COVERPAGE MT-11 TRIAL PROTOCOL

Official trial title	A phase III trial evaluating the efficacy and safety of the house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet in children and adolescents (5-17 years) with HDM allergic asthma
NCT number	NCT03654976
Document date	18-Feb-2021

Clinical Trial Protocol for US

Trial ID: MT-11

Title of Trial

A phase III trial evaluating the efficacy and safety of the house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet in children and adolescents (5-17 years) with HDM allergic asthma

Investigational Medicinal Product: HDM SLIT-tablet

Phase: III

EudraCT No.: 2016-004363-39
IND No: 17691

Sponsor: Global Clinical Development
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Table of abbreviations

ACQ	Asthma control questionnaire
AE	Adverse event
AIT	Allergy immunotherapy
ALK	ALK-Abelló A/S
ALT	Alanine aminotransferase
AMP	Auxiliary Medicinal Product
AR	Allergic rhinitis
AST	Aspartate aminotransferase
BP	Blood pressure
CHMP	The Committee for Medicinal Products for Human Use
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRF	Case report form
CSMS	Combined symptom and medication score (recommended by EAACI task force (**Pfaar et al. 2014**))
D. farinae	*Dermatophagoides farinae*
D. pteronyssinus	*Dermatophagoides pteronyssinus*
DMC	Data monitoring committee
DMS	Daily medication score
DSS	Daily symptom score
eCRF	Electronic case report form
eDiary	Electronic diary
EMA	European Medicines Agency
EMEA	European Medicines Agency
EudraCT	European Union drug regulating authorities clinical trials database
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSFV	First subject first visit
FVC	Forced vital capacity
GCP	Good clinical practice
GINA	Global initiative for asthma
GLMM	Generalised linear mixed model
HDM	House dust mite
IB	Investigator's brochure
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
ICS	Inhaled corticosteroid
ICTR	Integrated clinical trial report
IEC	Independent ethics committee
IgE	Immunoglobulin E
IgE-BF	Immunoglobulin E blocking factor

IgG4	Immunoglobulin G4
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine system
LABA	Long-acting β_2-agonist
LDH	Lactate dehydrogenase
LR	Likelihood ratio
LSLV	Last subject last visit
LTRA	Leukotriene receptor antagonist
MAR	Missing at random
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effect model repeated measurement
NB	Negative binominal
NIH	National Institutes of Health
OCS	Oral corticosteroid
[redacted]	[redacted]
PDCO	Paediatric Committee
PEF	Peak expiratory flow
[redacted]	[redacted]
SABA	Short-acting β_2-agonist
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCIT	Subcutaneous immunotherapy
[redacted]	[redacted]
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLIT	Sublingual immunotherapy
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPT	Skin prick test
SSR	Sample size reassessment
TC	Telephone call
TCRS	Total combined rhinitis score
TCS	Total combined score
UN	Unscheduled visit
USPI	United States Prescribing Information
VAS	Visual analogue scale
WAO	World Allergy Organisation

WHO	World Health Organisation

Table of definitions

Background treatment	Standard of care treatment administered to all subjects in addition to the investigational medicinal product (IMP), in agreement with the European Medicines Agency (EMA) Definition of Investigational Medicinal products (IMPs) and use of Auxiliary Medicinal Products (AMPs) consultation document (**EMA 2016a**). The background treatment in this trial is low dose inhaled corticosteroid (ICS) plus long-acting β_2-agonists (LABA) or medium/high dose ICS with or without LABA
Clinically relevant asthma exacerbation	• Doubling of ICS dose compared to background treatment, or • Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, or • Emergency room visit due to asthma, requiring systemic corticosteroids, or • Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids
Completed subject	A randomised subject is considered as completed if he/she has not discontinued the trial
Concomitant medication	All medications being continued by a subject on entry into the trial and all medications given in addition to the background treatment during the trial, e.g. montelukast
End of trial	The end of trial is defined as the date of the last subject last visit
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
Life-threatening asthma	Asthma worsening that requires intubation and/or is associated with hypercapnia requiring non-invasive ventilator support
Rescue medication	Medicinal products provided by ALK when the efficacy of the IMP is not sufficient or likely to cause an adverse event (AE) to the subject or to manage an emergency situation in relation to HDM allergy symptoms in agreement with the EMA Definition of IMPs and use of AMPs consultation document (**EMA 2016a**). The asthma rescue medication in this trial is • Oral corticosteroid (OCS) • Short-acting β_2-agonist (SABA) • Additional ICS for treatment of asthma exacerbations (optional)

	The rhinoconjunctivitis rescue medication in this trial is • Antihistamine tablets/solution • Antihistamine eye drops • Corticosteroid nasal spray Rescue medication for severe allergic reaction in countries where this is a regulatory requirement: • Adrenaline/epinephrine auto-injector
Severe asthma exacerbation	• Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, or • Emergency room visit due to asthma, requiring systemic corticosteroids, or • Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids
Solicited AE	An AE recorded by the investigator at visit 4 based on the symptoms reported in the subject's eDiary during the first 28 days after randomisation
Source documents	Source documents are original documents, data, and records from which the subjects' electronic case report form (eCRF) data are obtained. These include, but are not limited to, hospital records (from which medical history and concomitant medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence
Systemic corticosteroids	Oral, intramuscular, or intravenously administered corticosteroids
Trial completion	The trial is completed once the integrated clinical trial report (ICTR) is signed

Table of revisions

Date	Version	Description of document
12-Jul-2017	1.0	Final protocol
07-Aug-2017	2.0	Final protocol
31-Aug-2017	3.0	Final protocol
25-Jan-2018	4.0	UK – Amendment due to request from HRA REC. Amendment only applicable in the UK
02-Feb-2018	5.0	German amendment due to request from the Paul Erhlich Institute, Germany. Amendment only applicable in Germany
21-Sep-2018	6.0	US specific amendment due to request from the Food and Drug Administration and incorporating the UK and Germany country-specific amendment
21-Sep-2018	7.0	Europe specific amendment due to request from the Food and Drug Administration and incorporating the UK and Germany country-specific amendment
13-May-2019	8.0	Europe specific amendment to expand the period of randomisation and to accommodate the upcoming change of the European Union trial regulation, No 536/2014
15-May-2019	9.0	US specific amendment to expand the period of randomisation and to accommodate the upcoming change of the European Union trial regulation, No 536/2014
11-Nov-2020	10.0	Europe specific amendment to include COVID-19 measures, extend the recruitment period, add an additional SSR due to COVID-19 impact and to align the new SSR with previous SSR updates in the statistical analysis plan.
11-Nov-2020	11.0	US specific amendment to include COVID-19 measures, extend the recruitment period, add a second SSR due to COVID-19 potential impact on power and to align the new SSR with previous SSR updates in the statistical analysis plan.
18-Feb-2021	12.0	US specific amendment to include updated versions of “MT-11 remote visit 11 guidance during the COVID-19 pandemic”, “MT-11 remote visit 4-10 guidance during the COVID-19 pandemic” and “MT-11 site-to-patient shipments of trial medication” (appendices 7-9) in order to implement home pregnancy testing during remote visits caused by COVID-19.

Protocol synopsis

Title of trial: A phase III trial evaluating the efficacy and safety of the house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet in children and adolescents (5-17 years) with HDM allergic asthma

Trial ID: MT-11

Development phase: Paediatric phase III

Regulatory trial identifier: EudraCT No: 2016-004363-39

IND No: 17691

Objectives:

The primary objective is to demonstrate efficacy of the HDM SLIT-tablet versus placebo as add-on treatment in children and adolescents (5-17 years) with HDM allergic asthma based on clinically relevant asthma exacerbations after at least 4 months of treatment.

For this trial, clinically relevant asthma exacerbations are defined by at least one of the following criteria:

- Doubling of ICS dose compared to background treatment
- Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
- Emergency room visit due to asthma, requiring systemic corticosteroids
- Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids

The key secondary objectives are to demonstrate efficacy of the HDM SLIT-tablet versus placebo after at least 4 months as add-on treatment in children and adolescents with HDM allergic asthma with respect to:

- Nocturnal awakening due to asthma which require SABA rescue medication
- Rescue medication use (SABA)
- Lung function (FEV_1)

Additional secondary objectives, based on endpoints measured at different timepoints throughout the trial, are to evaluate the HDM SLIT-tablet versus placebo for treatment of HDM allergic asthma with respect to:

- Asthma symptoms
- Asthma control

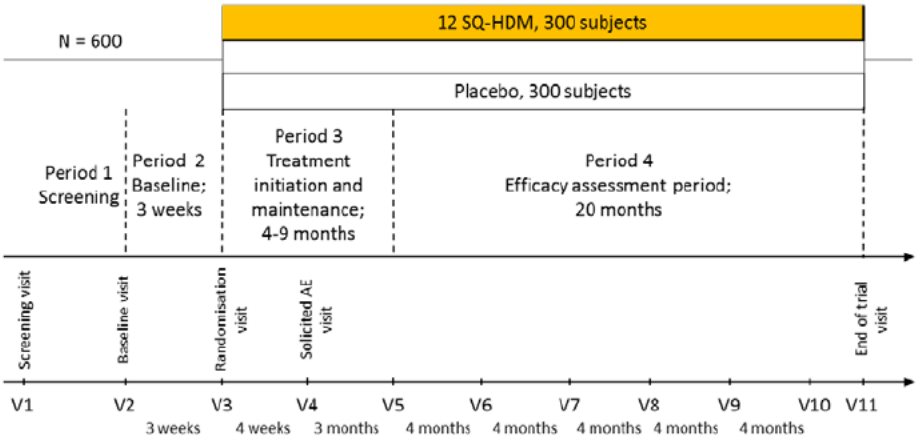
- Severe asthma exacerbations[1]
- Treatment of HDM allergic rhinitis (AR)
- Treatment of HDM allergic rhinoconjunctivitis
- The changes in immunological parameters
- The safety and tolerability

The exploratory objectives are to evaluate:

- [redacted]

Trial design:

This trial is a randomised, parallel-group, double-blind, placebo-controlled multi-national phase III trial conducted in Europe and North America. Subjects will be randomised (1:1) to receive treatment with the HDM SLIT-tablet or placebo.



Period 1 is the screening period. Subjects screened before 10 April 2018 will be included in cohort 1. Subjects screened between 10 April 2018 and 10 April 2019 will be included in cohort 2. Subjects screened between 10 April 2019 and 10 April 2020 will be included in cohort 3. Subjects screened between 01 August 2021 and 10 April 2022 will be included in a cohort 4.

Period 2 is the baseline period of 3 weeks following screening. For cohort 1, the baseline period is during Q1 - Q2 2018. For cohort 2, the baseline period is during Q4 2018 - Q2 2019. For cohort 3 , the baseline period is during Q4 2019 - Q2 2020. For cohort 4, the baseline period will occur during Q4 2021 – Q2 2022.
During the baseline period, eligible subjects or their parent/caregiver will fill in their asthma and rhinoconjunctivitis

[1] A severe asthma exacerbation is defined as one of the following criteria: a) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, or b) Emergency room visit due to asthma, requiring systemic corticosteroids, or c) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids.

symptoms and medication use in an electronic diary (eDiary). Subjects will continue with their regular asthma background treatment. With the exception of additional sponsor provided ICS, which is optional, the subjects' regular asthma rescue medication and rhinoconjunctivitis rescue medication must be replaced with the rescue medication provided by ALK at visit 2.

Period 3 is the treatment initiation and maintenance period to allow the treatment with the HDM SLIT-tablet to take effect. It starts at randomisation and lasts for at least 4 months. The period ends on 1 September 2018 for cohort 1, on 1 September 2019 for cohort 2, on 1 September 2020 for cohort 3, and on the 1 September 2022 for cohort 4.
During the first 28 days of period 3, pre-specified symptoms occurring after IMP intake will be recorded by the subject/parent/caregiver in the eDiary. The reported symptoms will be evaluated by investigator and reported in the eCRF as solicited AEs.

Period 4 is the efficacy assessment period. Period 4 lasts until the end of trial or discontinuation from IMP and during this period, the rate of clinically relevant asthma exacerbations will be evaluated from 1 September 2018 to 30 April 2020 (cohort 1), 1 September 2019 to 30 April 2021 (cohort 2), 1 September 2020 to 30 April 2022 (cohort 3), and 1 September 2022 to 30 April 2024 (Cohort 4).

Subjects will be treated for 24-30 months in total since subjects can commence treatment in a predefined period lasting from 1 November until 10 April. The efficacy period starts on 1 September for all subjects resulting in a pretreatment period of 4 to 10 months. The efficacy period ends 30 April for all subjects. As a result, some subjects may have 5-6 months between visit 10 and 11 while others may have their last visit 11 on the same day as visit 10. Subjects with less than 1 month between visit 10 and 11 will only have one visit to the clinic where all the procedures of 11 are performed.

Approximately every 4 months after randomisation, subjects or their parent/caregiver will be asked to complete the eDiary for a period of 14 days 3 weeks prior to V5 (at 4 months), V6 (at 8 months), V7 (at 12 months), V8 (at 16 months), V9 (at 20 months), V10 (at 24 months) and V11 (25-30 months).

Subject safety precautions:

All subjects will be provided with an Asthma Action Plan to provide guidance to effectively manage the subject's symptoms, and asthma rescue medication (OCS, SABA and a separate inhaler with ICS).

Subjects experiencing 2 severe asthma exacerbations within 12 consecutive months or 1 hospitalisation due to asthma requiring

treatment with systemic corticosteroids must be discontinued from the IMP treatment and should continue in the trial.

Subjects will be provided with a Local and Systemic Allergic Reaction Emergency Plan . In countries where it is a regulatory requirement, subjects will also be provided with an adrenaline/epinephrine auto-injector.

Trial safety precautions:

A sponsor independent data monitoring committee (DMC) will monitor the subjects' safety data in an unblinded fashion. The DMC Charter will specify the frequency of the DMC meetings.

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

1. Treatment-related death of an individual;
2. Treatment-related anaphylactic shock in at least 2 subjects[2] 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 blood pressure (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 plus (2 x age) from 1 to 10 years, and less than 90 mmHg for 11 to 17 years of age.
3. A substantial increase in the rate of clinically relevant asthma exacerbations during period 3 defined by the following two criteria:
    a. the rate of clinically relevant asthma exacerbations in the active treatment arm is at least 3 times higher than the expected background rate (≥3*1.4 = ≥4.2 exacerbations/subject/year) AND
    b. the rate of clinically relevant asthma exacerbations in the active treatment arm is at least 3 times higher than the rate observed in the placebo arm

    The DMC will monitor the rate of clinically relevant asthma exacerbations during period 3 to be able to pause the trial for safety review should a substantial increase in the active treatment arm compared to placebo occur.

IMP intake may only be resumed after the information has been presented to health authorities, and health authorities concur with continued IMP intake. In case of complete premature IMP discontinuation, participating investigators, subjects, caregivers,

[2] 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.

the IRB/IEC, and the relevant health authorities will be promptly informed.

Trial schedule:

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
First subject first visit (FSFV)	Q1 2018	Q3 2018	Q3 2019	Q3 2021
Last subject randomised	Q2 2018	Q2 2019	Q2 2020	Q2 2022
Last subject last visit (LSLV)	Q2 2020	Q2 2021	Q2 2022	Q2 2024

Duration of treatment per subject: 24-30 months

End of trial is defined as LSLV for the last cohort initiated

Trial population:

Subjects randomised in this trial will be children and adolescents 5-17 years of age, with HDM allergic asthma who are at risk of asthma exacerbations despite being on treatment with low dose ICS plus LABA or medium/high dose ICS with or without LABA and who have HDM allergic rhinitis (AR).

45% of the subjects will be 5-11 years of age in accordance with the recommendation of EMA Paediatric Committee (PDCO Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy.

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

Inclusion criteria:

I1. Written informed consent obtained from parents/caregivers before any trial related procedures are performed[3]. Consent or assent from the subject must be obtained according to national requirements.

I2. Male or female of any race/ethnicity aged ≥4 to ≤17 years on the day informed consent is obtained from the parent/caregiver. The subject must be ≥5 to ≤17 years old at the randomisation visit

I3. A female subject of childbearing potential[4] must have a negative pregnancy test and be willing to practise appropriate[5] contraceptive methods until the follow-up telephone call (TC)

[3] At least one parent/caregiver must be able to read.
[4] Females, after the first menstrual period.
[5] 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.

I4. A clinical history of HDM allergic asthma of at least 1 year duration diagnosed by a physician[6]

I5. Use of low daily dose of ICS plus LABA or medium/high daily dose of ICS with or without LABA for the control of asthma symptoms within the past year prior to randomisation. For definition of ICS doses please see Table 3 and Table 4

I6. ≥3 clinically relevant asthma exacerbations[7] in the past two years or ≥2 clinically relevant asthma exacerbations in the past year or ≥1 severe asthma exacerbation[8] in the past year prior to randomisation while being on asthma controller medication (low dose ICS plus LABA or medium/high dose ICS with or without LABA)[9]. The asthma controller medication at the screening visit must be at a dose equivalent to or below the dose the subject received before the last asthma exacerbation occurred

I7. One or more of the following within the past 4 weeks prior to randomisation:

a. Daytime asthma symptoms more than twice/week

b. Any nocturnal awakening due to asthma which require use of SABA rescue medication

c. SABA rescue medication needed for treatment of asthma symptoms more than twice/week

d. Any activity limitation due to asthma

I8. Lung function measured by FEV_1 ≥ 70% of predicted value[10] or according to local requirements while on background treatment following at least a 6-hour washout of SABA at screening and randomisation

I9. Clinical history of HDM AR within the last year prior to randomisation[11]

I10. An average total combined rhinitis score (TCRS) > 0 during the baseline period (period 2)

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.*

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

[7] A clinically relevant asthma exacerbation is defined as at least one of the following criteria: a) Doubling of ICS dose compared to background treatment, b) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, c) Emergency room visit due to asthma, requiring systemic corticosteroids or d) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids.

[8] A severe asthma exacerbation is defined as at least one of the following: a) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, b) Emergency room visit due to asthma, requiring systemic corticosteroids or c) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids.

[9] One asthma exacerbation within the last year must be documented including asthma medication and dosage immediately prior to this exacerbation.

[10] Interpretation of normal range for spirometric test should be based on the Quanjer reference equations (Quanjer et al. 1995).

