data for house dust mite sublingual immunotherapy tablets in adolescents. Pediatr Allergy Immunol, 28, 661-667.

National Institutes of health . WHO/GINA workshop report: Global Strategy for asthma management and prevention. NIH publication No 02-3659, 1-192. 2002.
Ref Type: Report

Nolte,H., Bernstein,D.I., Nelson,H.S., Kleine-Tebbe,J., Sussman,G.L., Seitzberg,D., Rehm,D., Kaur,A., Li,Z. & Lu,S. 2016. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol, 138, 1631-1638.

Nolte,H., Maloney,J., Nelson,H.S., Bernstein,D.I., Lu,S., Li,Z., Kaur,A., Zieglmayer,P., Zieglmayer,R., Lemell,P. & Horak,F. 2015. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol, 135, 1494-1501.

Okubo,K., Masuyama,K., Imai,T., Okamiya,K., Stage,B.S., Seitzberg,D. & Konno,A. 2016. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. J Allergy Clin Immunol.

Passalacqua,G., Baena-Cagnani,C.E., Bousquet,J., Canonica,G.W., Casale,T.B., Cox,L., Durham,S.R., Larenas-Linnemann,D., Ledford,D., Pawankar,R., Potter,P., Rosario,N., Wallace,D.

& Lockey,R.F. 2013. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language. J Allergy Clin Immunol, 132, 93-98.

Platts-Mills,T.A., Ward,G.W., Jr., Sporik,R., Gelber,L.E., Chapman,M.D. & Heymann,P.W. 1991. Epidemiology of the relationship between exposure to indoor allergens and asthma. Int. Arch. Allergy Appl. Immunol., 94, 339-345.

Reddel,H.K., Taylor,D.R., Bateman,E.D., Boulet,L.P., Boushey,H.A., Busse,W.W., Casale,T.B., Chanez,P., Enright,P.L., Gibson,P.G., de Jongste,J.C., Kerstjens,H.A., Lazarus,S.C., Levy,M.L., O'Byrne,P.M., Partridge,M.R., Pavord,I.D., Sears,M.R., Sterk,P.J., Stoloff,S.W., Sullivan,S.D., Szefler,S.J., Thomas,M.D. & Wenzel,S.E. 2009. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am. J. Respir. Crit Care Med., 180, 59-99.

Sampson,H.A., Munoz-Furlong,A., Campbell,R.L., Adkinson,N.F., Jr., Bock,S.A., Branum,A., Brown,S.G., Camargo,C.A., Jr., Cydulka,R., Galli,S.J., Gidudu,J., Gruchalla,R.S., Harlor,A.D., Jr., Hepner,D.L., Lewis,L.M., Lieberman,P.L., Metcalfe,D.D., O'Connor,R., Muraro,A., Rudman,A., Schmitt,C., Scherrer,D., Simons,F.E., Thomas,S., Wood,J.P. & Decker,W.W. 2006. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 117, 391-397.

The European parliament . Regulation (EU) No 679/2016 General Data Protection Regulation. 2016.
Ref Type: Generic

Virchow,J.C., Backer,V., Kuna,P., Prieto,L., Nolte,H., Villesen,H.H., Ljorring,C., Riis,B. & de,B.F. 2016. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA., 315, 1715-1725.

World Medical Association . Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2013. Adopted by the WMA General Assembly in Helsinki (1964) and as amended by the WMA General Assembly.
Ref Type: Report

Appendix 3: List of suppliers

Clinical Research Organisation (CRO)

Services: Project management, clinical study management, planning of investigator meeting and site monitoring, regulatory and IRB/EC submission, clinical trial non-drug supplies and logistics. Central laboratory and translation services are sub-contracted through CRO.
Name: Syneos Health Netherlands B.V.
Address: De Entrée 99-197, 14th floor, 1101 HE AMSTERDAM, The Netherlands
Phone: +31 20 30 18 579
Mobile: +31 6 25 03 00 27
Web: www.syneoshealth.com

Data management (eCRF):

Services: eCRF
Company Name: Pharma Consulting Group (PCG)
Brand Name: Viedoc
Company Address: Kungsängsvägen 19, 753 23 Uppsala, Sweden