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

I11. Positive specific immunoglobulin E (IgE) (defined as ≥class 2, ≥0.70 kU/l) against *Dermatophagoides pteronyssinus (D. pteronyssinus)* and/or *Dermatophagoides farinae (D. farinae)* at screening

I12. Positive skin prick test (SPT)[12] to *D. pteronyssinus* and/or *D. farinae* at screening

I13. Subject willing and able to comply with trial protocol

Exclusion criteria:

E1. Has a clinically relevant history and is sensitised, symptomatic, and regularly exposed to animal dander, molds, and/or cockroach (e.g., present in the home, job, school, etc.) or other perennial allergen

E2. Has experienced a life-threatening asthma attack defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia requiring non-invasive ventilator support

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

E4. Within the last 3 months before the randomisation visit (visit 3) while on high dose ICS treatment, has had an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalisation, or treatment with systemic corticosteroids

E5. SLIT treatment with *D. pteronyssinus* or *D. farinae* for more than 1 month within the last 5 years. In addition, any SLIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months

E6. Subcutaneous immunotherapy (SCIT) treatment with *D. pteronyssinus* or *D. farinae* reaching the maintenance dose within the last 5 years. In addition, any SCIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months

E7. Ongoing treatment with any allergy immunotherapy product

E8. Severe chronic oral inflammation

E9. Any nasal or naso/oropharyngeal condition that could confound the efficacy or safety assessments (e.g., hypertrophy of the pharyngeal/palatine tonsils, clinically relevant nasal polyps, a history of paranasal sinus surgery or surgery of nasal turbinates)[13]

[12] A positive SPT is defined in the SPT Guideline. Briefly, for subjects in North America, a positive SPT is defined as a wheal size ≥5 mm larger than the negative control. For subjects in Europe, a positive SPT is defined as a wheal size ≥3 mm.
[13] If in doubt, nasal endoscopy is recommended

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

E11. Has a diagnosis or history of eosinophilic oesophagitis

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. Ongoing treatment with OCS

E15. Treatment with restricted and prohibited concomitant medication listed in Table 2

E16. Treatment with an investigational drug within 30 days/5 half-lives of the drug (which ever longest) prior to screening

E17. A history of allergy, hypersensitivity or intolerance to any of the excipients or active substance of the IMP (except *D. pteronyssinus* and *D. farinae*) or to any excipient of the rescue medication provided in this trial

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

E19. A history of alcohol or drug abuse

E20. Has previously been randomised 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

E21. Has 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

E22. Has a condition or treatment that increase the risk of the subject developing severe adverse reactions after adrenaline/epinephrine administration

E23. Is unable to or will not comply with the use of adrenaline/epinephrine auto-injectors for countries where this is a regulatory requirement

Assessments:

<u>The following data will be collected:</u>

- Demographics

- Medical history
- Concomitant medication
- Asthma history, including, but not limited to the history of asthma symptoms and exacerbations
- Rhinitis, conjunctivitis, atopic dermatitis and food allergy medical history
- Adverse events (AEs)
- Vital signs
- Height and weight
- Physical examination
- Pregnancy test results (only applicable for female subjects of childbearing potential)
- Clinical safety laboratory (blood chemistry, hematology, urinalysis)[14]
- SPT

Biomarker assessments:

- Immunological and serological parameters such as IgE, IgG_4 and IgE-blocking factor (IgE-BF) and other antibody isotypes against relevant allergens as well as other serological components
- Pharmacogenetics

[14] Haematology: Erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelets, leukocytes, neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Blood chemistry: Creatinine, urea, sodium, potassium, chloride, calcium, glucose, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/ serum glutamic-oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT) and lactate dehydrogenase (LDH). Urinalysis: pH, protein, glucose, ketone, leukocytes, urobilinogen, bilirubin, blood, nitrite and specific gravity.

Efficacy assessments:

- Clinically relevant asthma exacerbations
- Severe asthma exacerbations
- Asthma symptom score
- Asthma rescue medication use
- Lung function (FEV_1)
- Nocturnal awakenings requiring SABA use
- Rhinoconjunctivitis symptom score
- Rhinoconjunctivitis rescue medication use
- Asthma control questionnaire (ACQ or ACQ-IA)
- Global evaluation of asthma
- Global evaluation of AR

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Trial endpoints:

The primary endpoint of the trial is the annualised rate of clinically relevant asthma exacerbations calculated as the number per year per subject during the efficacy evaluation period (period 4).

A clinically relevant asthma exacerbation must be medically confirmed and is defined as asthma worsening leading to at least one of the following criteria:

- Doubling of ICS dose compared to background treatment

- Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
- Emergency room visit due to asthma, requiring systemic corticosteroids
- Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids

The key secondary endpoints are:

- Proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication during the 14 days eDiary recording every 4 months after randomisation
- The average daily dose of SABA during the 14 days eDiary recording every 4 months after randomisation
- Percentage predicted FEV_1 assessed every 4 months after randomisation

Additional secondary efficacy endpoints are:

- Time to first clinically relevant asthma exacerbation
- Time to recurrent clinically relevant asthma exacerbation
- Rate of severe asthma exacerbation during the efficacy period (period 4), defined as asthma worsening leading to at least one of the following criteria:
    - Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
    - Emergency room visit due to asthma, requiring systemic corticosteroids
    - Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids
- Time to first severe asthma exacerbation
- Time to recurrent severe asthma exacerbations
- ACQ or ACQ-IA

Endpoints derived from the two week daily diary collected every 4 months after treatment initiation include:

- The average TCRS (TCRS is the sum of the rhinitis daily symptom score (DSS) and the rhinitis daily medication score (DMS)).
- Average rhinitis DSS
- Average rhinitis DMS

- Average rhinoconjunctivitis total combined score (TCS)
- Average rhinoconjunctivitis DSS
- Average rhinoconjunctivitis DMS
- The average combined symptom and medication score (CSMS)
- Rhinoconjunctivitis visual analogue scale (VAS)
- Average asthma DSS
- Asthma VAS
- Global evaluation of allergic asthma
- Global evaluation of AR

The immunology endpoints are:

- Changes from baseline in specific IgE, IgE-BF and IgG_4 to *D. pteronyssinus* and *D. farinae* measured at visit 7 and visit 11

The safety and tolerability endpoints are:

- Treatment-emergent AEs , solicited AEs, IMP-related AEs, treatment-emergent serious AEs (SAEs), treatment-emergent AEs leading to discontinuation, time to discontinuations due to treatment-emergent AEs
- Vital signs, FEV_1, clinical laboratory values and physical examination during treatment and at the last visit (V11)

The explorative endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Trial medication:

Investigational medicinal product:

Active treatment

Active ingredients:	Standardised allergen extract from the HDMs *D. pteronyssinus* and *D. farinae*
Dosage form:	Oral lyophilisate
Dose/Strength:	12 SQ-HDM
Excipients:	Gelatine (fish source), mannitol and sodium hydroxide

Placebo treatment

Active ingredients:	None
Dosage form:	Oral lyophilisate
Dose/Strength:	Placebo
Excipients:	Gelatine (fish source), mannitol and sodium hydroxide

Asthma background treatment:

Subjects stay on the asthma background treatment (low dose ICS plus LABA or medium/high dose ICS with or without LABA) they were on before entering the trial.

If a subject presents with worsening of asthma symptoms, investigator or designee should always evaluate if the subject requires treatment at emergency room. If emergency room visit is not required initial treatment can be either:

- Doubling of ICS dose compared to background treatment for 2 weeks, or
- Systemic corticosteroids for treatment of asthma symptoms

For the doubling of ICS dose a separate inhaler with ICS will be provided by ALK as part of the asthma rescue medication. Subjects may also double their ICS dose by using their background medication. Subjects that receive high dose ICS as

background treatment are not allowed to double the dose of ICS. Please note that local regulations and Summary of product characteristics (SmPCs) / United States Prescribing Information (USPI) must be followed.

In case of an asthma exacerbation requiring systemic corticosteroids, the subjects should be treated with OCS in the form of Prednisolone/Prednisone tablets. Dosing regimen should follow recommendations by GINA guideline (**GINA Executive Committee 2017**), NIH guidelines (**National Heart Lung and Blood Institute 2007**) or national guidelines (**Reddel et al. 2009**). See Section 8.3.

Asthma rescue medication:

- Salbutamol, inhaler 100 µg/dose
- Prednisolone or Prednisone tablets, 5 mg
- Budesonide, inhaler 100 µg/dose and/or 200 µg/dose
- Fluticasone propionate inhaler 50 µg/dose

Rhinoconjunctivitis rescue medication:

- Desloratadine tablets, 5 mg
- Desloratadine, oral solution, 0.5 mg/ml
- Azelastine eye drops, 0.5 mg/ml
- Mometasone furoate nasal spray, 50 µg/dose

The above generic names of rescue medication are the International Nonproprietary Names. Synonymous generic names may be used in local labelling.

For the inhalers, the strength and dosage may be stated differently in local labelling; nominal dosage or the dosage as being delivered by the device. For example, the nominal strength for Fluticasone propionate, 50 µg/dose, may be labelled as 44 µg delivered per actuation.

Rescue medication for severe allergic reaction in countries where this is a regulatory requirement:

- Adrenaline/epinephrine auto-injector, dose selection should follow SmPC/USPI for product, i. e. for
    - Epipen:
        - For children <25 kg; 0.15 mg
        - For children ≥25 kg; 0.3 mg
    - Adrenaclick (Anapen):
        - For children <30 kg; 0.15 mg
        - For children ≥30 kg; 0.3 mg

The use of leukotriene receptor antagonists (LTRA) is permitted as concomitant medication for continued use on same dose only but will not be provided.

Flow chart

Table 1 Flow chart[15]

Visit ID:	V1	TC1	V2	TC2	V3	V4	TC3, 4	V5	TC5, 6, 7	V6	TC8, 9, 10	V7	TC11, 12, 13	V8	TC14, 15, 16	V9	TC17, 18, 19	V10[16]	TC20[17]	V11[18]	TC21	UN
Visit:	Screening	Retention	Baseline	Mid baseline call	Randomisation	Visit 4		Visit 5		Visit 6		Visit 7		Visit 8		Visit 9		Visit 10		Final visit	Follow-up	Unscheduled visit
Time[19] from randomisation (IMP initiation) for all visits and TCs, except for visit 11 (actual date of visit)	Max 12 wk before V3		- 3 wk - 7 d	- 2 wk ± 2 d	-	+ 4 wk + 7 d	+ 2m ±2d + 3m ±2d	+ 4m ± 7 d	+ 5m ±2d + 6m ±2d + 7m ±2d	+ 8m ± 7 d	+9m ±2d +10m ±2d +11m ±2d	+ 12m ± 7 d	+13m ±2d +14m ±2d +15m ±2d	+ 16m ± 7 d	+17m ±2d +18m ±2d +19m ±2d	+ 20m ± 7 d	+21m ±2d +22m ±2d +23m ±2d	+ 24m ± 7 d	2 wk prior to V11 ± 2 d	30 Apr ± 7 d	+ 2 wk from V11 + 7 d	
Informed consent and assent[20]	X																					
Demography	X																					
Medical history incl. evaluate previous asthma exacerbations	X																					
SPT[21]	X		(X)																			
Review of in-/exclusion criteria	X		X		X																	

[15] To the extent possible, all examinations scheduled for the final visit must be performed on subjects who receive the IMP but do not complete the trial according to the protocol. If poss ble, the TC follow-up (TC21) should be performed and the corresponding eCRF pages should be filled in.

[16] Visit 10 is not applicable for subjects randomised in cohort 1 after 31-Mar-2018; for subjects randomised in cohort 2 after 31-Mar-2019, for subjects randomised in cohort 3 after 31-Mar-2020 and for subejcts randomised in cohort 4 after 31-Mar-2022, if applicable.

[17] TC20 performed 2 weeks prior to final visit.

[18] Visit 11 will take place on 30-Apr-2020 ± 7 days for cohort 1, 30-Apr-2021 ± 7 days for cohort 2, 30-Apr-2022 ± 7 days for cohort 3 and 30-Apr-2024 ± 7 days for cohort 4.

[19] One month (m) is considered 30 days.

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

[21] If medication that could interfere with the SPT, according to Table 9, has not been washed out and the positive control is <3 mm for subjects in Europe or < 5 mm for subjects in North America, the SPT must be repeated after the interfering medication has been washed out.

Visit ID:	V1	TC1	V2	TC2	V3	V4	TC3, 4	V5	TC5, 6, 7	V6	TC8, 9, 10	V7	TC11, 12, 13	V8	TC14, 15, 16	V9	TC17, 18, 19	V10[16]	TC20[17]	V11[18]	TC21	UN
Randomisation					X																	
Physical examination[22]	X																			X		(X)
Oropharyngeal Examination			X		X[23]	X		X		X		X		X		X		X				(X)
Height and weight[24]	X		X		X	X		X		X		X		X		X		X		X		X
Vital signs	X		X		X	X		X		X		X		X		X		X		X		(X)
FEV_1 [25]	X		X		X	X		X		X		X		X		X		X		X		X
Urine pregnancy test, if applicable[26]	X		X		X	X		X		X		X		X		X		X		X		(X)
Blood and urine samples for safety laboratory assessments	X											X								X		(X)
Blood sample for specific IgE[27]	X	(X)[28]																				(X)
Recording of asthma exacerbations[29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess and record AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[30]	X
Assess eosinophilic oesophagitis	X		X		X	X		X		X		X		X		X		X		X		(X)
Record concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[22] Oropharyngeal examination is included in physical examination
[23] Oropharyngeal examinations will be done before and 60 mins after IMP administration at Visit 3, see section 9.2.
[24] If applicable, adjust the Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan
[25] Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA.
[26] For female subjects of childbearing potential, additional urine pregnancy tests should be performed during the trial, if a menstrual period is missed.
[27] IgE against *D pteronyssinus, D farinae, Cladosporium herbarum* and *Blattella germanica*
[28] Inform subjects of continued participation in trial depending on the blood sample for specific IgE against *D. pteronyssinus* and *D. farinae*
[29] In case of an asthma exacerbation the subject should be called in for an unscheduled visit.
[30] If an AE was ongoing at the previous visit, if a new AE is identified at the telephone contact or if one of the safety laboratory parameters measured at the previous visit showed a clinically significant abnormality, the subject could be asked to return to the trial site.

Visit ID:	V1	TC1	V2	TC2	V3	V4	TC3, 4	V5	TC5, 6, 7	V6	TC8, 9, 10	V7	TC11, 12, 13	V8	TC14, 15, 16	V9	TC17, 18, 19	V10[16]	TC20[17]	V11[18]	TC21	UN
[redacted]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Issue and review Asthma Action Plan[31]			X																			
Issue and review Local and Systemic Allergic Reaction Emergency Plan [32]			X		X																	
ACQ or ACQ-IA					X			X		X		X		X		X		X		X		X
[redacted][33]					X			X		X				X				X		X		X
[redacted]					X					X										X		X
[redacted][34]			X					X				X				X				X		X
[redacted]			X		X			X		X		X		X		X		X		X		X
Global Evaluation (asthma and AR)																				X		
Blood sample for Immunological assessments					X							X								X		(X)
Blood sample for pharmacogenetics					X															X		
Biobank blood and urine sample					X							X								X		
Dispense IMP					X			X		X		X		X		X		X				(X)
Intake of IMP at clinic					X[35]																	(X)

[31] Dispense Peak Expiratory Flow (PEF) meters.

[32] Instruct in the use of rescue medication for severe allergic reaction, in countries where it is a regulatory requirement.

[33] [redacted]

[34] [redacted]

Visit ID:	V1	TC1	V2	TC2	V3	V4	TC3, 4	V5	TC5, 6, 7	V6	TC8, 9, 10	V7	TC11, 12, 13	V8	TC14, 15, 16	V9	TC17, 18, 19	V10[16]	TC20[17]	V11[18]	TC21	UN
Dispense asthma and rhinoconjunctivitis rescue medication[36]			X		X	X		X		X		X		X		X		X				(X)
Evaluate inhalation technique			X									X										
Collect IMP, perform compliance check and drug accountability								X		X		X		X		X		X		X		
Collect rescue medication as applicable and perform drug accountability					X	X		X		X		X		X		X		X		X		
Show and discuss Trial video			X																			
Issue and instruct in the use of an eDiary			X																			
Instruct in the recording of prespecified symptoms in eDiary					X																	
Review eDiary and record solicited AEs in eCRF						X																
Activate eDiary for the next period			X		X	X		X		X		X		X		X		X				
Daily eDiary recording					-3 wk	-4 wk[37]		-3 wk		-3 wk		-3 wk		-3 wk		-3 wk		-3 wk		-3 wk		
Check eDiary compliance					X	X		X		X		X		X		X		X		X		
Collect eDiary																				X		

[35] Perform oropharyngeal examination before and 60 mins after IMP intake. 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.
[36] Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine) in countries where this is applicable.
[37] eDiary recording of prespecified symptoms

1 Introduction

1.1 Disease background and current treatment modalities

HDM allergy is an IgE-mediated hypersensitivity reaction to allergens contained in HDM fragments and faeces. These particles are airborne and are therefore inhaled reaching the human immune system primarily through the mucosal membrane of the airways, causing rhinitis and/or asthma **(Arlian & Platts-Mills 2001)**. Thus, HDM respiratory allergic disease has two main clinical manifestations: allergic rhinitis/rhinoconjunctivitis and allergic asthma **(Bousquet et al. 2001)**.

HDM is an important allergen among children and adolescents. Among inhalant allergens, HDM sensitisation was found to be the most important risk factor for asthma development in children (**Arshad et al. 2001**; **Lodge et al. 2011**; **Sears et al. 1989**; **Sporik et al. 1990**; **Terreehorst et al. 2002**). In addition to HDM sensitisation being linked to the development of asthma in early childhood, it is also linked to chronic asthma, characterised by the impairment of lung function in school-aged children (**Lau et al. 2000**; **Lodge et al. 2011**) and persistence of asthma into adulthood (**Illi et al. 2006**). Patients sensitised to HDM have a significantly higher risk of recurrent asthma exacerbations (**ten et al. 2005**).

Currently, treatment of allergic diseases is based on allergen avoidance, pharmacotherapy and allergy immunotherapy (AIT) (**Bacharier et al. 2008; Bousquet et al. 2008; Bousquet et al. 1998; GINA Executive Committee 2017; van Cauwenberge et al. 2000**). However, evidence shows that allergen avoidance is not possible to an extent that relieves patients from their symptoms **(Gotzsche & Johansen 2008; Valovirta et al. 2008)**, and international treatment guidelines question whether the effect justifies the cost and effort **(Brozek et al. 2010; GINA Executive Committee 2017)**.

Pharmacotherapy for HDM respiratory allergy most commonly includes antihistamines (oral or topical), local corticosteroids (nasal and/or inhaled) and inhaled β_2-agonist, depending on the clinical manifestation and severity. None of the mentioned treatment options provide long-term, post-treatment benefits or alter the natural course of the allergic disease and most have effects in only one disease manifestation (i.e. AR or allergic asthma).
The treatment algorithm in asthma is based on the concept of disease control, as described in the National Institutes of Health (NIH) guideline for the Diagnosis and Management of Asthma (**National Heart Lung and Blood Institute 2007**) and the Global Initiative for Asthma (GINA) guideline **(GINA Executive Committee 2017**) where SLIT is recommended as an option for the treatment of adult HDM-sensitive patients with asthma and allergic rhinitis who have exacerbations despite ICS treatment. The goals of asthma management are to achieve good symptom control and to minimise future risk of exacerbations, as based on an expectation that when asthma is controlled, patients will experience no more than occasional recurrence of symptoms and exacerbations will be rare. In paediatric asthma, a seasonal fluctuation in the occurrence of asthma exacerbations is well documented, with a rapid and substantial increase in asthma-related hospitalisations at the beginning of each school year (the 'September epidemic') (**GINA Executive Committee 2017; Sears 2008**). Evidence indicates that respiratory viral infections may play a causative role in this peak of asthma exacerbations (**Sears 2008**), and treatment to improve asthma control is central for reducing patients' susceptibility towards virus-induced exacerbations (**Busse et al. 2011**).

Briefly, the asthma treatment algorithm defined by GINA and NIH recommends using one or a combination of daily controller medications, with ICS as the preferred option, in combination with LABA upon increasing severity. A stepwise approach is recommended, with an increase in dose or addition of other controller options if the patient is not well-controlled, and a corresponding step-down adjustment if the patient has been controlled for a while. At all steps, break-through symptoms are treated with reliever medication, typically a SABA.

Thus, for patients with HDM allergic asthma, ICS either dispensed alone or in combination with LABA (combination products) are considered first-line treatment. While ICS constitute the most effective anti-inflammatory medications for treatment of asthma at the present time and provide disease control, ICS do not treat the underlying allergic disease and discontinuation is typically followed by a recurrence in inflammation and asthma symptoms. For children 6 years of age and above with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids, treatment with monoclonal antibodies, particularly Xolair, is increasingly being used. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.

AIT treats the underlying immunological mechanisms responsible for allergic inflammation and represents a treatment option for HDM allergy that is complementary to pharmacotherapy. AIT is performed by repeated subcutaneous or sublingual administration of specific allergen to an allergic person in order to gradually induce immunological tolerance towards the allergen. Considerations for initiating AIT include disease severity, lack of efficacy of pharmacotherapy, side effects of pharmacotherapy, patient preference and the presence of more than one manifestation of the underlying allergic disease (**Bousquet et al. 2008**).

1.2 Stage of development

The HDM SLIT-tablet is approved in the United States, Europe, Japan, and Australia as AIT for treatment of HDM respiratory allergic disease in the adult population. Additionally, it is approved in Europe and Japan for treatment of adolescents (12-17 years) with HDM AR.

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 and targets the underlying HDM allergy to provide clinical benefit in both HDM AR and HDM allergic asthma.

To date, the HDM SLIT-tablet has been investigated in 13 clinical trials and is currently being investigated in 1 ongoing trial in the paediatric population (5-17 years). The completed trials comprised 5 phase I trials, 2 phase II trials, and 6 phase III trials. This included 2 phase I trials conducted in children (5-14 years) and adolescents (12-17 years), respectively. In addition, adolescent subjects were included in 3 of the completed phase III efficacy trials.

All trials were randomised, double-blind, placebo-controlled trials. Four efficacy trials had a primary endpoint related to HDM AR and 3 efficacy trials had a primary endpoint related to HDM allergic asthma. Safety was evaluated throughout the spectrum of the intended target population, i.e. subjects with persistent moderate-to-severe HDM AR despite the use of rhinitis pharmacotherapy and/or with HDM allergic asthma.

The MT-02 trial investigated the efficacy and safety of the HDM SLIT-tablet in adolescents and adults (14-74 years) with mild to moderate persistent HDM allergic asthma and mild to severe HDM AR (**Mosbech et al. 2014**). The results of the MT-02 trial demonstrated that adding the HDM SLIT-tablet to ICS treatment for 1 year allowed patients with mild to moderate HDM allergic asthma to reduce their ICS dose without affecting asthma control.

The MT-04 trial investigated the efficacy and safety of the HDM SLIT-tablet in adults (18-65 years) with HDM allergic asthma and AR, a baseline ACQ score of 1.0-1.5 and daily baseline ICS use corresponding to GINA steps 2-3 (**Virchow et al. 2016**). The primary efficacy analysis of the time to first asthma exacerbation showed a statistically significant reduced risk for 12 SQ-HDM compared to placebo with a hazard ratio of 0.69 (p=0.027). Thus, the MT-04 trial demonstrated that for patients with HDM allergic asthma, adding the HDM SLIT-tablet to ICS treatment significantly reduced the risk of experiencing an asthma exacerbation.

The TO-203-3-1 trial conducted in Japan evaluated the efficacy and safety of the HDM SLIT-tablet in adults with HDM allergic asthma with or without HDM AR as assessed by a reduction in the risk of experiencing an asthma exacerbation. This trial was not able to verify efficacy of the HDM SLIT-tablet in HDM allergic asthma. The TO-203-3-1 trial design, endpoints, and population were modified from MT-04 to accommodate local requirements and treatment traditions.

The approved adult dose of the HDM SLIT-tablet is 12 SQ-HDM. As pharmacodynamic effects of AIT products involve uptake by the immune system with limited absorption into the vascular system (**Bagnasco et al. 2005**), the doses of AIT used for adults and for children ≥5 years of age are identical (i.e. independent of age and body weight) (**Alvarez-Cuesta et al. 2006**).

During clinical development of the HDM SLIT-tablet, a total of 810 paediatric subjects (<18 years) have been included in the completed clinical trials, 283 of which were treated with the 12 SQ-HDM dose. The majority of paediatric subjects were adolescents.

The safety profile of the HDM SLIT-tablet in children and adolescents was investigated in two phase I safety trials MT-03 (children 5-14 years) and P008 (adolescents 12-17 years) **(Corzo et al. 2014; Maloney et al. 2016)**. Results demonstrated safety profiles in children and adolescents that were similar to the safety profile observed for adult populations. Thus, in children (MT-03) and in adolescents (P008), the most frequently reported TEARs in active dose groups were mild to moderate local reactions in mouth and throat such as oral pruritus, throat irritation and mouth oedema. These events typically occurred within minutes the first 1-2 days after initial tablet intake and generally lasted from minutes to hours. There was a dose-response relationship in the observed AEs. In the completed clinical trials, no serious anaphylactic reactions or anaphylactic shock have been reported related to treatment with the HDM SLIT-tablet. However, serious systemic allergic reactions and anaphylactic reactions have been reported post-marketing and are considered a class effect of AIT.

In addition, adolescent subjects were included in the trial populations of the efficacy trials MT-02, TO-203-3-2, and MK-8237-001. The available efficacy data provide no indication that the treatment effect of the HDM SLIT-tablet in paediatric subjects would differ from the treatment effect observed in adults. Also, across trials, data stratified for age showed similar safety profiles in adults (≥18 years) and adolescents (12-17 years).

Please refer to the current Investigator's Brochure (IB) for more details.

1.3 Trial rationale

The rationale behind the present trial is to investigate whether add-on treatment with the HDM SLIT-tablet has an acceptable safety profile and can provide a relevant treatment benefit in terms of a reduced number of asthma exacerbations for children and adolescent subjects with HDM allergic asthma on low dose ICS plus LABA or medium/high dose ICS with or without LABA and with HDM AR. Further, the trial will generate information on the [redacted] of the HDM SLIT-tablet.

The trial population will include children and adolescents (5-17 years of age) with HDM allergic asthma on low dose ICS plus LABA or medium/high dose ICS with or without LABA who are at risk of asthma exacerbations and who have HDM AR. Eligible subjects have experienced asthma exacerbations in the last couple of years. This population is identified as patients with an unmet medical need. Despite being on asthma controller medication, these paediatric patients continue to experience asthma exacerbations which may involve hospitalisation and be a significant source of anxiety for patients as well as caregivers. In addition, a trial population with a history of frequent asthma exacerbations is in accordance with the EMA guideline (**EMA 2016b**). Finally, the selected population experiences rhinitis symptoms and/or a need for rhinitis medication as a result of their HDM allergic disease and treating the underlying immunological mechanisms responsible for allergic inflammation would thus provide relief from both manifestations of HDM respiratory allergy in these patients.

In this trial, subjects will be randomised (1:1) to treatment with the HDM SLIT-tablet (12 SQ-HDM) or placebo in addition to their usual asthma background treatment and the asthma and rhinoconjunctivitis rescue medication for a treatment period of approximately 2 years. Primary efficacy will be assessed based on the rate of clinically relevant asthma exacerbations. This is in agreement with professional society guidelines and EMA guidelines, which specifies that a treatment effect on asthma exacerbations remains a relevant endpoint in paediatric patients (**EMA 2016b; Reddel et al. 2009**). In addition, data from the MT-04 trial demonstrated that in an adult trial population, the HDM SLIT-tablet was able to prevent asthma exacerbations when ICS was reduced (**Virchow et al. 2016**). Similarly, while the present trial design does not evaluate efficacy during a period of reduction in asthma controller medication, the trial rationale is that for a paediatric population, adding the HDM SLIT-tablet to asthma controller medication will provide therapeutic benefit in the form of improved asthma control and a reduced susceptibility towards asthma exacerbations.

1.4 Benefit-risk assessments and ethical considerations

Despite substantial improvements in the treatment of asthma and the use of guideline-based therapy, approximately 50% of adult US asthma patients have inadequately controlled asthma (**CDC 2015**). Patients with unstable severe asthma suffer from limited control of symptoms, frequent exacerbations, and compromised quality of life. Exacerbations are particularly disabling for the patient and typically require treatment with high doses of systemic corticosteroids and may require hospital admission. A proportion of these patients with inadequately controlled asthma who require emergency room visits and hospitalisations due to exacerbations drive a substantial amount of the cost burden associated with asthma treatment. Treatments that can reduce the risk of future asthma exacerbations and improve measures of current impairment address a major unmet need in asthma management in North America and Europe today.

Among inhalant allergens, HDM sensitisation was found to be the most important risk factor for asthma development in children (**Arshad et al. 2001**; **Lodge et al. 2011**; **Sears et al. 1989**; **Sporik et al. 1990**; **Terreehorst et al. 2002**). Treatment with the HDM SLIT-tablet targets the underlying HDM allergy to provide clinical benefit in both HDM allergic asthma and HDM AR. Thus, in the present trial, subjects in the active treatment group may experience treatment benefits in terms of improved asthma symptom control and a reduced number of asthma exacerbations, as well as a reduced burden of symptoms related to HDM AR.

When developing the HDM SLIT-tablet, the sublingual route was selected over subcutaneous injection to provide a product with a safety profile allowing for at-home administration. This results in improved convenience for patients and caregivers to those who have a fear of injections or who cannot set aside time off work or school for frequent doctor's visits over a treatment period of several years. In addition, orodispersible dosage forms hold great promise for children as they are easy to administer, do not require additional water and, as long as dispersion is rapid, are difficult to spit out (**EMEA 2006**).

The most prevalent AEs observed with the HDM SLIT-tablet include local reactions in the mouth and throat (e.g. oral pruritus, throat irritation, and mouth oedema) of mild to moderate severity. The risk of severe swelling is low and no AEs have involved local allergic swelling that compromised the airways in completed clinical trials. 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.

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

A placebo group will be used as a control-group in the trial. An active comparator is not included in the trial as there are no available authorised HDM SLIT-tablets. A placebo group is considered ethically justifiable since subjects in both treatment groups will be provided with background treatment and rescue medication to treat their asthma and rhinitis symptoms during the trial. Furthermore, subjects will be medically monitored during the trial and provided with appropriate treatment if warranted. Finally, subjects can withdraw from the trial at any time if they find the treatment intolerable or without giving reason.

The population selected for this trial is characterised by a history of asthma exacerbations despite asthma treatment, which means the future risk of exacerbations in these subjects is considerable. In order to minimise the risk relating to severe asthma exacerbations, the trial protocol specifies that subjects who experience severe asthma exacerbations be treated appropriately, and a maximum number of severe asthma exacerbations allowed in any single subject has been defined, after which a subject must be discontinued from the IMP treatment.

In order to minimise any risk related to the trial activities, the following tools have been incorporated in the protocol:

- Each subject will be provided with self-monitoring tools in the form of a preprogrammed eDiary and a peak flow meter to increase awareness of asthma control

- Each subject will receive a supply of asthma and rhinoconjunctivitis rescue medication to be used as needed. In countries where it is a regulatory requirement, adrenaline/epinephrine auto-injectors will be dispensed

- Each subject will receive a personal written Asthma Action Plan containing specific instructions on the actions required in case asthma symptoms increase or lung function decreases

- Each subject will be provided with a pocket-size patient card containing investigator contact information

- An independent DMC will be established for safety monitoring of the trial

- Considerations regarding COVID-19 pandemic:
    - 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. If regional circumstances related to COVID-19 change, local guidelines should be followed, see appendix 6.

    - If an on-site visit is not possible due to COVID-19 pandemic, appendix 7-8 enables the conduct of a remote visit at the discretion of the Investigator.

    - If an on-site visit is not possible due to COVID-19 pandemic, IMP and rescue medication can be shipped directly from site to patient at the discretion of the Investigator, see appendix 9.

In summary, the benefits of add-on treatment with the HDM SLIT-tablet which are expected to include improved asthma control and a reduced risk of asthma exacerbations as well as reduced rhinitis symptoms are deemed to outweigh the risks and inconveniences associated with the treatment. The safety profile of the HDM SLIT-tablet in the paediatric population is expected to be favourable and to make the tablet suitable for at-home administration with a low risk of systemic adverse reactions and with mild to moderate local reactions in the oral cavity representing the most frequent adverse reactions. Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and informed consent documents.

In conclusion, the risks and benefits of trial participation are considered to be well balanced.

2 Objectives and endpoints

2.1 Primary objective

The primary objective is to demonstrate efficacy of the HDM SLIT-tablet versus placebo as add-on treatment in children and adolescents (5-17 years) with HDM allergic asthma based on clinically relevant asthma exacerbations[38] after at least 4 months of treatment.

[38] A clinically relevant asthma exacerbation is defined as at least one of the following criteria: a) Doubling of ICS dose compared to background treatment, b) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, c) Emergency room visit

2.2 Key secondary objective

The key secondary objectives are to demonstrate efficacy of the HDM SLIT-tablet versus placebo after at least 4 months as add-on treatment in children and adolescents with HDM allergic asthma with respect to:

- Nocturnal awakening due to asthma which require SABA rescue medication
- Rescue medication use (SABA)
- Lung function (FEV_1)

2.3 Secondary objectives

The additional secondary objectives, based on endpoints measured at different timepoints throughout the trial, are to evaluate the HDM SLIT-tablet versus placebo for treatment of HDM allergic asthma with respect to:

- Asthma symptoms
- Asthma control
- Severe asthma exacerbations[39]
- Treatment of HDM AR
- Treatment of HDM allergic rhinoconjunctivitis
- Changes in immunological parameters
- Safety and tolerability

2.4 Exploratory objectives

The exploratory objectives are to evaluate:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.5 Primary endpoint

The primary endpoint of the trial is the annualised rate of clinically relevant asthma exacerbations calculated as the number per year per subject during the efficacy evaluation period (period 4).
A clinically relevant asthma exacerbation must be medically confirmed and is defined as asthma worsening leading to at least one of the following criteria:

due to asthma, requiring systemic corticosteroids or d) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids.

[39] A severe asthma exacerbation is defined as at least one of the following: a) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, or b) Emergency room visit due to asthma, requiring systemic corticosteroids, or c) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids.

- Doubling of ICS dose compared to background treatment
- Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
- Emergency room visit due to asthma, requiring systemic corticosteroids
- Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids

2.6 Key secondary endpoints

The key secondary endpoints are:

- Proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication during the 14 days eDiary recording every 4 months after randomisation
- The average daily dose of SABA during the 14 days eDiary recording every 4 months after randomisation
- Percentage predicted FEV_1 assessed every 4 months after randomisation

2.7 Additional secondary endpoints

- Asthma exacerbations
  - Time to first clinically relevant asthma exacerbation measured in days from start of the efficacy evaluation period
  - Time to recurrent clinically relevant asthma exacerbation measured in days from start of the efficacy evaluation period
  - The rate of severe asthma exacerbations during the efficacy assessment period (period 4). A severe asthma exacerbation meets at least one of the following criteria:
    - Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
    - Emergency room visit due to asthma, requiring systemic corticosteroids
    - Hospitalisation for more than 12 hours because of asthma, requiring treatment with systemic corticosteroids
  - Time to first severe asthma exacerbations from start of the efficacy assessment period (period 4)
  - Time to recurrent severe asthma exacerbations from start of the efficacy assessment period (period 4)
- Asthma symptoms
  - Average asthma DSS during the two week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - Asthma VAS
  - Global evaluation for allergic asthma
  - Overall ACQ/ACQ-IA measured at V5, V6, V7, V8, V9, V10 and V11
- Rhinitis symptoms and symptomatic medication
  - The average TCRS during the two week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinitis DSS during the two weeks assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinitis DMS during the two week assessment period before V5, V6, V7, V8, V9, V10 and V11

  - The average rhinitis CSMS during the two weeks assessment period before V5, V6, V7, V8, V9, V10 and V11
  - Global evaluation for AR
- Rhinoconjunctivitis symptoms and symptomatic medication
  - The average rhinoconjunctivitis TCS during the two week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinoconjunctivitis CSMS during the two week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinoconjunctivitis DSS during the two week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - Rhinoconjunctivitis VAS
  - The average rhinoconjunctivitis DMS during the two week assessment period before V5, V6, V7, V8, V9, V10 and V11
- Immunology
  - Changes from baseline in specific IgE, IgE-BF and IgG_4 against *D. pteronyssinus and D. farinae* measured at V7 and V11
- Safety and tolerability endpoints:
  - Treatment-emergent AEs, solicited AEs, IMP-related AEs, treatment-emergent SAEs, treatment-emergent AEs leading to discontinuation, time to discontinuation due to treatment-emergent AEs
  - Vital signs, FEV_1, clinical laboratory values and physical examination during treatment and at the final visit (V11)

2.8 Exploratory endpoints

- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
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- [redacted]
  - [redacted]

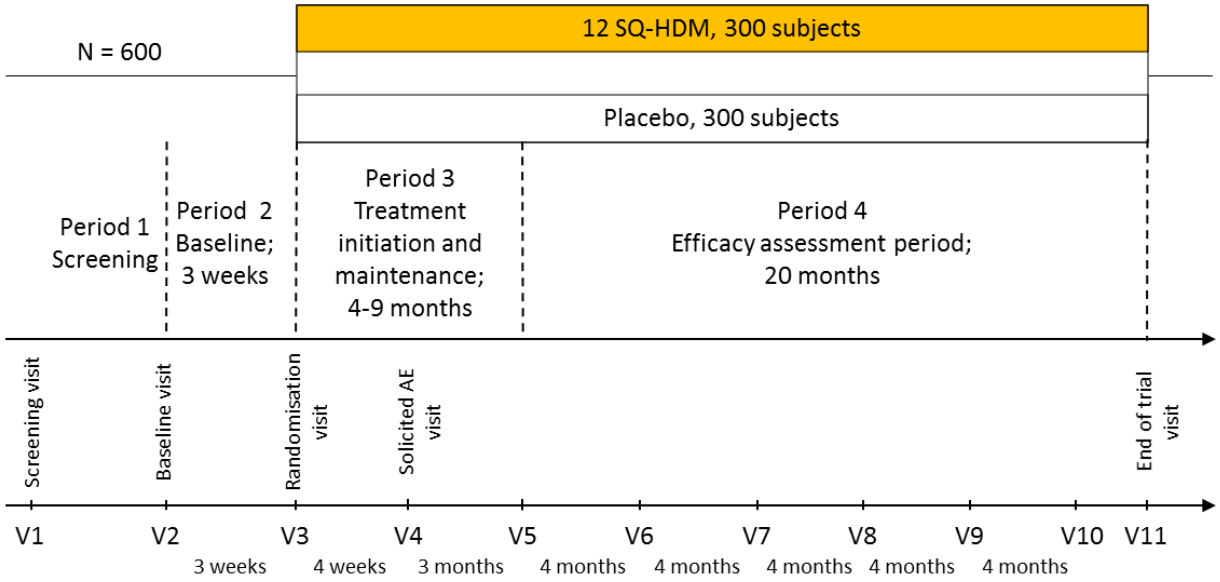
3 Trial design

3.1 Summary of trial design

This trial is a randomised, parallel-group, double-blind, placebo-controlled multi-national phase III trial conducted in Europe and North America. Approximately 600 subjects will be randomised (1:1) to receive treatment with the HDM SLIT-tablet or placebo, see Figure 1. A blinded SSR will be performed based on data from the first 17 months of efficacy assessment period for cohort 1 and data from the first 5 months of efficacy assessment for cohort 2. Due to the COVID-19 pandemic and the potential consequences of social distancing, a second SSR will be performed based on data from the completed efficacy period for cohort 1, data from the first 18 months of efficacy assessment for cohort 2, and data from the first 6 months of efficacy assessment for cohort 3. The result of the second SSR will replace the result of the first SSR, see Section 15.2.