Central Laboratory (sub-contracted through CRO):

Services: Assessment of blood chemistry, hematology and safety urinalysis, and delivering lab kits and urine pregnancy test to sites
Service: Central laboratory
Name: Covance Central Laboratory Services SA
Address: 7 rue Moise-Marcinhes, 1217 Meyrin, Geneva, Switzerland
Phone: +1 317.361.8767
Email: karen.borg@covance.com
Web: www.covance.comServices:

Packaging/labelling of IMP:

Service: Packaging labelling of IMP.
Name: Klifo
Address: Smedeland 36, 2600 Glostrup, Denmark
Phone: +45 44222900
Web: www.klifo.dk

Skin Prick Test:

Service: Distribution of skin prick test
Name: Klifo
Address: Smedeland 36, 2600 Glostrup, Denmark
Phone: +45 44222900
Web: www.klifo.dk

Translation vendor:

Service: Translation of patient facing material
Name: TRANSPERFECT TRANSLATIONS INTERNATIONAL INC
Address: 1250 Broadway, 32nd Fl, New York, NY 10001
Phone: +1 212 689 5555
Web: https://www.transperfect.com/

Text messages for visit reminder:

Service:	SMS text reminders for patients visit
Name:	Signant Health
Address:	785 Arbor Way, Blue Bell, PA 19422
Phone:	+1 267 422 1700
Fax:	+1 215 565 0001
Web:	https://signanthealth.com/

Creative design, copywriting, and printing
Service: Creative design, copywriting, and printing of patient facing material
Name: Creative Studios
Address: 500 Olde Worthington Rd., Westerville, OH 43082
Main Phone: 614-848-4848
Fax: 614-848-3477
Web: https://syenoshealth.com/

Appendix 4: Patient paper diary

In order to aid the AE and concomitant medication reporting, subjects will be given a paper diary to fill in daily. The diary will be used by the subject to help remember details and dates, when discussing AEs and concomitant medication with the investigator at the visits.

The diary will be used to capture 15 pre-specified symptoms/signs.

Subjects and their legal representative will be trained by the investigator or designee at V2 on the proper method to complete the diary. The subject will be instructed to report other symptoms, that are not part of the diary solicited list, to the investigator. The reported symptoms will be discussed with the subjects and medically evaluated by investigator and reported as AEs on the AE form in the eCRF. at the discretion of the investigator. The evaluation of the solicited signs/symptoms should be documented in the medical records.

The English master version of the diary can be seen in its full text below.

Protocol: MT-18	**Diary for registration of medication intake and symptoms**
Treatment period Visit 2-3	
This section should be completed by the clinic	Start date: __/___/____ (day/month/year) Stop date: __/___/____ (day/month/year)

Welcome to the MT-18 study.

As part of this study, you need to complete this Diary each day with support from your parent/caregiver. You will need to do this from the day you start your study medication and then every day for the next 28 days until you come to the clinic for your final visit.

The purpose of this Diary is to register the following on a daily basis:

- to record if you took your study medication as planned
- to record whether you experience any of the listed symptoms after taking your study medication
- to record if you took any medication to treat any of the listed symptoms

Complete this diary each day and bring the diary to the clinic at your next study visit

Date:	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take your study medication today?														
For each day you took your study medication, mark whether or not you experienced any of the symptoms listed below:														
Symptom	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1) Food tasting different														
2) Mouth Ulcer/sore in the mouth														
3) Swelling in the back of the mouth														
4) Itching of the mouth														
5) Itching in the ear														
6) Swelling of the lips														
7) Swelling of the tongue														
8) Tongue pain														
9) Tongue ulcer/sore on the tongue														
10) Throat irritation/tickle														
11) Throat swelling														
12) Stomach pain														
13) Nausea (feel like throwing up)														

14) Vomiting														
15) Diarrhoea														

For each day you experienced any of the above listed symptoms, mark whether or not you took any medications to treat these symptoms

	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take any medication today to treat the symptoms you experienced today?														
Please enter all medications taken today to treat the symptoms you reported above. Please include the symptom (s) treated with this medication. For example "medication x for No 4 " Itching in the mouth"														

If you experienced other symptoms than the ones listed above, please report the symptoms to the study doctor at the next visit.