The trial evaluates the efficacy and safety of the HDM SLIT-tablet in children and adolescents (5-17 years) with HDM allergic asthma and AR. The treatment duration is approximately two years for all subjects. The primary endpoint is not a common event so the efficacy assessment period is approximately 20 months. Since there is a well-established peak in asthma exacerbations in children at the beginning of each school year (**Sears 2008**) and the increased HDM exposure during autumn and winter months (**Bousquet et al. 2008**), the efficacy assessment period will begin on 1 September for all subjects and run for approximately 20 months in order to capture 2 autumn and winter seasons.

Figure 1 Trial design



Period 1 is the screening period. Subjects screened before 10 April 2018 will be included in cohort 1. Subjects screened between 10 April 2018 and 10 April 2019 will be included in cohort 2. Subjects screened between 10 April 2019 and 10 April 2020 will be included in cohort 3. Subjects screened between 01 August 2021 and 10 April 2022 will be included in cohort 4.

Period 2 is the baseline period of 3 weeks following screening. For cohort 1, the baseline period is during Q1 - Q2 2018. For cohort 2, the baseline period is during Q4 2018 - Q2 2019. For cohort 3, the baseline period is during Q4 2019 - Q2 2020. For cohort 4, the baseline period will occur during Q4 2021 – Q2 2022. During the baseline period, eligible subjects or their parent/caregiver will fill in their asthma and rhinoconjunctivitis symptoms and medication use in an eDiary. Subjects will continue with their regular asthma background treatment. The subjects' regular asthma rescue mediation and rhinoconjunctivitis rescue medication must be replaced with the rescue medication provided by ALK at visit 2 with the exception of additional sponsor provided ICS, which is optional.

Period 3 is the treatment initiation and maintenance period to allow the treatment with the HDM SLIT-tablet to take effect. It starts at randomisation and lasts for at least 4 months. The period ends on 1 September 2018 for cohort 1, on 1 September 2019 for cohort 2, on 1 September 2020 for cohort 3 and on 1 September 2022 for cohort 4.
During the first 28 days of period 3, prespecified symptoms[40] occurring after IMP intake will be recorded by the subject/parent/caregiver in the eDiary. The reported symptoms will be evaluated by investigator and reported in the eCRF as solicited AEs.

Period 4 is the efficacy assessment period. Period 4 lasts until the end of trial or discontinuation from the IMP[41] and during this period the rate of clinically relevant asthma exacerbations will be

[40] AEs identified by the World Allergy Organization (WAO) as local side effects of SLIT (Passalacqua et al. 2013).
[41] Subjects will be discontinued from the IMP treatment after 2 severe asthma exacerbations in 12 consecutive months or 1 hospitalisation due to asthma requiring treatment with systemic corticoteroids.

evaluated from 1 September 2018 to 30 April 2020 (cohort 1), 1 September 2019 to 30 April 2021 (cohort 2), 1 September 2020 to 30 April 2022 (cohort 3) and 1 September 2022 to 30 April 2024 (cohort 4).

Subjects will be treated for 24-30 months in total since subjects can commence treatment in a predefined period lasting from 1 November until 10 April. The efficacy period starts on 1 September for all subjects resulting in a pretreatment period of 4 to 10 months. The efficacy period ends 30 April for all subjects. As a result, some subjects may have 5-6 months between visit 10 and 11 while others may have their last visit 11 on the same day as visit 10. Subjects with less than 1 month between visit 10 and 11 will only have one visit to the clinic where all the procedures of 11 are performed.

Approximately every 4 months after randomisation, subjects or their parent/caregiver will be asked to complete the eDiary for a period of 14 days 3 weeks prior to V5 (at 4 months), V6 (at 8 months), V7 (at 12 months), V8 (at 16 months), V9 (at 20 months), V10 (at 24 months) and V11 (25-30 months).

3.2 Trial schedule

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
First subject first visit (FSFV):	Q1 2018	Q3 2018	Q3 2019	Q3 2021
Last subject randomised	Q2 2018	Q2 2019	Q2 2020	Q2 2022
Last subject last visit (LSLV):	Q2 2020	Q2 2021	Q2 2022	Q2 2024

Duration of treatment per subject: 24-30 months
End of trial defined as LSLV for the last cohort initiated.

3.3 Discussion of design

The selected design for the present trial is based on the EMA The Committee for Medicinal Products for Human Use (CHMP) guideline on the clinical investigation of medicinal products for the treatment of asthma (**EMA 2016b**) and incorporates the recommendations of the EMEA CHMP guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (**EMA 2008**), the needs stated in the World Health Organisation (WHO) position paper on allergen immunotherapy for development of sublingual immunotherapy (**Bousquet et al. 1998**), the EMA/PDCO Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy (**EMA & PDCO 2015**), and the Food and Drug Administration (FDA) guidance for industry on the content and format for paediatric use supplements (**FDA 1996**).

The clinical efficacy endpoint has been chosen based on the guidelines referenced above as well as the joint statement on endpoints for clinical asthma trials and clinical practice from the American Thoracic Society and the European Respiratory Society (**Reddel et al. 2009**). The trial design is also based on the experience from previous ALK trials with allergy immunotherapy in general and with the HDM SLIT-tablet in particular for treatment of allergic asthma and rhinitis.

The trial population comprises children (5-11 years) and adolescents (12-17 years) with a clinical history consistent with HDM allergic asthma who are at risk of asthma exacerbations despite being on treatment with low dose ICS plus LABA or medium/high dose ICS with or

without LABA and who have HDM AR. This trial population reflects a population that is suitable for treatment with specific allergy immunotherapy since the aim is to treat the underlying inflammation in asthma, thereby minimising the risk for exacerbations.

The duration of treatment is approximately 2 years for all subjects. All subjects should be randomised before 1 May to ensure at least 4 months of treatment initiation and maintenance. The duration of the treatment initiation and maintenance period is based on the results from previous trials with the HDM SLIT-tablet for treatment of asthma and rhinitis symptoms (**Demoly et al. 2016**; **Mosbech et al. 2014**; **Virchow et al. 2016**) where onset of significant effect was seen after approximately 14 weeks of treatment.

For the primary objective, efficacy measurements are to be performed during the autumn and winter where HDM allergic patients typically have more symptoms (**Bousquet et al. 2008**). Efficacy measurement duration will be approximately 20 months in order to capture two autumn and winter seasons. This means that the efficacy assessment period will start 1 September for all subjects.

Safety endpoints include AEs, vital signs and laboratory values that are normally used in characterising the safety profile of an IMP.

The active dosage chosen in the trial is 12 SQ-HDM, which is the approved dose for adults in the United States, Europe and Australia and for adolescents (12-17 years) in Europe. The dose is based on 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) will constitute the relevant dose for all populations ≥5 years of age, in accordance with the general practice for AIT (**Alvarez-Cuesta et al. 2006**).

Besides treatment with IMP, the subjects will use background treatment with low dose ICS plus LABA or medium/high dose ICS with or without LABA. Throughout the trial the ICS or ICS and LABA combination treatment will be at the same dose as when the subjects enter the trial. LABA treatment when not being used in combination with ICS is not allowed as it is no longer recommended as an option for add-on treatment at any step of therapy unless used in combination (**GINA Executive Committee 2017**). A separate inhaler with ICS alone will be allowed as asthma rescue medication in case of deterioration of symptoms or following a severe exacerbation. Alternatively, subjects can double the dose of their background ICS for an exacerbation rather than using sponsor provided ICS. SABA and OCS will also be provided as asthma rescue medication. Please note that the terms “background treatment” and “rescue medication” follows the EMA “Definition of IMPs and use of AMPs consultation document” from 2016 (**EMA 2016a**) rather than the EMA “Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases” from 2008 (**EMA 2008**).

Asthma exacerbations constitute the greatest unmet medical need for patients, are a cause of anxiety to patients and their families, resulting in the greatest stress on health care providers, and generate the greatest cost to the health care system (**Lane et al. 2006**). The exacerbation rate is a clinically relevant endpoint to assess treatment effect in patients with asthma (**EMA 2016b**). Hence, the primary endpoint in this trial is the rate of exacerbations.

The definition of a clinically relevant asthma exacerbation used in this trial is based on the recommendations given in the joint statement from the American Thoracic Society and the

European Respiratory Society 2009 (**Reddel et al. 2009**) and recommendations from GINA (**GINA Executive Committee 2017**).

If the subject experiences one of the following events, this will be characterised as a clinically relevant asthma exacerbation:

- Doubling of ICS dose compared to background treatment
- Systemic corticosteroids for treatment of asthma symptoms for at least 3 days
- Emergency room visit due to asthma, requiring systemic corticosteroids
- Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids

The key secondary endpoints consist of:

- Proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication during the 14 days eDiary recording every 4 months after randomisation
- The average daily dose of SABA during the 14 days eDiary recording every 4 months after randomisation
- Percentage predicted FEV_1 assessed every 4 months after randomisation

These endpoints has been chosen to underline the effect on asthma symptoms, asthma medication use and lung function.

The expected rate of clinically relevant asthma exacerbations is 1.4 (**Lanier et al. 2009**) in this trial. A 20% reduction in the rate corresponds to an absolute reduction of 0.28 clinically relevant asthma exacerbations per subject per year. This can further be translated to saving 1 clinically relevant asthma exacerbation per year per 3.6 treated subjects. It has been proposed that any reduction in the rate of severe exacerbations (e.g., requiring treatment with systemic corticosteroids) is clinically relevant (**Glacy et al. 2013**).

This trial is a randomised, parallel-group, double-blind, placebo-controlled multi-national trial. Randomisation introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments (**ICH Harmonised Tripartite Guideline 1998**). It is desirable for statistical purposes to compare groups of equal size and therefore the randomisation procedure is planned as a 1:1 randomisation.

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

A placebo arm has been introduced to establish the superiority of the HDM SLIT-tablet compared to placebo and background treatment with respect to reducing the frequency of the severe asthma exacerbations. Placebo has been chosen as comparator since no well-established comparator exist.

4 Trial population

Subjects randomised in this trial will be children and adolescents 5-17 years of age, with HDM allergic asthma who are at risk of asthma exacerbations despite being on treatment with low dose ICS plus LABA or medium/high dose ICS with or without LABA and who have HDM AR. The trial will include 45% subjects of 5-11 years of age in accordance with the recommendation of EMA/PDCO Standard Peadiatric Investigation Plan for Allergen Products for Specific Immunotherapy (**EMA & PDCO 2015**). The age groups follow the EMA/PDCO Standard Paediatric Investigation Plan for Allergen Products for Specific Immunotherapy (**EMA & PDCO 2015**), and the FDA guidance for industry on the content and format for paediatric use supplements (**FDA 1996**) rather than the EMA Guideline on the clinical investigation of medicinal products for the treatment of asthma (**EMA 2016b**).

Subjects meeting all of the inclusion criteria listed in Section 4.1 and none of the exclusion criteria listed in Section 4.2 will be considered eligible for the trial. Please also refer to the general dosing precautions in Section 9.2.

4.1 Inclusion criteria

I1. Written informed consent obtained from parents/caregivers before any trial related procedures are performed[42]. Consent or assent from the subject must be obtained according to national requirements.

I2. Male or female of any race/ethnicity aged ≥4 to ≤17 years on the day informed consent is obtained from the parent/caregiver. The subject must be ≥5 to ≤17 years old at the randomisation visit

I3. A female subject of childbearing potential[43] must have a negative pregnancy test and be willing to practise appropriate[44] contraceptive methods until the follow-up TC

I4. A clinical history of HDM allergic asthma of at least 1 year duration diagnosed by a physician[45]

I5. Use of low daily dose of ICS plus LABA or medium/high daily dose of ICS with or without LABA for the control of asthma symptoms within the past year prior to randomisation. For definition of ICS doses, please see Table 3 and Table 4

[42] At least one parent/caregiver must be able to read.

[43] Females, after the first menstrual period.

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

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

I6. ≥3 clinically relevant asthma exacerbations[46] in the past two years or ≥2 clinically relevant asthma exacerbations in the past year or ≥1 severe asthma exacerbation[47] in the past year prior to randomisation while being on asthma controller medication (low dose ICS plus LABA or medium/high dose ICS with or without LABA)[48]. The asthma controller medication at the screening visit must be at a dose equivalent to or below the dose the subject received before the last asthma exacerbation occurred

I7. One or more of the following within the past 4 weeks prior to randomisation:

a. Daytime asthma symptoms more than twice/week

b. Any nocturnal awakening due to asthma which require use of SABA rescue medication

c. SABA rescue medication needed for treatment of asthma symptoms more than twice/week

d. Any activity limitation due to asthma

I8. Lung function measured by FEV_1 ≥ 70% of predicted value[49] or according to local requirements while on background treatment following at least a 6-hour washout of SABA at screening and randomisation

I9. Clinical history of HDM AR within the last year prior to randomisation[50]

I10. An average TCRS>0 during the baseline period (period 2)

I11. Positive specific IgE (defined as ≥class 2, ≥0.70 kU/l) against *D. pteronyssinus* and/or *D. farinae* at screening

I12. Positive SPT[51] to *D. pteronyssinus* and/or *D. farinae* at screening

I13. Subject willing and able to comply with trial protocol

[46] A clinically relevant asthma exacerbation is defined as at least one of the following criteria: a) Doubling of ICS dose compared to background treatment, b) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, c) Emergency room visit due to asthma, requiring systemic corticosteroids or d) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids.
[47] A severe asthma exacerbation is defined as at least one of the following: a) Systemic corticosteroids for treatment of asthma symptoms for at least 3 days, b) Emergency room visit due to asthma, requiring systemic corticosteroids or c) Hospitalisation for more than 12 hours due to asthma, requiring treatment with systemic corticosteroids.
[48] One asthma exacerbation within the last year must be documented including asthma medication and dosage immediately prior to this exacerbation.
[49] Interpretation of normal range for spirometric test should be based on the Quanjer reference equations (Quanjer et al. 1995).
[50] If medical records are not available, verbal history from subject/parent/caregiver can be used to fulfill this criterion and this must be documented in the medical records by the investigator.
[51] A positive SPT is defined in the SPT Guideline. Briefly, for subjects in North America, a positive SPT is defined as a wheal size ≥5 mm larger than the negative control. For subjects in Europe, a positive SPT is defined as a wheal size ≥3 mm.

4.2 Exclusion criteria

E1. Has a clinically relevant history and is sensitised, symptomatic, and regularly exposed to animal dander, molds, and/or cockroach (e.g., present in the home, job, school, etc.) or other perennial allergen

E2. Has experienced a life-threatening asthma attack defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia requiring non-invasive ventilator support

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

E4. Within the last 3 months before the randomisation visit (visit 3) while on high dose ICS treatment, has had an occurrence of any clinical deterioration of asthma that resulted in emergency treatment, hospitalisation, or treatment with systemic corticosteroids

E5. SLIT treatment with *D. pteronyssinus* or *D. farinae* for more than 1 month within the last 5 years. In addition, any SLIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months

E6. SCIT treatment with *D. pteronyssinus* or *D. farinae* reaching the maintenance dose within the last 5 years. In addition, any SCIT treatment with *D. pteronyssinus* or *D. farinae* within the previous 12 months

E7. Ongoing treatment with any allergy immunotherapy product

E8. Severe chronic oral inflammation

E9. Any nasal or naso/oropharyngeal condition that could confound the efficacy or safety assessments (e.g., hypertrophy of the pharyngeal/palatine tonsils, clinically relevant nasal polyps, a history of paranasal sinus surgery or surgery of nasal turbinates)[52]

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

E11. Has a diagnosis or history of eosinophilic oesophagitis

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

[52] If in doubt, nasal endoscopy is recommended

E14. Ongoing treatment with OCS

E15. Treatment with restricted and prohibited concomitant medication listed in Table 2

E16. Treatment with an investigational drug within 30 days/5 half-lives of the drug (which ever longest) prior to screening

E17. A history of allergy, hypersensitivity or intolerance to any of the excipients or active substance of the IMP (except *D. pteronyssinus* and *D. farinae*) or to any excipient of the rescue medication provided in this trial

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

E19. A history of alcohol or drug abuse

E20. Has previously been randomised 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

E21. Has 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

E22. Has a condition or treatment that increase the risk of the subject developing severe adverse reactions after adrenaline/epinephrine administration

E23. Is unable to or will not comply with the use of adrenaline/epinephrine auto-injectors for countries where this is a regulatory requirement

5 Subject discontinuation

5.1 Discontinuation from IMP treatment

Subjects must be discontinued from IMP treatment and should continue in the trial for safety assessments only under the following circumstances:

- If the subject experiences 2 severe asthma exacerbations within a 12 consecutive months period
- If the subject is hospitalised due to asthma requiring treatment with systemic corticosteroids
- The subject experiences severe or persistent symptoms of oesophagitis
- If the subject becomes pregnant
- If, in the investigator's opinion, continuation with IMP treatment would be detrimental to the subject's well-being

5.2 Discontinuation from trial

The subject and/or subjects parent/caregiver will be advised in the informed consent form that he/she has the right to withdraw from the trial at any time without prejudice. Where discontinuation from the trial is initiated by the subject, the investigator is to ascertain the primary reason for discontinuation from the list below:

- An AE for which the investigator did not consider discontinuation from the trial necessary
- Perceived insufficient therapeutic effect
- Co-existing disease
- Withdrawal of consent
- Other reasons

Additionally, the subject may at any time be discontinued from the trial at the discretion of the investigator or ALK.

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

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

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

- If subject is treated with prohibited medication as defined in Table 2
- In case of protocol deviation, violation of eligibility criteria or deviation from the treatment plan specified in the protocol (e.g. incorrect administration of the IMP)
- If IMP is discontinued for several months

In case a subject discontinues from the trial, the discontinuation page in the eCRF should be completed. On the discontinuation page the investigator should record the date of the discontinuation, 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. Follow-up on the subject is necessary to establish whether the reason was an AE. If so, this must be reported in accordance with the appropriate procedures.

To the extent possible, all examinations scheduled for the final visit must be performed on subjects who receive IMP but did not complete the trial according to the protocol. If possible, the TC follow-up (TC21) should be performed and the corresponding eCRF pages should be filled in.

Reasonable effort should be made to contact any subject lost to follow-up during the course of the trial in order to complete assessments and retrieve any outstanding data and medication/supplies. If the subject is lost to follow-up, 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.