Date:	Day 8		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take your study medication today?														
For each day you took your study medication, mark whether or not you experienced any of the symptoms listed below:														
Symptom	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1) Food tasting different														
2) Mouth Ulcer/sore in the mouth														
3) Swelling in the back of the mouth														
4) Itching of the mouth														
5) Itching in the ear														
6) Swelling of the lips														
7) Swelling of the tongue														
8) Tongue pain														
9) Tongue ulcer/sore on the tongue														
10) Throat irritation/tickle														
11) Throat swelling														
12) Stomach pain														
13) Nausea (feel like throwing up)														
14) Vomiting														

15) Diarrhoea														

For each day you experienced any of the above listed symptoms, mark whether or not you took any medications to treat these symptoms

	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take any medication today to treat the symptoms you experienced today?														
Please enter all medications taken today to treat the symptoms you reported above. Please include the symptom (s) treated with this medication. For example "medication x for No 4 " Itching in the mouth"														

If you experienced other symptoms than the ones listed above, please report the symptoms to the study doctor at the next visit.

Date:	**Day 15**		**Day 16**		**Day 17**		**Day 18**		**Day 19**		**Day 20**		**Day 21**	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take your study medication today?														
For each day you took your study medication, mark whether or not you experienced any of the symptoms listed below:														
Symptom	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1) Food tasting different														
2) Mouth Ulcer/sore in the mouth														
3) Swelling in the back of the mouth														
4) Itching of the mouth														
5) Itching in the ear														
6) Swelling of the lips														
7) Swelling of the tongue														
8) Tongue pain														
9) Tongue ulcer/sore on the tongue														
10) Throat irritation/tickle														
11) Throat swelling														
12) Stomach pain														
13) Nausea (feel like throwing up)														

14) Vomiting														
15) Diarrhoea														

For each day you experienced any of the above listed symptoms, mark whether or not you took any medications to treat these symptoms

	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take any medication today to treat the symptoms you experienced today?														
Please enter all medications taken today to treat the symptoms you reported above. Please include the symptom (s) treated with this medication. For example "medication x for No 4 " Itching in the mouth"														

If you experienced other symptoms than the ones listed above, please report the symptoms to the study doctor at the next visit.

Date:	Day 22		Day 23		Day 24		Day 25		Day 26		Day 27		Day 28	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take your study medication today?														
For each day you took your study medication, mark whether or not you experienced any of the symptoms listed below:														
Symptom	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
1) Food tasting different														
2) Mouth Ulcer/sore in the mouth														
3) Swelling in the back of the mouth														
4) Itching of the mouth														
5) Itching in the ear														
6) Swelling of the lips														
7) Swelling of the tongue														
8) Tongue pain														
9) Tongue ulcer/sore on the tongue														
10) Throat irritation/tickle														
11) Throat swelling														
12) Stomach pain														
13) Nausea (feel like throwing up)														
14) Vomiting														

15) Diarrhoea

For each day you experienced any of the above listed symptoms, mark whether or not you took any medications to treat these symptoms

	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Did you take any medication today to treat the symptoms you experienced today?														
Please enter all medications taken today to treat the symptoms you reported above. Please include the symptom (s) treated with this medication. For example "medication x for No 4 " Itching in the mouth"														

If you experienced other symptoms than the ones listed above, please report the symptoms to the study doctor at the next visit.

MT-18 protocol
Appendix 5
Preferred terms for solicited AEs and preferred terms in aggregated terms

Trial ID: MT-18

Investigational Medicinal Product: HDM SLIT-tablet

Phase: IV

EudraCT No.: 2020-000446-34

Sponsor: Global Clinical Development
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Table of Contents

1 Solicited signs/symptoms

Preferred terms (PTs) representing the solicited signs/symptoms have been selected (MedDRA 22.1, PTs will be updated to current MedDRA version at the time of reporting).All AEs with these PTs occurring during the 28 days treatment period will be defined as solicited AEs.

Solicited signs/symptoms patient card term	Solicited AE PT
Food taste different	Dysgeusia
Mouth ulcer/sore in the mouth	Mouth ulceration
Swelling of the uvula/back of the mouth	Enlarged uvula
	Oedema uvula
	Palatal swelling
	Palatal oedema
	Mouth swelling
	Oedema mouth
Itching of the mouth	Oral pruritus
Itching in the ear	Ear pruritus
Swelling of the lips	Lip swelling
	Lip oedema
Swelling of the tongue	Swollen tongue
	Tongue oedema
Tongue pain	Glossodynia
Tongue ulcer/sore on the tongue	Tongue ulceration
Throat irritation/tickle	Throat irritation
Throat swelling	Pharyngeal edema
	Pharyngeal swelling
Stomach pain	Abdominal pain upper
	Abdominal pain
Nausea (feel like throwing up)	Nausea
Vomiting	Vomiting
Diarrhea	Diarrhea

2 Systemic allergic reactions including anaphylactic reactions

Cases of possible systemic allergic reaction and/or anaphylaxis are identified by using the following criteria (MedDRA version 22.1, PTs will be updated to current MedDRA version at the time of reporting):

Standardised MedDRA Query (SMQ):

- Anaphylactic reaction, including algorithm:
  - A narrow term from catgory A;
  - A term from category B – (upper airway/respiratory) AND a term from category C – (angioedema/urticaria/pruritus/flush). Events co-occuring within 24 hours.
  - A term from category D – (cardiovascular/hypotension) AND a term from category B – (upper airway/respiratory) OR a term from category C (angioedema/urticaria/pruritus/flush). Events co-occurring within 24 hours.

PT	Scope	Category
Anaphylactic reaction	Narrow	A
Anaphylactic shock	Narrow	A
Anaphylactic transfusion reaction	Narrow	A
Anaphylactoid reaction	Narrow	A
Anaphylactoid shock	Narrow	A
Circulatory collapse	Narrow	A
Dialysis membrane reaction	Narrow	A
Kounis syndrome	Narrow	A
Procedural Shock	Narrow	A
Shock	Narrow	A
Shock symptom	Narrow	A
Type I hypersensitivity	Narrow	A
Acute respiratory failure	Broad	B
Asthma	Broad	B
Bronchial oedema	Broad	B
Bronchospasm	Broad	B
Cardio-respiratory distress	Broad	B
Chest discomfort	Broad	B
Choking	Broad	B
Choking sensation	Broad	B
Circumoral oedema	Broad	B

PT	Scope	Category
Cough	Broad	B
Cyanosis	Broad	B
Dyspnoea	Broad	B
Hyperventilation	Broad	B
Irregular breathing	Broad	B
Laryngeal dyspnoea	Broad	B
Laryngeal oedema	Broad	B
Laryngospasm	Broad	B
Laryngotracheal oedema	Broad	B
Mouth swelling	Broad	B
Nasal obstruction	Broad	B
Oedema mouth	Broad	B
Oropharyngeal oedema	Broad	B
Oropharyngeal spasm	Broad	B
Oropharyngeal swelling	Broad	B
Pharyngeal oedema	Broad	B
Pharyngeal swelling	Broad	B
Respiratory arrest	Broad	B
Respiratory distress	Broad	B
Respiratory failure	Broad	B
Reversible airways obstruction	Broad	B
Sensation of foreign body	Broad	B
Sneezing	Broad	B
Stridor	Broad	B
Swollen tongue	Broad	B
Tachypnoea	Broad	B
Throat tightness	Broad	B
Tongue oedema	Broad	B
Tracheal obstruction	Broad	B
Tracheal oedema	Broad	B
Upper airway obstruction	Broad	B
Wheezing	Broad	B
Acquired C1 inhibitor deficiency	Broad	C