6 Randomisation and treatment blinding/unblinding

6.1 Subject ID number

All subjects enrolled must be identifiable throughout the trial. Thus, at the screening visit all subjects will receive a unique subject number. The subject number will be generated when the subjects' data are entered into the eCRF.

6.2 Randomisation

The randomisation list will be generated by a trial-independent statistician and will not be accessible to trial personnel involved in the conduct of the trial, until the database has been locked. 45% of the subjects will be 5-11 years of age at the time of randomisation in accordance with the recommendation of EMA/PDCO standard paediatric investigation plan for allergen products for specific immunotherapy (**EMA & PDCO 2015**). No other stratification will be used in this trial.

When a subject is randomised a unique number is assigned for the first dispensing of IMP.

6.3 Subject card

All randomised 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.

6.4 Treatment blinding/unblinding

A double-blind set-up will be used. The HDM SLIT-tablet and the matching placebo will be similar in appearance and taste and will be packaged identically to maintain the treatment blind. Neither the sponsor, the subject, nor the trial site staff will know which treatment the subject is receiving. DMC members will be unblinded to treatment.

The randomisation code for a particular subject can be broken in a medical emergency if knowledge of the IMP is necessary for the optimal treatment of the subject. If possible the trial site must contact ALK prior to unblinding the subject's treatment. However, in case of an emergency necessitating the knowledge of the IMP, unblinding and appropriate treatment should be the very first action by the site.

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

The IRT will notify the clinical research associate (CRA) and the safety department at the sponsor immediately after the randomisation code is broken.

The subject must be discontinued from the trial after randomisation code breaking.

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

7 Restricted and prohibited concomitant medication

Restricted and prohibited concomitant medications are listed below.

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 2 is restricted or prohibited unless it is provided by ALK.

Table 2 Restricted and prohibited concomitant medications

Drug	Time window	Reason
An investigational drug other than the IMP	30 days/5 half-lives of the drug (which ever longest) before visit 1 and until end of trial	Possible interaction between IMPs. Interferes with efficacy and safety evaluations
Anti-IgE treatment, e.g. Omalizumab	< 130 days/5 half-lives of the drug (which ever longest) prior to visit 1 and until end of trial	Interferes with rhinoconjunctivitis and/or asthma efficacy assessments
Antihistamine, unless provided by ALK		
- Oral, intravenous, nasal or ocular	From visit 2 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments Interferes with safety evaluation
- Long-acting (astemizole)	≤ 90 days before visit 2 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments. Interferes with safety evaluation
Antidepressant medications: - Antidepressant medication with antihistaminic effect (e.g. doxepin, mianserine) - Tricyclic antidepressants (e.g. amitriptyline, clomipramine)	≤ 14 days before visit 1 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments Interferes with safety evaluation Tricyclic antidepressants may potentiate the effect of adrenaline/epinephrine

Drug	Time window	Reason
Antipsychotic medications with antihistaminic effects (e.g. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine)	≤ 7 days before visit 1 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments due to antihistaminic effect. Interferes with safety evaluation
Glucocorticosteroids, unless provided by ALK		
• topical (nasal or ocular)	From visit 2 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments. Interferes with safety evaluation
• oral	From visit 2 and until end of trial	Interferes with asthma and rhinoconjunctivitis efficacy assessments. Interferes with safety evaluation
• systemic (depot formulations parenteral administration, regardless of treatment days and dose)	≤ 90 days before visit 2 and until end of trial	Interferes with asthma and rhinoconjunctivitis efficacy assessments. Interferes with safety evaluation
Immunosuppressive treatment (ATC code L04 or L01) (e.g. dupilumab, mepolizumab, reslizumab, lebrikizumab)	≤ 90 days before visit 1 and until end of trial	Interferes with rhinoconjunctivitis and/or asthma efficacy assessments
Immunotherapy with any other allergen(s)	From visit 1 and until end of trial	Interferes with rhinoconjunctivitis and/or asthma efficacy assessments. Interferes with safety evaluation
Inhaled, topical or oral nedocromil or cromolyn sodium	≤ 14 days before visit 2 and until end of trial	Interferes with rhinoconjunctivitis and/or asthma efficacy assessments
Long-acting muscarinic antagonists (LAMA) (e.g. Tiotropium)	From visit 2 and until end of trial	Interferes with asthma efficacy assessments
LABA monotherapy	From visit 2 and until end of trial	Interferes with safety evaluation

Drug	Time window	Reason
Methylxantin (e.g. theophylline)	From visit 2 and until end of trial	Interferes with asthma efficacy assessments
LTRA (e.g. montelukast, zafirlukast)	From visit 1 and until end of trial. Unless treatment has started prior to subject entering the trial	Interferes with asthma efficacy assessments
Nasal decongestants	From 3 days before each eDiary period and until end of eDiary period starting from visit 2 and until end of trial	Interferes with rhinitis efficacy assessments
Pizotifene	≤ 7 days before visit 1 and until end of trial	Interferes with rhinoconjunctivitis efficacy assessments due to antihistaminic effect
SABA, unless provided by ALK	From visit 2 and until end of trial	Interferes with asthma efficacy assessments

8 Trial products

8.1 Investigational Medicinal Product

The IMP provided in the trial is HDM SLIT-tablet or placebo.

Each subject will be randomly assigned to receive active treatment with 12 SQ-HDM or placebo.

All subjects enrolled must be identifiable throughout the trial. This will be done by using a subject number, allocated to the subject at visit 1 (screening visit).

The IMP will be provided by ALK. The treatment will start at visit 3 (randomisation visit), where the first IMP will be dispensed. Hereafter, IMP will be dispensed at the visits 5, 6, 7, 8, 9 and 10. When the first dose is administered, the subject will be under medical supervision for at least 30 minutes after the tablet intake. For the recording of onset and duration of solicited AEs that occur on Day 1 (visit 3), the subject should remain in the clinic for 60 minutes after IMP intake.

The IMP is manufactured by ALK. The placebo tablets are similar to the active tablet with respect to appearance, smell and taste.

Active treatment

Active ingredients:	Standardised allergen extracts from the HDMs *D. pteronyssinus* and *D. farinae*
Dosage form:	Oral lyophilisate
Dose/strength:	12 SQ-HDM
Excipients:	Gelatine (fish source), mannitol and sodium hydroxide

Placebo treatment

Active ingredients:	None
Dosage form:	Oral lyophilisate
Excipients:	Gelatine (fish source), mannitol and sodium hydroxide

8.2 Background treatment

Asthma background treatment

Subjects will continue on the asthma background treatment (low dose ICS plus LABA or medium/high dose ICS with or without LABA) they were on before entering the trial. For a definition of low, medium and high dose ICS, please see Table 3 and Table 4.

Table 3 Definition of low, medium and high dose ICS for subjects aged 5-11 years

Inhaled corticosteroid	Low daily dose (micrograms (µg))	Medium daily dose (micrograms (µg))	High daily dose (micrograms (µg))
Beclomethasone dipropionate	100 - 200	> 200 – 400	> 400
Budesonide DPI	100 - 200	> 200 – 400	> 400
Budesonide nebs	250 - 500	> 500 – 1000	> 1000
Flunisolide	500 - 750	> 750 – 1250	> 1250
Fluticasone propionate	100 - 200	> 200 – 500	> 500
Ciclesonide	80 - 160	> 160 – 320	> 320
Mometasone furoate	100	200	> 200
Triamcinolone acetonide	400 - 800	> 800 – 1200	> 1200

Note: Dose delivery by method or modality other than those noted above must be equivalent

Table 4 Definition of low, medium and high dose ICS for subjects aged 12 years and above

Inhaled corticosteroid	Low daily dose (micrograms (µg))	Medium daily dose (micrograms (µg))	High daily dose (micrograms (µg))
Beclomethasone dipropionate	200 - 500	> 500 – 1000	> 1000
Budesonide DPI	200 - 400	> 400 – 800	> 800
Flunisolide	500 - 1000	> 1000 – 2000	> 2000
Fluticasone furoate	100	n.a.	200
Fluticasone propionate	100 - 250	> 250 – 500	> 500
Ciclesonide	80 - 160	> 160 – 320	> 320
Mometasone furoate	≥ 200	≥ 400	> 400
Triamcinolone acetonide	400 - 1000	> 1000 – 2000	> 2000

8.3 Rescue medication

All rescue medication in this trial will be provided by ALK except adrenaline/epinephrine auto-injector. For ICS, subjects can choose to utilise their current background medication during exacerbations rather than using sponsor provided ICS.

The asthma and rhinoconjunctivitis rescue medication will be dispensed at the baseline visit. If needed, nebuliser or spacer will be re-imbursed by ALK. The rescue medication will be re-supplied as described in the Flowchart (Table 1) when needed.

Asthma rescue medication

- Salbutamol, inhaler 100 µg/dose
- Prednisolone or Prednisone tablets, 5 mg
- Budesonide, inhaler 100 µg/dose and/or 200 µg/dose
- Fluticasone propionate inhaler 50 µg/dose

The above generic names of rescue medication are the International Nonproprietary Names. Synonymous generic names may be used in local labelling.

For the inhalers, the strength and dosage may be stated differently in local labelling; nominal dosage or the dosage as being delivered by the device. For example, the nominal strength for Fluticasone propionate, 50 µg/dose, may be labelled as 44 µg delivered per actuation.

The rescue medication should be used in accordance with the product's labelling (e.g. SmPC or USPI).

The Salbutamol inhaler should be used when necessary according to the dosage instruction for Salbutamol inhaler: Up to 2 doses 4 times per day.

Prednisolone/Prednisone tablets may only be used under the supervision of the investigator or designee. The dosing should be in accordance with the product's labelling for the treatment of an asthma exacerbation and the dosing recommendations by **GINA Executive Committee**

2017, NIH guidelines (National Heart Lung and Blood Institute 2007) or national guidelines (Reddel et al. 2009).

For children, the dosing of prednisolone/prednisone is typically 1-2 mg/kg body weight divided into 1-2 doses daily for 3-5 days.

The doubling of ICS, either by using a Budesonide or Fluticasone propionate inhaler, based on equipotency of the corticosteroids, or by using the subject's own background medication, should only be used under the supervision of the investigator or designee. Doubling of ICS is not permitted for subjects on high dose ICS.

Rhinoconjunctivitis rescue medication
During the trial, subjects may experience allergy symptoms that require additional treatment. Rescue medication for AR or conjunctivitis will be provided by ALK to subjects at visit 2 as pre-defined, open-labelled rescue medication and must be used in addition to the IMP to which the subjects have been randomised.

For the rhinitis symptoms the subject will be provided with:

- Oral antihistamine tablets (Desloratadine tablets, 5 mg)
- Oral antihistamine solution (Desloratadine, oral solution, 0.5 mg/ml)
- Nasal corticosteroid spray (Mometasone furoate 50 µg/dose)

For the conjunctivitis symptoms the subject will be provided with:

- Antihistamine eye drops (Azelastine 0.5 mg/ml)

The rhinitis and conjunctivitis rescue medication provided to the subject should be used according to the product's labelling (e.g. SmPC or USPI). The dosage instructions are described in Table 5.

Table 5 Schedule for rhinitis and conjunctivitis rescue medication

Allergy rescue medication	Subject dosage instructions
Desloratadine tablets, 5 mg[53]	1 tablet once daily as needed for control of AR symptoms (subjects aged ≥12years)
Desloratadine solution, 0.5 mg/ml*	2.5 ml (subjects aged 5 years) / 5 ml (subjects aged 6-11 years) / 10 ml (subjects aged 12 years and above) solution once daily as needed for control of AR symptoms
Mometasone furoate 50 µg/dose	Subjects aged 5-11 years: 1 spray in each nostril once daily as needed for control of AR symptoms. Subjects ≥12 years: 2 spray in each nostril daily as needed for control of AR symptoms. Dose can be reduced to 1 spray in each nostril when the treatment has become effective.
Azelastine eye drops, 0.5 mg/ml	1 drop in the affected eye(s) twice daily, morning and evening as needed in case of persisting allergic conjunctivitis symptoms

Rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector)

In countries where it is a regulatory requirement, two adrenaline/epinephrine auto-injectors will be provided to each subject/parent/caregiver at the baseline visit (visit 2) and should be available around the time that the tablets are administered at home.

Adrenaline/epinephrine auto-injectors are intended for immediate self-administration for an anaphylactic reaction, including symptoms/signs of upper airway obstruction (see Section 9.3 for further details).

Adrenaline/epinephrine auto-injector will be supplied by the investigators, and will be reimbursed by ALK.

8.4 Packaging and labelling

The IMP will be supplied in blister cards containing 10 tablets each. The blister cards will be packed in specific boxes containing a sufficient number of tablets to cover the treatment period between the dispensing visits and the end of trial visit.

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

For Europe: Rescue medication will be sourced as commercially available products in a member state of the European Union. The products will be labelled with an additional label including trial specific information such as trial ID and the statement: “For clinical trial use only”.

For US: For rescue medication commercially available in both EU and US by the same marketing authorisation holder (marketing authorisation holders belonging to the same mother company or group of companies are regarded as the same company in this respect), the products will be sourced in a member state of the European Union and labelled with an additional label including trial specific information such as trial ID, the statement: “For clinical trial use only”, and “Caution: New Drug--Limited by Federal (or United States) law to

[53] Desloratadine will also have an effect on the conjunctivitis symptoms, and will be counted in both the rhinitis and the conjunctivitis medication score.

investigational use". For further details, please see the **Rescue medication product information** document.

Products which are not commercially available in the same form in US as in EU (i.e. Prednisolone and Budesonide inhaler) will be sourced as commercially available in US to be used by US subjects only without additional labelling.

Rescue medication supplied by ALK will be dispensed together with product information leaflets in local language.

Packaging and labelling will be outsourced.

8.5 Handling and storage

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

IMP, asthma and rhinoconjunctivitis rescue medication and SPT must be stored in a secure, limited-access location separately from normal clinic stocks and according to label specifications. IMP and rescue medication returned by the subject must be stored separately from other medication, e.g. unused IMP that has not yet been dispensed.

Site storage conditions for IMP, asthma and rhinoconjunctivitis rescue medication and SPT must be monitored by the site staff for adherence to label specifications and reviewed by the CRA during monitoring visits. Any temperature deviation must be reported to ALK immediately according to the instruction.

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

8.6 IMP and rescue medication accountability

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

- Inventory at the site
- Dispensing to each subject
- Return by each subject to site (unused, partly used and used e.g. empty blister)
- Return by site to ALK

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

Full drug accountability will be performed for the IMP by tablet count. Full drug accountability will not be performed on asthma and rhinoconjunctivitis rescue medication.

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

At the final visit, the investigator should return all unused and partly used IMP and asthma and rhinoconjunctivitis rescue medication and a copy of the completed drug accountability form to the ALK-appointed CRA or to the ALK address provided. The investigator must not destroy any IMP or asthma and rhinoconjunctivitis rescue medication without written agreement with ALK.

8.7 Reporting of technical complaints

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

9 Treatment

9.1 Posology and method of administration

The IMP-tablet 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 5 minutes after intake of IMP. The daily dose of IMP is 1 SLIT-tablet, which should preferably be taken in the morning.

9.2 Precautions in relation to first dosing

First intake of IMP should be at the clinic with a minimum of 30 minutes observation period after the intake. For the recording of onset and duration of solicited AEs that occur on Day 1 (visit 3), the subject should remain in the clinic for 60 minutes after IMP intake.

Prior to IMP intake an oropharyngeal examination should be performed. This should be repeated 60 minutes after IMP intake.

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.

For subjects with symptoms of, or in treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infections, initiation of IMP treatment should be postponed until the condition has improved.

For subjects with a severe asthma exacerbation within the last 30 days prior to randomisation treatment initiation should be postponed by minimum 30 days from the time of the severe asthma exacerbation (start of OCS treatment or first day of hospitalisation). The treatment initiation can be postponed maximum 3 times.

Only subjects meeting all inclusion criteria listed in Section 4.1 and none of the exclusion criteria in Section 4.2 are considered eligible for randomisation and first dosing.

9.3 Rescue medication for severe allergic reactions

In countries where it is a regulatory requirement, the subject/parent/caregiver will be provided with two adrenaline/epinephrine auto-injectors at the randomisation visit (visit 2). The

investigator will instruct the subject/parent/caregiver on how to use the adrenaline/epinephrine auto-injectors and to have it available when tablet is administered.

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

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

At visit 2, the subject/parent/caregiver will also be provided with educational information regarding symptoms of anaphylaxis and treatment, including a written Local and Systemic Allergic Reaction Emergency Plan (**Epstein et al. 2017**). The investigator will provide written instructions and explain to the subject/parent/caregiver , when to administer the adrenaline/epinephrine auto-injectors. The investigator will complete a Local and Systemic Allergic Reaction Emergency Plan for each subject, provide a copy to the subject/parent/caregiver, and keep a copy for the site's records (Section 11.20).

In the event that the adrenaline/epinephrine auto-injector is used, the subject/parent/caregiver must immediately call the local emergency number. The subject must inform the investigator and an unscheduled visit should be arranged to further evaluate the subject. The investigator must report the event to the Sponsor within 24 hours of first becoming aware of the use of an adrenaline/epinephrine auto-injector. The symptoms and/or circumstances that triggered the use of the adrenaline/epinephrine auto-injector must be clearly recorded on the eCRF.

At each visit following the dispensing, the investigator or designee will verify that the subject has adrenaline/epinephrine auto-injectors and will review instructions for use. Unused adrenaline/epinephrine auto-injectors will be collected at visit 11.

9.4 Temporary interruption and discontinuation of treatment

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

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

Interruptions should be kept to a minimum. If IMP is interrupted for more than 7 days in a row, the subject should contact the investigator before restarting the treatment.

If IMP treatment is permanently discontinued, the subject may be discontinued from the trial.

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

In case of a severe asthma exacerbation, IMP treatment should be discontinued temporarily while the subject is treated with OCS or while hospitalised. If the interruption is lasting for more than 7 days, the subject should contact the investigator before restarting the treatment.

9.5 IMP compliance

Subjects must be instructed to bring all residual and unused IMPs and all empty packaging to the site at every visit. Compliance will be assessed at each visit by SLIT-tablets counts. If IMP compliance is less than 80% or more than 100%, the investigator should discuss the reason and educate the subject to comply with the protocol.

The site staff should in cooperation with the subject aim at keeping the IMP compliance above 80%.

9.6 Post-trial treatment

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

10 Visit schedule

In Table 6, the procedures that should be performed at each visit is described. The procedures are listed in the chronological order in which they should preferably be performed:

Table 6 Visit schedule

Visit ID	Procedures to be performed at the visit
Visit 1 (screening)	• Obtain written informed consent for the trial, storage of serum samples in the ALK Research Biobank, and for pharmacogenetic testing, before any other trial procedures are performed • Obtain demographic data (sex, date of birth, race, ethnic origin) • Record medical history • Rhinoconjunctivitis and asthma medication history • Evaluate previous asthma exacerbations • Assess eosinophilic oesophagitis • Record use of relevant concomitant medication • Height and weight • Measure vital signs • Perform physical examination • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test if applicable (No data are available for SPT in pregnant subjects, therefore perform the urine pregnancy test before SPT) • Perform SPT and evaluate results[54] (to be performed at visit 2, if wash-out of concomitant medication is required) • Assess compliance with inclusion and exclusion criteria • Collect blood and urine sample for safety laboratory assessments

[54] If medication that could interfere with the skin prick test, according to Table 9, has not been washed out and the positive control is <3 mm for subjects in Europe and <5 mm for subjects in North America, the skin prick test must be repeated after the interfering medication has been washed out.