PT	Scope	Category
Allergic oedema	Broad	C
Angioedema	Broad	C
Circumoral swelling	Borad	C
Erythema	Broad	C
Eye oedema	Broad	C
Eye pruritus	Broad	C
Eye swelling	Broad	C
Eyelid oedema	Broad	C
Face oedema	Broad	C
Flushing	Broad	C
Hereditary angioedema with C1 esterase inhibitor deficiency	Broad	C
Injection site urticaria	Broad	C
Lip oedema	Broad	C
Lip swelling	Broad	C
Nodular rash	Broad	C
Ocular hyperaemia	Broad	C
Oedema	Broad	C
Oedema blister	Broad	C
Periorbital oedema	Broad	C
Perorbital swelling	Broad	C
Pruritus	Broad	C
Pruritus allergic	Broad	C
Rash	Broad	C
Rash erythematous	Broad	C
Rash pruritic	Broad	C
Skin swelling	Broad	C
Swelling	Broad	C
Swelling face	Broad	C
Swelling of eyelid	Broad	C
Urticaria	Broad	C
Urticaria papular	Broad	C
Blood pressure decreased	Broad	D

PT	Scope	Category
Blood pressure diastolic decreased	Broad	D
Blood pressure systolic decreased	Broad	D
Cardiac arrest	Broad	D
Cardio-respiratory arrest	Broad	D
Cardiovascular insufficiency	Broad	D
Diastolic hypotension	Broad	D
Hypotension	Broad	D

3 Local swelling or oedema of the mouth and/or throat

Preferred terms (PTs) indicating swelling or oedema in the mouth and/or throat have been selected (MedDRA 22.1, PTs will be updated to current MedDRA version at the time of reporting). AEs with these PTs will be used for summary of the ESI local swelling or oedema if the mouth and/or throat.

PTs for identification of laryngo-pharyngeal swellings/oedemas
Dysphagia
Dysphonia
Epiglottic oedema
Laryngeal dyspnoea
Laryngeal obstruction
Laryngeal oedema
Laryngotracheal oedema
Mouth swelling
Oedema mouth
Oropharyngeal swelling
Oropharyngeal oedema
Palatal oedema
Palatal swelling
Pharyngeal oedema
Pharyngeal swelling
Sensation of foreign body
Suffocation feeling
Swollen tongue
Throat tightness
Tongue oedema
Tracheal oedema

4 Medication errors

Preferred terms (PTs) related to medication errors have been selected by using the following criteria (MedDRA version 22.1, PTs will be updated to current MedDRA version at the time of reporting):

Standardised MedDRA Query (SMQ):

- Medication errors

PTs for identification of medication errors
Accidental device ingestion
Accidental device ingestion
Accidental device ingestion by a child
Accidental exposure to product
Accidental exposure to product by child
Accidental exposure to product packaging
Accidental exposure to product packaging by child
Accidental overdose
Accidental poisoning
Accidental underdose
Accidental use of placebo
Booster dose missed
Circumstance or information capable of leading to device use error
Circumstance or information capable of leading to medication error
Contraindicated device used
Contraindicated product administered
Contraindicated product prescribed
Deprescribing error
Device dispensing error
Device monitoring procedure not performed
Device programming error
Device use confusion
Device use error
Dietary supplement prescribing error
Discontinued product administered
Documented hypersensitivity to administered product
Dose calculation error
Drug administered in wrong device
Drug dispensed to wrong patient
Drug dose omission by device
Drug dose titration not performed
Drug monitoring procedure incorrectly performed

PTs for identification of medication errors
Drug monitoring procedure not performed
Drug titration error
Duplicate therapy error
Expired device used
Expired product administered
Exposure via direct contact
Exposure via eye contact
Exposure via skin contact
Extra dose administered
Failure of child resistant mechanism for pharmaceutical product
Failure to suspend medication
Inadequate aseptic technique in use of product
Inappropriate schedule of product administration
Incomplete course of vaccination
Incorrect disposal of product
Incorrect dosage administered
Incorrect dose administered
Incorrect dose administered by device
Incorrect dose administered by product
Incorrect drug administration rate
Incorrect product administration duration
Incorrect product dosage form administered
Incorrect product formulation administered
Incorrect route of product administration
Intercepted accidental exposure to product by child
Intercepted medication error
Intercepted product administration error
Intercepted product dispensing error
Intercepted product monitoring error
Intercepted product preparation error
Intercepted product prescribing error
Intercepted product selection error
Intercepted product storage error
Intercepted wrong patient selected
Labelled drug-disease interaction medication error
Labelled drug-drug interaction medication error
Labelled drug-food interaction medication error
Lack of administration site rotation
Lack of application site rotation
Lack of infusion site rotation
Lack of injection site rotation