Visit ID	Procedures to be performed at the visit
	• Collect blood sample for specific IgE against *D. pteronyssinus*, *D farinae*, *Cladosporium herbarum* and *Blattella germanica* • Assess AEs • Schedule date for visit 2
TC1	• Inform subjects of continued participation in trial depending on the blood sample for specific IgE against *D. pteronyssinus* and *D. farinae* • Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted]
Visit 2 (baseline)	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Record changes to concomitant medication • Re-assess compliance with inclusion and exclusion criteria • Perform oropharyngeal examination • Measure height and weight • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • SPT, if not possible at visit 1 due to necessary wash-out of concomitant medication • Evaluate inhalation technique • Instruct the subject and/or parent/caregiver on how to use the asthma and rhinoconjunctivitis rescue medication • Dispense asthma and rhinoconjunctivitis rescue medication • Show Trial Video • Issue and instruct the subject and/or their parent/caregiver in the use of the Asthma Action Plan. Dispense Peak Expiratory Flow (PEF) Meter • Instruct the subject and/or their parent/caregiver in the use of rescue medication for severe allergic reaction • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector) in countries where this is a regulatory requirement • Issue and instruct the subject and/or their parent/caregiver in the use of the Local and Systemic Allergic Reaction Emergency Plan • Issue and instruct the subject and/or their parent/caregiver in the use of the eDiary for the next 21 days • Activate the eDiary • [redacted] • Schedule date for visit 3
TC2	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication

Visit ID	Procedures to be performed at the visit
Visit 3 (Randomisation)	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit[55] • Assess eosinophilic oesophagitis • Record changes to concomitant medication • Check eDiary compliance • Re-assess compliance with inclusion and exclusion criteria • Randomise the subject • Measure height and weight. If necessary adjust Asthma Action Plan • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • Dispense asthma and rhinoconjunctivitis rescue medication as needed • Instruct in the use of asthma and rhinoconjunctivitis rescue medication • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed • Instruct in the use of rescue medication for severe allergic reaction • Collect used rescue medication if new rescue medication is dispensed • Evaluate ACQ/ACQ-IA, [redacted] • [redacted] • [redacted] • [redacted] • Collect blood sample for immunological assessments • Collect blood and urine samples for biobank (should only be performed if the specific consent has been obtained) • Collect blood sample for pharmacogenetic analysis (should only be performed if the specific consent has been obtained) • Perform oropharyngeal examination before and 60 minuttes after IMP intake[56] • Instruct the subject and/or parent/caregiver on how to use the IMP First intake of IMP at the clinic. The first dose will be administered at the clinic with a minimum subsequent 60 minutes observation period[57] • Dispense IMP to the subject • Instruct in recording of prespecifed symptomes in eDiary • Activate subject eDiary for the next period • Schedule date for visit 4
Visit 4 (Solicited AEs)	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Perform oropharyngeal examination • Record changes to concomitant medication

[55] For subjects with a severe asthma exacerbation within the last 30 days prior to randomisation treatment initiation should be postponed by minimum 30 days from the time of the severe asthma exacerbation (start of OCS treatment or first day of hospitalisation). The treatment initiation can be postponed maximum 3 times, see Section 9.2

[56] 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, see Section 9.2

[57] For subjects with symptoms of, or in treatment for, upper respiratory tract infection, acute sinusitis, acute otitis media or other relevant infections, initiation of IMP treatment should be postponed until the condition has improved, see Section 9.2

Visit ID	Procedures to be performed at the visit
	• Assess prespecified symptoms in eDiary and record solicited AEs in eCRF • Check eDiary compliance • Activate subject eDiary for the next period • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • Follow-up on IMP compliance • Dispense asthma and rhinoconjunctivitis rescue medication as needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine), if needed • Collect used rescue medication if new rescue medication is dispensed. • [redacted] • Schedule date for visit 5
TC3, 4	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted] • Instruct subject and/or their parent/caregiver in the use of the eDiary prior to next visit and remind them to charge the device
Visit 5	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Perform oropharyngeal examination • Record changes to concomitant medication • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • Check eDiary compliance • Activate subject eDiary for the next period • Collect used IMP and rescue medication as applicable and perform drug accountability and a compliance check • Dispense IMP to the subject • Dispense asthma and rhinoconjunctivitis rescue medication, as needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed • Evaluate ACQ/ACQ-IA, [redacted] (subjects aged 12 years or above) • [redacted]

Visit ID	Procedures to be performed at the visit
	• Schedule date for visit 6
TC5, 6, 7	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted] • Instruct subject and/or their parent/caregiver in the use of the eDiary prior to next visit and remind them to charge the device
Visit 6	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Perform oropharyngeal examination • Record changes to concomitant medication • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • Check eDiary compliance • Activate subject eDiary for the next period • Collect used IMP and rescue medication as applicable and perform drug accountability and a compliance check • Dispense IMP to the subject • Dispense asthma and rhinoconjunctivitis rescue medication as needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed • Evaluate ACQ/ACQ-IA, [redacted] • Schedule date for visit 7
TC8, 9, 10	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted] • Instruct subject and/or their parent/caregiver in the use of the eDiary prior to next visit and remind them to charge the device
Visit 7	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Perform oropharyngeal examination • Record changes to concomitant medication • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs

Visit ID	Procedures to be performed at the visit
	• Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Evaluate inhalation technique • Collect urine for pregnancy test (if applicable) • Check eDiary compliance • Activate subject eDiary for the next period • Collect used IMP and rescue medication as applicable and perform drug accountability and a compliance check • Dispense IMP to the subject • Dispense asthma and rhinoconjunctivitis rescue medication as needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed • Evaluate ACQ/ACQ-IA, [redacted] (subjects aged 12 years or above) • [redacted] • Collect blood and urine sample for safety laboratory assessments • Collect blood sample for immunological assessments • Collect blood and urine sample for biobank (should only be performed if the specific consent has been obtained) • Schedule date for visit 8
TC11, 12, 13	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted] • Instruct subject and/or their parent/caregiver in the use of the eDiary prior to next visit and remind them to charge the device
Visit 8	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Oropharyngeal examination • Record changes to concomitant medication • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs • Measure FEV1 and calculate the % of predicted FEV1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • Check eDiary compliance • Activate subject eDiary for the next period • Collect used IMP and rescue medication as applicable and perform drug accountability and a compliance check • Dispense IMP to the subject • Dispense asthma and rhinoconjunctivitis rescue medication as needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed • Evaluate ACQ/ACQ-IA, [redacted] • [redacted]

Visit ID	Procedures to be performed at the visit
	• [redacted] • Schedule date for visit 9
TC14, 15, 16	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted] • Instruct subject and/or their parent/caregiver in the use of the eDiary prior to next visit and remind them to charge the device
Visit 9	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Perform oropharyngeal examination • Record changes to concomitant medication • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • Check eDiary compliance • Activate subject eDiary for the next period • Collect used IMP and rescue medication as applicable and perform drug accountability and a compliance check • Dispense IMP to the subject • Dispense asthma and rhinoconjunctivitis rescue medication as needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed • Evaluate ACQ/ACQ-IA, [redacted] (subjects aged 12 years or above) • [redacted] • Schedule date for visit 10 or visit 11
TC17, 18, 19	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted] • Instruct subject and/or their parent/caregiver in the use of the eDiary prior to next visit and remind them to charge the device
Visit 10[58]	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis

[58] Visit 10 is not applicable for subjects randomised after 31-Mar-2018 for cohort 1 and after 31-Mar-2019 for cohort 2

Visit ID	Procedures to be performed at the visit
	• Perform oropharyngeal examination • Record changes to concomitant medication • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Collect urine for pregnancy test (if applicable) • Check eDiary compliance • Activate subject eDiary for the next period • Collect used IMP and rescue medication as applicable and perform drug accountability and a compliance check • Dispense IMP to the subject • Dispense asthma and rhinoconjunctivitis rescue medication as needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed • Evaluate ACQ/ACQ-IA, [redacted] • [redacted] • Schedule date for visit 11
TC20	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • [redacted] • Instruct subject and/or their parent/caregiver in the use of the eDiary for the next 14 days and remind them to charge the device
Visit 11 (Final)	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Assess eosinophilic oesophagitis • Record changes to concomitant medication • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Measure vital signs • Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA washout • Perform physical examination • Collect unused IMP/rescue medication and empty blistercards • Perform drug accountability • Check IMP compliance • Collect eDiary • Check eDiary compliance • Evaluate ACQ/ACQ-IA, [redacted] • Evaluate Global evaluation for asthma and AR. • [redacted] • Collect urine for pregnancy test (if applicable) and for safety laboratory

Visit ID	Procedures to be performed at the visit
	assessments • Collect blood and urine sample for safety laboratory assessments • Collect blood sample for immunological assessments • Collect blood and urine sample for biobank (should only be performed if the specific consent has been obtained) • Collect blood sample for pharmacogenetic analysis (should only be performed if the specific consent has been obtained) • Schedule date for a telephone follow-up contact approximately one week later
TC21 Follow-up phone contact	• Record AEs If an AE was ongoing at the previous visit, if a new AE is identified at the telephone contact or if one of the safety laboratory parameters measured at the previous visit showed a clinically significant abnormality, the subject could be asked to return to the trial site. • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication
Unscheduled visit	• Assess AEs occurring since the last visit • Evaluate asthma exacerbations occurring since the last visit • Record changes to concomitant medication • Measure FEV_1 and calculate the % of predicted FEV_1 • Measure height and weight. If necessary adjust Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan • Evaluate ACQ/ACQ-IA, [redacted] The following procedures will be performed if deemed necessary by the investigator: • Measure vital signs • Physical examination • Assess eosinophilic oesophagitis • Perform oropharyngeal examination (when physical examination is not performed) • Collect urine for pregnancy test (if applicable) • Collect blood and/or urine sample for safety laboratory assessments • Collect blood sample for specific IgE against D pteronyssinus and D farinae • Collect blood sample for immunological assessment • Dispense IMP, if needed • Intake of IMP at clinic • Dispense asthma and rhinoconjunctivitis rescue medication, if needed • Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine auto-injector), if needed

11 Assessments

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

The tasks listed below must be performed by a physician:

- Obtainment of informed consent
- Evaluation of in- and exclusion criteria
- Physical examination
- Assessment of AEs/serious adverse events (SAEs)
- Assessment of FEV_1 and laboratory results
- Decision to break the randomisation code for individual subjects

11.1 Informed consent

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

If the minor can understand the risks and benefits of the trial, he/she should also be informed and, if capable, provide written assent. Assent should be obtained according to national requirements. Subjects turning 18 years during the trial must sign the adult informed consent form.

It is the responsibility of the principal investigator or a sub-investigator to obtain the written informed consent/assent from the parents/caregivers and subject, respectively.

The investigator must explain the nature of the trial, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail and provide the subject with a copy of the information sheet and the consent form. Information to the parent/caregiver 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 to document this.

The parent/caregiver and subject must be given sufficient time to consider the trial before deciding whether to participate. Each subject must be informed that participation in the trial is voluntary, 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 informed consent/assent form must be signed and dated before the subject enters the trial (i.e. before any trial related activity). The investigator must give a copy of the signed informed consent/assent to the parent/caregiver and subject. The investigator should keep the original.

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

11.2 Consent for biobank blood and urine samples

When the subject/parent/caregiver is asked to consent to the participation in the trial, children with a body weight over 20 kg will be asked specifically if they will donate 3 blood samples of 5 ml each and 3 urine samples of 5 ml each. All samples will be stored in the ALK Research

Biobank. The answer to this question will be recorded on the consent form for retention of blood and urine samples for future research, as well as in the eCRF. The samples will be taken at visits 3, 7 and 11. The subject/parent/caregiver cannot consent to sample donation after visit 3 as the first sample has to be taken before first IMP intake. If sampling and storage of these blood and urine samples are not accepted by the subject/parent/caregiver, the samples must not be drawn. Subjects can participate in the trial without giving consent to donating biobank samples.

11.3 Consent for collection of blood samples for pharmacogenetic testing

When the subject/parent/caregiver is asked to consent/assent to the participation in the trial, children with a body weight over 20 kg will be asked specifically if they can accept sampling for pharmacogenetic tests and storage of a DNA and RNA sample. The answer to this question will be recorded on the consent form for retention of samples for future pharmacogenetic testing, as well as in the eCRF. The sample volume will be 2.5 ml and the samples will be taken at visit 3 and 11. The subject/parent/caregiver cannot consent to sample donation after visit 3 as the first sample has to be taken before first IMP intake. Collection of pharmacogenetic samples is not necessary for participation in the trial. If pharmacogenetic sampling and storage is not accepted by the subject/parent/caregiver, the samples must not be drawn.

11.4 Demographics

The following data will be recorded:

- Month and year of birth
- Race and ethnic origin
- Sex

11.5 Medical history

The relevant medical history, incl. diseases present at trial entry must be recorded in the eCRF.

The asthma history should include a detailed description of all asthma exacerbations including information on visits to emergency rooms, hospitalisations and changes in asthma treatment during the past 2 years. In addition a detailed allergy history including recording of the subject's history of rhinitis, conjunctivitis, atopic dermatitis and food allergy.

Information on exposure to cigarette smoke will be collected.

11.6 Concomitant medication

The subjects' use of all concomitant medication including rhinoconjunctivitis and asthma medication must be recorded. Standard information about the medication will be collected including name of medication, dose, administration route and treatment period.

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

At each visit the investigator should ask the subject about use of concomitant medication. All concomitant medication must be documented in the subject's medical records and in the eCRF.

Furthermore, each change in concomitant medication (e.g. new treatment, discontinuation of treatment and change in dosage/routine) during the trial must be documented in the same way.

11.7 Height and weight

The subject's body height and weight will be recorded as noted on the Flow chart.

11.8 Vital signs

Vital signs will include measurement of BP and heart rate in a seated position (after ≥ 5 minutes of seated inactivity).

11.9 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. The predicted FVC and FEV_1 will be based on the Quanjer equation (**Quanjer et al. 1995**). If the subject self-reports his/her race as Black, appropriate adjustments will automatically be made for race by programming the spirometer using the formula:

FEV_1 predicted x 0.88 = FEV_1 predicted adjusted for race.

Spirometry should be performed in accordance with guidelines established by the American Thoracic Society/European Respiratory Society (**Reddel et al. 2009**). The % of predicted FEV_1 will be calculated in the eCRF. Lung function will be measured with subjects on background treatment, though following a 6-hour washout of SABA.

11.10 Physical examination

The physical examination should be performed by a physician and should be based on the following body systems see Table 7.

Table 7 Physical examination

Body system	Minimum examinations to be completed
General appearance	Nutritional status, consciousness, skin colour and for children developmental status
Skin	Inspection of skin
Head	Ears - Inspection of auricles and external canal (otoscopy is not required) Eyes - Inspection of conjunctivae and eyelids, examination of pupils including reaction to light Nose - Inspection of nasal mucosa (nasal endoscopy is optional) Oral cavity – oropharyngeal inspection of lips, tongue, tonsils and uvula will be performed for signs of mouth irritation, edema, and any other abnormalities. When performed at visit 3, it will take place before and 60 minutes after IMP administration.
Lymph nodes	Examination of lymph nodes (cervical, axillary, and inguinal lymph nodes)
Respiratory	Assessment of respiratory effort, including respiratory rate Palpation and percussion of chest Auscultation/stethoscopy of lungs
Heart	Auscultation/stethoscopy of the heart
Abdomen	It is up to the investigators discretion to evaluate whether an examination of the abdomen is necessary. Questions regarding symptoms may be sufficient.
Urogenital	It is up to the investigators discretion to evaluate whether an examination of the urogenital system is necessary. Questions regarding symptoms may be sufficient.
Musculoskeletal and neurological	It is up to the investigators discretion to evaluate whether an examination of the musculoskeletal/neurological system is necessary. Questions regarding symptoms may be sufficient.
Other abnormality	If applicable

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

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

11.11 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 test will be performed by dip-stick at the trial site.

11.12 Skin prick test

All skin prick test (SPT) materials will be supplied by ALK. SPT must be performed according to the guideline provided by ALK. No data are available for SPT in pregnant subjects, therefore the urine pregnancy test must be performed before the SPT.

Subjects enrolled in the trial will be tested for the allergens listed in Table 8.

Table 8 Skin prick test

COUNTRY	ALLERGEN
All Countries	Positive control – Histamine
	Negative control – Saline
	HDM - *Dermatophagoides pteronyssinus*
	HDM - *Dermatophagoides farinae*
	Cat - *Felis domesticus*
	Dog - *Canis familiaris*
	Mold - *Alternaria alternata*
	Grass – *Phleum pratense*
	Ragweed – *Ambrosia artemisiifolia*
	Tree – *Betula verrucosa*

Some medications may affect the outcome of the SPT and should be washed out before performing the SPT. Concerned medications are listed in Table 9.

Table 9 Medications with a possible interference with SPT[59]

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

11.13 Blood and urine sampling

The following types of blood samples will be drawn during the trial:

Purpose	Volume	Number of samples
Safety / Hematology	2 ml	3
Safety / Blood chemistry	2.5 ml	3
Screening / IgE	5 ml	1
Immunology	5 ml	3
Total	33.5 ml	

The following types of urine samples will be collected during the trial:

Purpose	Volume	Number of samples
Safety / Urinalysis	10 ml	2
Pregnancy tests	NA	At each visit (if applicable)

[59] If medication that could interfere with the SPT, according to Table 9, has not been washed out and the positive control is <3 mm for subjects in Europe and <5 mm for subjects in North America, the SPT must be repeated after the interfering medication has been washed out.

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

Purpose	Sample type	Volume	Number of samples during the trial
Long term storage - serology sample (biobank samples)	Blood	5 ml	3
Long term storage - DNA + RNA sample (pharmacogenetics samples)	Blood	2,5 ml	2
Total Blood volume		20 ml	5
Long term storage – Urine sample	Urine	5 ml	3

11.14 Laboratory assessments

All laboratory assessments will be performed centrally at a certified laboratory selected by ALK with the exception of urine dipsticks, which will be handled on site.

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

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

Blood samples should be taken using standard venepuncture techniques. The planned total volume of blood drawn from each subject is 33.5 ml. Additional 15 ml will be collected for subjects who consent to the biobank samples and 5 ml for the pharmacogenetic samples. Local anestesia may be used in connection with blood sampling.

Urine will be collected for urinalysis. Urine dipsticks to be used on site will be provided by the central laboratory. A microscopic examination should be performed only if any of the urine evaluations are abnormal.

The following laboratory variables will be measured:

Hematology:

Erythrocytes, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), platelets, leukocytes, neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

Blood chemistry:

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

Urinalysis:

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

IgE:

To confirm the diagnosis of allergy against HDM, blood samples will be drawn at the screening visit for determination of specific IgE against *D. pteronyssinus* and *D. farinae*. Additionally, the blood samples will be analysed for [redacted] and specific IgE against *Blattella germanica* (cochroach) and *Cladosporium herbarum* (mold).

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

Immunology:

To assess the immunological response of the treatment, blood samples will be drawn for determination of antigen-specific antibodies (e.g. IgE and IgG_4), [redacted], and other immunological parameters. At each time point, 5 mL blood will be drawn in silicone-free serum gel tubes. The samples will be analysed by the Research Department at ALK.

Biobank blood sample

This blood sample will only be drawn if the subject has a body weight of more than 20 kg and consents to long term storage of an immunology sample. If blood sampling for the biobank is accepted, three 5 mL blood samples will be drawn. The blood sample will be drawn at visits 3, 7 and 11 where blood sampling already is planned. The subject will consequently only donate extra blood, no additional venepuncture is required.

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

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

Blood sample for pharmacogenetics

This blood sample will only be drawn if the subject has a body weight of more than 20 kg and consents to long term storage of a DNA sample.

DNA and RNA material will be extracted from the blood sample at a central laboratory selected by ALK. If pharmacogenetic sampling is accepted, two 2.5 mL blood samples will be drawn. The blood sample will be drawn at visits 3 and 11 where blood sampling already is planned. The

subject will consequently only donate an extra blood sample, no additional venepuncture is required.

The DNA and RNA samples collected in the current trial will be used to investigate various genetic causes for how subjects may respond to the treatment as well as the impact the treatment may have on the epigenetic profile of the subjects. The DNA and RNA samples will be stored to provide a resource for future studies conducted by ALK focused on the investigation of how genes can affect drug absorption, distribution and removal from the body, and drug action in the body or vice versa, how drugs can affect gene expression profiles.

Studies may include analyses for identifying for instance genomic markers of atopic diseases, efficacy of allergy treatment, AEs, or other genomic markers relevant for the atopic disease and treatment of allergy. Pharmacogenetic results may be compared to pharmacodynamic results or clinical outcomes. Any significant pharmacogenetic relationships to outcome will require validation in future clinical trials.

Since the complex interactions between allergy immunotherapy, rhinoconjunctivitis and asthma are currently not characterised to a level that translates to a meaningful clinical advantage, individual results from the pharmacogenetic analyses will not be given to the subjects. For the same reasons, individual results will not be added to the subjects' medical records.

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

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

11.15 Adverse event assessment

The investigator will question the subject about AEs since the last visit (as applicable), and will record the information on the eCRF (see Section 12 for instructions on assessment and reporting of (S)AEs and pregnancies to the sponsor).

The eDiary will be used to capture information on 15 specific symptoms identified as local effects of sublingual immunotherapy (Section 11.21) on a daily basis from the subject for the first 28 days of treatment (**Passalacqua et al. 2013**). The eDiary is to be completed by the subject/parent/caregiver. Subjects and/or their parent/caregiver will be trained by the investigator or designee at visit 3 on the proper method to complete the eDiary. The reported symptoms will be evaluated by investigator and reported in the eCRF as solicited AEs.

The solicited AEs that occur on Day 1 (visit 3) within 60 minutes of IMP intake, including the time of AE start and AE stop, will be monitored by site personnel, recorded in source documents, and entered into the eCRF.

11.16 Asthma exacerbation assessment

An Asthma Action Plan (Section 11.19) will be given to the subjects and parents/caregivers to provide guidance to effectively manage the subject's symptoms, as recommended by clinical practice guidelines. Subjects will be trained in their Asthma Action Plan by the investigator or designee.

According to the Asthma Action Plan subjects must contact the investigator when asthma symptoms increase or in cases with reduction in lung function. The investigator or designee will fill in the appropriate treatment for the subjects in the Asthma Action Plan.

Subjects will continue with a constant dose of low dose ICS plus LABA or medium/high dose ICS with or without LABA throughout the trial.

If a subject presents with worsening of asthma symptoms, investigator or designee should always evaluate if the subject requires treatment at emergency room. If emergency room visit is not required initial treatment can be either:

- Doubling of ICS dose compared to background treatment for 2 weeks, or
- Systemic corticosteroids for treatment of asthma symptoms for at least 3 days

For the doubling of ICS dose a separate inhaler with ICS will be provided by ALK as part of the asthma rescue medication. Subjects may also double their ICS dose by using their background medication. Subjects that receive high dose ICS as background treatment are not allowed to double the dose of ICS. Please note that local regulations and SmPCs or USPI must be followed. In case of an asthma exacerbation requiring systemic corticosteroids, the subjects should be treated with OCS in the form of Prednisolone/Prednisone tablets. Dosing regimen should follow recommendations by GINA guideline (**GINA Executive Committee 2017**), NIH guidelines (**National Heart Lung and Blood Institute 2007**) or national guidelines (**Reddel et al. 2009**). See Section 8.3.

The use of LTRA is permitted for continued use only but will not be provided by ALK.

If a subject has 2 severe asthma exacerbations within 12 consecutive months or is hospitalised due to asthma requiring treatment with systemic corticosteroids the subject must be discontinued from the IMP treatment.

Each severe asthma exacerbation must be separated by >7 days from the discontinuation of OCS to be considered an individual event (**Lanier et al. 2009**).

Each clinically relevant asthma exacerbation must be separated by >7 days from the discontinuation of additional ICS or OCS to be considered an individual event.

All clinically relevant asthma exacerbations and severe asthma exacerbations (as defined in Table of definitions on page 10) must be reported in the eCRF within 24 hours.

11.17 Assessment of symptoms

Rhinoconjunctivitis and asthma symptoms will be recorded in the eDiary by the subject with assistance from his/her caregiver at specified periods during the trial. A video with information on the rating will be available for the subjects.

A total of 10 symptoms; 6 rhinitis and/or conjunctivitis symptoms and 4 asthma symptoms will be measured on a scale from no symptoms to severe symptoms (for details, please see Table 10 and Table 11).

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

Table 10 Subject's symptom scoring

Scored by subject	Definition of score	Numerical Score[1]
No symptoms	No sign/symptom evident	0
Mild symptoms	Symptom clearly present, but minimal awareness; easily tolerated	1
Moderate symptoms	Definite awareness of symptom that is bothersome but tolerable	2
Severe symptoms	Symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping	3

[1] Scoring scales are not seen by the subjects

Table 11 Construction of symptom scores[1]

Rhinitis symptoms	Rhinitis DSS	[redacted]	Rhinoconjunctivitis DSS	Asthma DSS
Runny nose	0-3		0-3	
Blocked nose	0-3		0-3	
Sneezing	0-3		0-3	
Itchy nose	0-3		0-3	
Conjunctivitis symptoms				
Gritty feeling/red/itchy eyes			0-3	
Watery eyes			0-3	
Asthma symptoms				
Chest tightness				0-3
Wheezing				0-3
Cough				0-3
Shortness of breath				0-3
Total range	0-12		0-18	0-12

[1] Scoring scales are not seen by the subjects

11.18 Medication assessment

All subjects are provided with open-label rescue medication for treatment of rhinitis, conjunctivitis and asthma. Use of rhinoconjunctivitis and asthma rescue medication will be recorded by the subject with assistance from his/her caregiver on a daily basis during eDiary periods. The use of asthma background treatment will also be recorded.

Subjects are instructed to report their use of specific rhinoconjunctivitis or asthma rescue medication via the daily eDiary in the baseline period (period 2) and at specified timepoints during the trial. To transform the amount of rhinoconjunctivitis rescue medication used into medication scores the scoring principles detailed in Table 12 will be used.

Table 12 Scoring of rhinoconjunctivitis rescue medication

Rescue medication	Subject dosing instruction	Score/ Dose unit[1]	Maximum daily score
Rhinitis medication score			
Desloratadine tablets[2], 5 mg Or Desloratadine Oral solution 0.5 mg/ml	< 6 years old: 2.5 ml once daily	4	4
	6-11 years old: 5 ml once daily		
	Above 12 years: 1 tablet or 10 ml solution once daily		
Mometasone furoate nasal spray, 50 µg/dose	<12 years old: 1 puff in each nostril once daily	4	8
	>12 years: 2 puffs in each nostril once daily	2	
Maximum daily rhinitis medication score[3]			12
Conjunctivitis medication score			
Desloratadine tablets[2], 5 mg Or Desloratadine Oral solution 0.5 mg/ml	5 years old: 2.5 ml once daily	2	2
	6-11 years old: 5 ml once daily		
	Above 12 years: 1 tablet or 10 ml solution once daily		
Azelastine eye drops, 0.5 mg/ml	1 drop in each eye twice daily	1.5	6
[redacted]			
Maximum daily rhinoconjunctivitis medication score[3]			20

[1] Scoring scales are not seen by the subjects
[2] Desloratadine will count 4 in the rhinitis score and 2 in the conjunctivitis score, based on assumed equal efficacy of antihistamine on the 4 nasal symptoms and 2 eye symptoms (**Salmun & Lorber 2002**)
[3] If any subject exceed the recommended daily dose of symptomatic medication, the actual score will be used

11.19 Asthma Action Plan

An Asthma Action Plan will be given to the subjects and parents/caregivers to provide guidance to effectively manage the subject's symptoms, as recommended by clinical practice guidelines. Subjects will be trained in their Asthma Action Plan by the investigator or designee. According to the Asthma Action Plan, subjects must contact the investigator when asthma symptoms increase or in cases with reduction in lung function. Signs and symptoms of asthma worsening include:

- Cough, wheeze, chest tightness or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities, or
- Increased need for reliever medication, or
- Peak flow 50-79% of personal best

The investigator or designee will fill in the appropriate treatment for the subjects in the Asthma Action Plan.

The subject is instructed to call an ambulance while taking reliever medication at regular intervals as pre-specified by the investigator for serious situations when the subjects experience that:

- Symptoms worsens very quickly
- Wheeze, chest tightness or shortness of breath continue after taking reliever medication, or
- There is severe shortness of breath, inability to speak comfortably, blueness of lips, or
- Peak flow is below 50% of personal best

11.20 Anaphylaxis Emergency Action Plan

The subject/parent/caregiver will be provided with educational information regarding symptoms of anaphylaxis and treatment, including a written Local and Systemic Allergic Reaction Emergency Plan (**Epstein et al. 2017**). The Local and Systemic Allergic Reaction Emergency Plan will detail the mild to moderate local reactions that include:

- Mouth: bothersome itching, and/or mild swelling of lips and/or tongue
- Throat: bothersome itching, irritation, and/or mild tightness
- Ear: bothersome itching
- Gastrointestinal: mild abdominal pain, nausea, and/or cramps

The Local and Systemic Allergic Reaction Emergency Plan specifies that these symptoms may be treated with an anti-histamine, if treatment is required, where the dose is pre-specified by the investigator on the plan.

Severe reactions are defined as:

- Local reaction with swelling in the mouth/throat causing hoarseness and/or throat closing
- Systemic reactions such as
    - Skin: hives all over body and/or redness all over body
    - Lung: shortness of breath, cough, and/or wheezing
    - Heart: weak pulse, dizziness, and/or passing out
    - Gastrointestinal: severe abdominal pain, vomiting, diarrhea, and/or cramping

Severe reactions should be treated in accordance with the Local and Systemic Allergic Reaction Emergency Plan as instructed by the investigator.

11.21 Solicited Adverse Events

The eDiary will be used to capture 15 specific symptoms, identified as local side effects of sublingual immunotherapy (**Passalacqua et al. 2013**):

- Food tastes different
- Mouth ulcer
- Swelling in the back of the mouth
- Itching in the mouth
- Itching in the ear
- Swelling of the lips
- Swelling of the tongue
- Tongue pain
- Tongue ulcer
- Throat irritation/tickle
- Throat swelling
- Stomach pain
- Nausea (feel like throwing up)
- Diarrhea
- Vomiting

If the subject answers “yes” to any of the symptoms, the subject will be asked if any medication was used to treat the symptom.

These local side effects will be collected by a daily eDiary during the first 28 days of treatment. The eDiary is to be completed by the subject/parent/caregiver. Subjects will be trained by the investigator or designee at visit 3 in the proper way to complete the eDiary. The reported symptoms will be evaluated and reported in the eCRF as solicited AEs at the discretion of the investigator.

The duration in minutes of the solicited AEs occurring on Day 1 will also be assessed. The AE start and stop time of solicited AEs that occur on Day 1 within 60 minutes of IMP intake, will be monitored by site personnel, recorded in source documents, and entered into the eCRF. After Day 1, standard AE reporting conventions will be utilised.

Summary statistics for adverse event severity of the solicited AEs will be performed using the World Allergy Organization (WAO) grading system for SLIT local adverse events.

A review of the severity grading by the WAO criteria and severity grading as determined by the investigator’s review of prespecified symptoms with their subjects will be conducted. For the purpose of the analysis, a modified WAO severity grading will be applied as follows:

- Mild (Grade 1) - No symptomatic treatment required and no discontinuation of SLIT because of local side effects
- Moderate (Grade 2) - Requires symptomatic treatment and no discontinuation of SLIT because of local side effects

- Severe (Grade 3) - Grade 2 and SLIT discontinued because of local side effects

11.22 Eosinophilic oesophagitis

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

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

If a subject presents with any of the above, the investigator should consider referring the subject to a gastroenterologist for evaluation.

11.23 Subject [redacted] reported outcomes

A number of outcomes will be reported by the subjects during the trial. To minimise the burden to the subjects, the subject reported outcomes have been distributed to alternating visits whenever possible. The following questionnaires will be completed by the subject, by the caregiver or via an interview by the trial staff during the visits at the site:

- eDiary assessments
- ACQ
  - ACQ-IA (subjects aged 5 to 10 years) Interviewer administered
  - ACQ (subjects aged 11 years and above) Self-completed by the subjects
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
- [redacted]
  - [redacted]

- Global evaluation of allergic asthma
    - Interviewer administered
- Global evaluation of AR
    - Interviewer administered

11.23.1 eDiary assessments

During the trial, the subjects and/or their parent/caregiver will complete an eDiary. The eDiary is a hand-held electronic device that will be issued to the subjects before the start of the baseline period (period 2).

The following items will be outlined in the eDiary at pre-specified intervals during the trial:

- Asthma symptoms and VAS
    - Nocturnal awakenings due to asthma requiring SABA
- Use of asthma rescue medication
- Rhinoconjunctivitis symptoms and VAS
- Use of rhinoconjunctivitis medication
- Specific symptoms identified as local effect of sublingual immunotherapy, see Section 12.3, for capturing solicited AEs

The eDiary is to be completed by the subject/parent/caregiver for 21 days between baseline (V2) and randomisation visit (V3). After randomisation, the eDiary is to be completed for 2 weeks before visit 5, 6, 7, 8, 9, 10 and 11. Finally, the eDiary is to be completed for 4 weeks following randomisation for capturing specific symptoms identified as local effect of sublingual immunotherapy.

11.23.2 Asthma quality of life questionnaire

The ACQ will be completed by all subjects during the trial at most regular visits and at all unscheduled visits. Subjects aged ≥11 years will self-complete the questionnaire when possible. An interviewer administered version will be used to subjects aged 5-10 years. The ACQ-IA will be used for all subjects aged 5 to 10 years of age although it is only validated for children from 6 years of age. However, since this is a two year trial, all 5 year old children will be 7 years of age at the end of the trial.

ACQ-IA

The ACQ-IA questionnaire will be completed by subjects aged 5 to 10 years during the trial. Questions will be administered by a trained interviewer. The questionnaire contains five scoring symptoms, one question about SABA medication use and another about FEV_1, the latter being completed by the clinic staff. Subjects are asked to recall their experiences during the previous 7 days and respond to each question using a 7-point scale. The items are equally weighted and the ACQ-IA score is the mean of the 7 items and therefore between 0 (well controlled) and 6 (extremely poorly controlled).

Derivation of answers and the scales used has been provided in Appendix 5.

ACQ

The ACQ questionnaire will be completed by subjects aged ≥11 years during the trial if possible. Alternatively the interviewer administered version will be used. The questionnaire contains five scoring symptoms, one question about SABA medication use and another about FEV_1, the latter being completed by the clinic staff. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale. The items are equally weighted and the ACQ score is the mean of the 7 items and therefore between 0 (well controlled) and 6 (extremely poorly controlled).

[redacted]

[redacted]

11.23.7 Global evaluation

At the final visit the subjects will be asked about their perception of the treatment efficacy during the treatment period answering the following question:

Rhinitis

"Compared to your rhinitis symptoms before starting treatment with the IMP, how are you feeling overall now?"

1. Much better
2. Better
3. The same
4. Worse
5. Much worse

Asthma

"Compared to your asthma before starting treatment with the IMP, how are you feeling overall now?"

1. Much better
2. Better
3. The same
4. Worse
5. Much worse

[redacted]

11.23.9 Peak flow meter

The subjects will perform peak flow measurements when symptoms worsen according to the Asthma Action Plan, see Section 11.19.

12 Adverse events

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

Any AE occurring from the time the informed consent was signed by the subject and until the last follow-up phone contact must be recorded and reported on an 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 procedures and conduct of the trial.

12.1 Definitions

Adverse event

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

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

The following events should not be recorded as AEs:

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

Serious adverse event

A 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 inpatient hospitalisation, regardless of duration, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is judged to be medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above)

Events of special interest

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

- Severe asthma exacerbations and clinically relevant asthma exacerbations (as defined in Table of definitions)
- Anaphylactic reactions, anaphylaxis[60] and/or systemic allergic reactions
- Events treated with adrenaline/epinephrine
- Severe local swelling or oedema of the mouth and/or throat
- Eosinophilic oesophagitis

Severe and clinically relevant asthma exacerbations reported during the trial are expected as a result of subjects' background disease and will be collected in the eCRF as ESIs throughout the trial in order to get detailed information related to the primary efficacy endpoint. Severe and clinically relevant asthma exacerbations will not be considered a safety endpoint unless an exacerbation fulfils the criteria for an SAE. Severe and clinically relevant asthma exacerbations reported during periods 3 and 4 will be summarised as part of the efficacy results in the integrated clinical trial report (ICTR).

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

The definition of an AE also covers medication errors and use 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 systemic allergic reactions or severe local reactions.

- 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

[60] 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, togue, 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 (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

- Abuse: Persistent or sporadic, intentional excessive use which is accompanied by harmful physical or psychological effects
- Misuse: Intentional and inappropriate use

12.2 Assessments

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

Causal relationship to IMP

The causal relationship between an (S)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.

Outcome

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

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

12.3 Collection, recording and reporting of adverse events

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

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

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

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

Solicited Adverse Events

The eDiary will be used to capture 15 specific 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 first 28 days of treatment (Section 11.21). The eDiary is to be completed by the subject/parent/caregiver. Subjects or their parent/caregiver will be trained by the investigator or designee at visit 3 on the proper method to complete the eDiary. The reported symptoms will be evaluated by investigator and reported in the eCRF as AEs on the AE form in the eCRF.

The duration in minutes of the solicited AEs occurring on Day 1 (visit 3) will be collected. The AE start and stop time of solicited AEs that occur on Day 1 within 60 minutes of IMP intake, will be monitored by site personnel, recorded in source documents, and entered into the eCRF. After Day 1, standard AE reporting conventions will be utilised, as described above. For more details on solicited AEs, please see Section 11.21.

Eosinophilic Oesophagitis

During the trial, subjects will be monitored for emerging symptoms of eosinophilic oesophagitis at the scheduled visits. Subjects will be referred to a gastroenterologist based on a clinical suspicion of eosinophilic oesophagitis. At each visit, subjects/caregivers will be asked whether any of the following has occurred since the last clinic visit:

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

Reporting of adverse events

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. Non-serious AEs should be reported as soon as possible.