PTs for identification of medication errors
Lack of vaccination site rotation
Medical device monitoring error
Medication error
Multiple use of single-use product
Paravenous drug administration
Poor quality product administered
Product administered at inappropriate site
Product administered to patient of inappropriate age
Product administration error
Product appearance confusion
Product barcode issue
Product confusion
Product design confusion
Product dispensing error
Product dosage form confusion
Product dose omission
Product label confusion
Product monitoring error
Product name confusion
Product packaging confusion
Product preparation error
Product prescribing error
Product selection error
Product storage error
Product substitution error
Recalled product administered
Single component of a two-component product administered
Therapeutic drug monitoring analysis incorrectly performed
Therapeutic drug monitoring analysis not performed
Transcription medication error
Transfusion with incompatible blood
Unintentional use for unapproved indication
Vaccination error
Wrong device used
Wrong dosage form
Wrong dosage formulation
Wrong dose
Wrong drug
Wrong patient received product
Wrong product administered
Wrong product procured

PTs for identification of medication errors
Wrong product stored
Wrong rate
Wrong schedule
Wrong strength
Wrong technique in device usage process
Wrong technique in product usage process
Complication of device insertion
Complication of device removal
Complication of drug delivery system removal
Contraindication to medical treatment
Contraindication to vaccination
Device adhesion issue
Device connection issue
Device difficult to use
Device infusion issue
Device malfunction
Device use issue
Device-device incompatibility
Drug delivery system issue
Drug delivery system malfunction
Exposure to contaminated device
Exposure via contaminated device
Exposure via ingestion
Exposure via inhalation
Exposure via partner
Exposure via unknown route
Implantation complication
Injury associated with device
Interchange of vaccine products
Needle issue
Occupational exposure to product
Occupational exposure to radiation
Overdose
Poor quality device used
Prescribed overdose
Prescribed underdose
Product adhesion issue
Product administration interrupted
Product commingling
Product communication issue
Product compounding quality issue

PTs for identification of medication errors
Product dispensing issue
Product dosage form issue
Product dropper issue
Product expiration date issue
Product identification number issue
Product label issue
Product label on wrong product
Product lot number issue
Product packaging difficult to open
Product packaging issue
Product preparation issue
Product prescribing issue
Product reconstitution quality issue
Product use complaint
Product use in unapproved indication
Product use in unapproved therapeutic environment
Product use issue
Radiation overdose
Radiation underdose
Syringe issue
Treatment noncompliance
Underdose
Unintentional medical device removal

5 Drug abuse, misuse and overdose

Preferred terms (PTs) related to drug abuse, misuse and overdose have been selected by using the following criteria (MedDRA version 22.1):

Standardised MedDRA Query (SMQ):

- Drug abuse and dependence

PTs for identification of drug abuse, misuse and overdose
Dopamine dysregulation syndrome
Drug abuse
Drug abuser
Drug dependence
Drug dependence, antepartum
Drug dependence, postpartum
Drug use disorder
Drug use disorder, antepartum
Drug use disorder, postpartum
Intentional overdose
Intentional product misuse
Maternal use of illicit drugs
Neonatal complications of substance abuse
Substance abuse
Substance abuser
Substance dependence
Substance use disorder
Accidental overdose
Dependence
Disturbance in social behaviour
Drug detoxification
Drug diversion
Drug level above therapeutic
Drug level increased
Drug screen
Drug screen positive
Drug tolerance
Drug tolerance decreased
Drug tolerance increased
Intentional product use issue
Medication overuse headache
Narcotic bowel syndrome
Needle track marks
Overdose

PTs for identification of drug abuse, misuse and overdose
Prescription drug used without a prescription
Prescription form tampering
Reversal of opiate activity
Substance use
Substance-induced mood disorder
Substance-induced psychotic disorder
Toxicity to various agents