Adverse events must be recorded in the eCRF. The initial eCRF report must contain as much information as possible. 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 eCRF pages e.g. demography, medical history, concomitant medication) must be reported by email or fax to ALK.

In case of additional supporting documents (e.g. discharge letter, laboratory pages, electrocardiogram), these must be sent to ALK via fax (please state trial ID, subject ID and site ID on the documents). All subject personal identifiers must be redacted on the supporting documents.

Email address: [redacted]

Fax number: [redacted]

Emergency phone: [redacted]

The assessment of listedness is performed by ALK according to the current version of the reference safety information (i.e. Investigator's Brochure).

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

Follow-up on adverse events

SAEs must be followed up until the outcome of the event is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved.

Ongoing SAEs can be closed with the term "not recovered" for chronic diseases (as evaluated upon medical evaluation by the investigator or the sponsor).

The investigator must respond to SAE follow-up requests from ALK without delay and no later than 14 days after receiving the request.

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

Non-serious AEs must be followed up until resolution or until the last follow-up phone contact.

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

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

- It is abnormal and clinically significant (medical judgement by investigator)
- It leads to a change or discontinuation of treatment
- It fulfils a seriousness criteria

It indicates a potential safety risk to the subject

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

- An elevated AST or ALT lab value that is greater than or equal to 3 times the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2 times the upper limit of normal and, at the same time an alkaline phosphatase lab value that is less than 2 times the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

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

Reporting of medication errors, including overdose, abuse and misuse

Medication errors, including events of overdose, abuse or misuse must be reported on an AE form within 7 calendar days of obtaining the information. Reporting of overdoses should be based on actual IMP exposure and not on e.g. 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.

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 12.5.

Reporting of SAE and pregnancies after last follow-up phone contact

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

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

12.4 Data monitoring committee

To supplement the routine trial monitoring performed by the sponsor, an independent DMC will be established. The DMC is an independent, external committee composed of members whose expertise covers relevant specialities. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the sponsor; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports,

minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor trial data at an appropriate frequency, as described in the detailed DMC charter. The DMC will make recommendations to the sponsor regarding appropriate actions to ensure both subject safety and the continued ethical integrity of the trial.

12.5 Pregnancy

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

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

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

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

13 Early termination of trial

ALK reserves the right to terminate the trial under the following conditions:

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

If the trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or ALK should promptly inform the independent ethics committee/institutional review boards (IEC/IRBs) 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[61] 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).

[61] 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.

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.

3. Recommendation by the DMC
    a. The DMC will monitor the rate of clinically relevant asthma exacerbations during period 3 to be able to pause the trial for safety review should a substantial increase in the active treatment arm compared to placebo occur. A substantial increase in the rate of clinically relevant asthma exacerbations during period 3 defined by the following two criteria:
        i. the rate of clinically relevant asthma exacerbations in the active treatment arm is at least 3 times higher than the expected background rate (≥3*1.4 = ≥4.2 exacerbations/subject/year) AND
        ii. the rate of clinically relevant asthma exacerbations in the active treatment arm is at least 3 times higher than the rate observed in the placebo arm

    The DMC will monitor the rate of clinically relevant asthma exacerbations during period 3 to be able to pause the trial for safety review should a substantial increase in the active treatment arm compared to placebo occur.

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

14 Data handling

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

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

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

14.1 eCRF

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

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

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

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

The information entered into the database is systematically checked and errors or omissions will result in queries, which will appear in the eCRF for resolution. Concomitant medications entered

into the database will be coded using the World Health Organisation Drug Reference List (WHO Drug, 2016Q1 or higher).

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA 20.0 or higher).

14.2 eDiary

Starting with the baseline phase (i.e. V2) an eDiary will be dispensed and diary data will be entered by the subject. Subjects and/or their parent/caregiver will be trained in the eDiary by the investigator. In addition, a video with information on the eDiary will be available for the subjects and their parent/caregiver.The eDiary data will be reviewed by the investigator.

During the trial, diary data will be entered in an eDiary by the subject and/or their parent/caregiver and transferred to the vendor database on a daily basis. The investigator/designee should check subject compliance on an ongoing basis (weekly within the baseline period). If the subject has missed more than 2 days in a row or the total compliance for a period is less than 80% the investigator should contact the subject. The aim is for the overall compliance for a subject in the trial not to be below 80%.

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

Once all eDiary data has been collected, the diary database will be closed and transferred from the vendor to ALK. The investigator will also be provided with an electronic copy of the diary data collected at the specific site at the latest 3 months after end of trial, by the vendor. The eDiary data will be subject to periodic review by the sponsor. Findings during the review of the eDiary data will be evaluated by the investigator and updates/correction to the data can only be executed by the investigator. Documentation of the data load from the eDiary vendor to ALK will be described in the data handling report.

14.3 Query handling

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

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

14.4 Laboratory data

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

Immunological samples will be processed at ALK Research Laboratory and data will be provided electronically after database lock to data management.

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

14.5 Database lock

When the database has been declared to be complete and accurate, the database will be locked, access for CRAs and non-sponsor staff/persons will be revoked and data may be unblinded.

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

A data archive for the site subject data files are produced and sent to the site.
The investigator must sign and date the data archive approval form and send it back to the sponsor.

15 Statistical methods

Statistical analyses will be carried out by ALK Biometrics Department.

If nothing else is mentioned, all the statistical tests described in this section use a significance level of 5% and all tests and confidence intervals are two-sided. The null hypothesis is the hypothesis of no difference and the alternative to the null hypothesis is the hypothesis of a difference.

Descriptive statistics for numerical variables includes summary tables displaying mean, SD, median, 5%-quantile, 25%-quantile, 75%-quantile, 95%-quantile, minimum and maximum. Descriptive statistics for categorical variables includes frequencies tables that display numbers and percentage.

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

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

15.1 Sample size and power considerations

The primary endpoint is the annualised rate of clinically relevant asthma exacerbations during the efficacy evaluation period (period 4). The rate of clinically relevant asthma exacerbations will be analysed using a negative binomial regression model.

From (**Lanier et al. 2009**) the rate of clinically relevant asthma exacerbations is expected to be approximately 1.4 exacerbations per subject per year. Over a period of 24 weeks the number of clinically relevant asthma exacerbation in the placebo group were 0.64 per subject (~0.64*52/24 =1.4 per subject per year).

Power calculation are both performed based on the negative binomial distribution assuming overdispersion and based on the poisson distribution when assuming no overdispersion. Overdispersion means that some subjects will tend to have more exacerbations than others. The dispersion parameter in the negative binominal distribution is assumed to be k=0.7 (**Pavord et al. 2012**). When there is no overdispersion (k->0) the negative binominal distribution will become a poisson distribution.

Table 13 displays the sample size calculations for different values of the treatment effect expressed as the reduction in exacerbation rates for active treatment compared to placebo (100%*(PLB-ACT/PLB)). The power is set to 90% and sample size calculations are performed using a close formula for the negative binomial regression model (**Keene et al. 2007**):

$$N = \left\{\frac{z_{1-\beta} + z_{1-\alpha/2}}{\log(\mu_1/\mu_2)}\right\}^2 \times \left\{\frac{\mu_1 + \mu_2}{\mu_1\mu_2} + 2k\right\}$$

where N is the number of subject per treatment arm, μ_1 is the rate per subject in the given timeinterval for the placebo group, μ_2 is the rate per subject in the given timeinterval for the active group, $1-\beta$ is the power, alpha is the level of significance and k is the dispersion parameter.

Table 13 Power calculation

Power	Alpha	Time for efficacy assessment (weeks)	Rate PLB	Reduction (%) 100%*(PLB-ACT)/PLB)	μ_1	μ_2	k	N per arm (NB*)	N per arm (POIS)
0.9	0.05	34	1.4	30%	0.91	0.63	0.7	334	219
	0.05	52			1.39	0.97		259	143
	0.05	86			2.29	1.61		202	87
	0.05	34		25%	0.91	0.68		501	324
	0.05	52			1.39	1.04		389	212
	0.05	86			2.29	1.72		306	128
	0.05	34		20%	0.91	0.73		814	519
	0.05	52			1.39	1.11		635	339
	0.05	86			2.29	1.83		500	205

PLB: placebo, ACT: active, NB: negative binominal, POIS: poisson distribution.

If assuming a drop-out rate of 30%, a power of at least 90% and an efficacy assessment period of 20 month (86 weeks), a sample size of approximately 300 (~205/0.7=293) subjects per arm should be sufficient to detect a difference in exacerbation rates of 20% when no overdispersion is present as shown in Table 13. In case of overdispersion defined by a dispersion parameter of k=0.7, a sample size of 300 (>202/0.7=288) subjects per arm would be sufficient to detect a difference in the exacerbation rates of 30%.

15.2 Sample size reassessment

15.2.1 First blinded sample size reassessment with data cuf off point 1 Feb 2020

A blinded sample size reassessment (SSR) will be performed. In case of a potentially insufficiently powered trial with respect to the primary efficacy analysis of clinically relevant asthma exacerbations, the sample size will be increased accordingly from the planned 600 subjects (=300 per treatment arm) up to a total maximum of 900 randomised subjects (=450 per treatment arm).

The blinded SSR will be performed based on data from the approximately first 17 months of efficacy assessment period for cohort 1 and data from the approximately first 5 months of

efficacy assessment for cohort 2. For each subject the data cut off point for SSR will be the visit (including TCs) closest to but not before the 1st of February 2020.

Blinded data will be used for estimating the total annual clinically relevant asthma exacerbation rate ($\hat{\mu}_{total}$) for both treatment groups, an overall overdispersion parameter ($\hat{k}_{total}$) and the overall drop-out rate. $\hat{\mu}_{total}$ and $\hat{k}_{total}$ will be estimated using a negative binominal regression model. Each subject will be included in the analysis with the time in years from start of period 4 and until the date for the cut off point and with the number of cumulated clinically relevant asthma exacerbation with a start date within this period. For a subject who discontinues IMP prior to the cut off point all available data in period 4 until IMP discontinuation will be used.

The drop-out rate prior to period 4 will be calculated as the number of subjects that have discontinued prior to period 4 divided by the number of randomised subjects.

Cohort 1 will be used to calculate the average time for efficacy assessment for subjects that continue into period 4 according to the expression:

$$\hat{\tau}_{p4} = \frac{\sum_{i=1}^{N_{disc}} time_i + \left(N_{p4} - N_{disc}\right) * 608}{N_{p4}}$$

where $\hat{\tau}_{p4}$ is the average time in days with efficacy assessment of the primary endpoint for subjects who continue into period 4, $time_i$ is the time in days in period 4 before IMP discontinuation for subject *i*, N_{disc} is the number of IMP discontinuations in period 4 and N_{p4} is the number of subjects who continue into period 4, and 608 days corresponds to the 20 months of efficacy assessment for subjects who complete the trial. The expression does not account for IMP discontinuations after the cut off point of approximately 17 months of efficacy assessment due to lack of data beyond this time point for sample size reassessment. Thus, it is assumed that no subjects will discontinue after approximately 17 months of efficacy assessment.

Power/sample size estimation can be reassessed using a rewriting of the closed formula presented in Section 15.1.

$$N = \left\{\frac{z_{1-\beta} + z_{1-\alpha/2}}{\log(\mu_1/\mu_2)}\right\}^2 \times \left\{\frac{\mu_1 + \mu_2}{\mu_1\mu_2} + 2k\right\} \Leftrightarrow$$

$$N = \left\{\frac{z_{1-\beta} + z_{1-\alpha/2}}{log\ (1/RR)}\right\}^2 \times \left\{\frac{(1+RR)^2}{2 * \hat{\mu}_{total} * (\frac{\hat{\tau}_{p4}}{365}) * RR} + 2\hat{k}_{total}\right\} \Big/ \left(1 - \widehat{DR}\right)$$

where

- $1-\beta$ is the power,
- α is the level of significance,
- Z is the quantile in the standard normal distribution,
- Ratio of rates (RR) is the assumed treatment effect expressed as the RR of active treatment relative to placebo ($RR = \mu_2/\mu_1$),
- $\hat{\mu}_{total}$ is the estimated total annual clinically relevant asthma exacerbation rate based on blinded data,
- $\hat{k}_{total}$ is the estimated overall overdispersion parameter based on blinded data,

- $\widehat{DR}$ is the estimated total drop-out rate prior to period 4 based on blinded data,
- $\hat{\tau}_{p4}$ is the average time in days with efficacy assesment of the primary endpoint for all subjects who continue into period 4.

The flow chart for the SSR is illustrated in Figure 2 below.

A relative decrease in the clinically significant asthma exacerbation rate of 30% (RR=0.7) of active compared to placebo is assumed in the SSR.

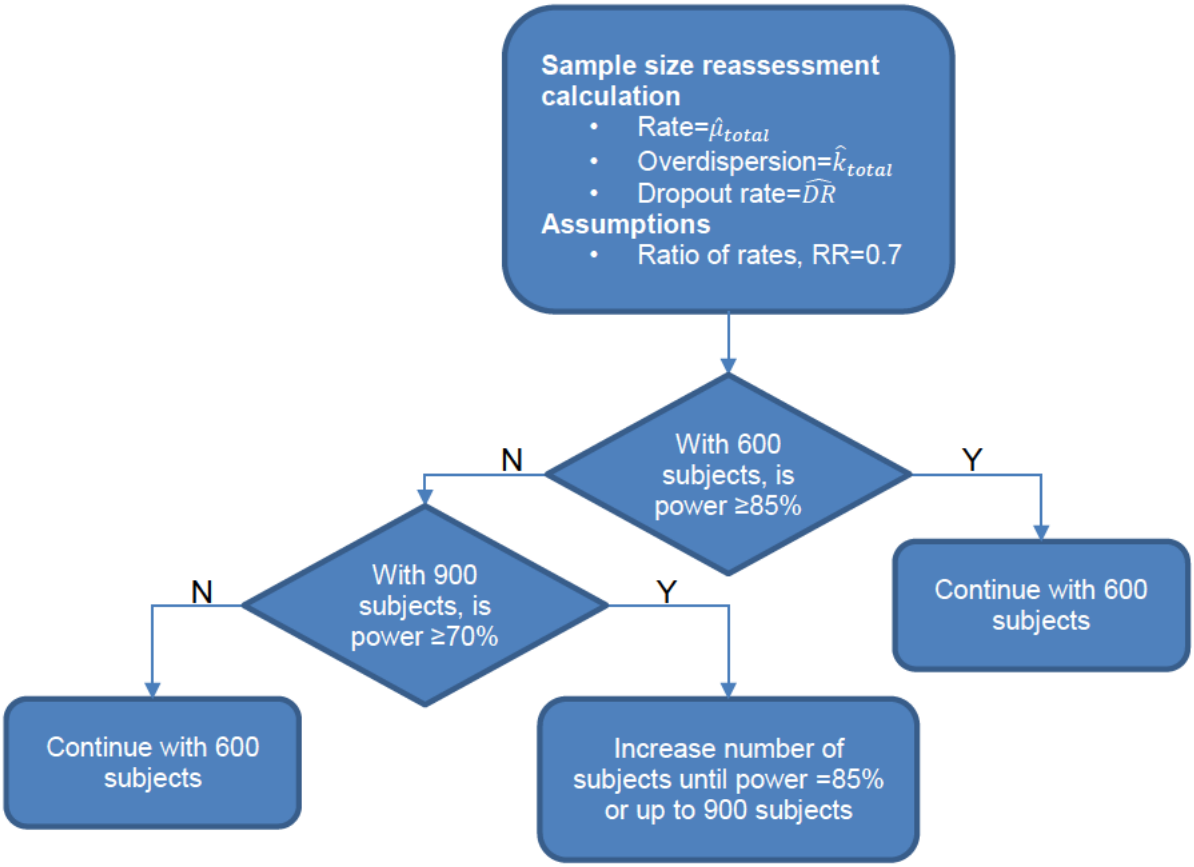
The upper limit for power is set to 85%. If the reassessed power for the planned 600 subjects is equal to or above 85%, no additional subjects will be randomized.

The lower limit for power is set to 70%. If the maximum sample size limit of 900 subjects does not result in a power of 70% or greater, no additional subjects will be randomized. That is, the trial will continue with the planned 600 subjects.

If the reassessed power for the planned 600 subjects is below 85% and the reassessed power for the maximum of 900 subjects is above 70%, additional subjects will be randomised until a power of 85% is achieved or until the maximum limit of 900 subjects is reached, see Figure 2.

The data and trial are blinded for the statistician responsible for conducting the sample size reassessment.

Figure 2 Flow chart for SSR



15.2.2 Second blinded sample size reassessment due to the COVID-19 pandemic with cut off point the 1 Mar 2021

Due to the COVID-19 pandemic that have impacted the MT-11 trial from Q1 2020 the blinded data used for the SSR described in section 15.2.1 with a data cut off point of 1st of February 2020 may not be fully representive for the MT-11 trial. The COVID-19 pandemic situation is likely to reduce the asthma exacerbation rate in the MT-11 trial population due to an increased social distancing and thus a reduction in the number of viral infections that are important triggers of asthma exacerbations. In addition, the COVID-19 pandemic may also increase the discontinuation rate from the trial due to for example an increased anxiety for the safety of the child. In conclusion, the COVID-19 pandemic situation might decrease the power of the MT-11 trial and the first SSR might not reflect this potential decrease in power since it was based on trial data assessed prior to the COVID-19 pandemic.

Therefore, it has been decided to replace the result of the first SSR with a second updated blinded SSR that will additionally include MT-11 trial data from the period with the COVID-19 pandemic. For each subject the data cut off point for the second SSR will be the visit (including TCs) closest to but not before the 1st of March 2021. The second SSR will be based on data from the complete efficacy period for cohort 1, approximately 18 months of efficacy data from cohort 2 and approximately 6 months of efficacy data from cohort 3. Table 14 illustrates MT-11 trial data for the second SSR collected before and during the COVID-19 pandemic. The start of

the COVID-19 pandemic is roughly anticipated to be mid-March 2020 were the pandemic situation escalated in many of the countries included in the MT-11 trial.

Table 14 Overview of MT-11 trial data to be included in an additional sample size reassessment with a cut of point for each subject closest to but not before 1st of March 2021

Cohort	Subjects randomised	Subjects in period 4	Start of period 4	Duration in month of period 4		
				Total	Prior to Covid-19	During Covid-19
1*	76	72	01 SEP 2018	20	17.5	2.5
2	249	244	01 SEP 2019	18	6.5	10.5
3	199	-	01 SEP 2020	6	0	6

*The overall start of the COVID-19 pandemic is roughly anticipated to be mid-March 2020. Site 613 in cohort 1 is excluded from SSR

In order to keep the second SSR as prespecified as possible the only change compared to the first SSR is the date for the data cut off point. Otherwise the principle for the second SSR will be similar to the first prespecified SSR using the same formulas presented in section 15.2.1.

15.3 Analysis data sets

The total analysis set

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

The full analysis set

The full analysis set (FAS) comprises all randomised subjects who received at least 1 dose of IMP. This analysis set will be the primary set for all efficacy analyses. The FAS will be used for all baseline/demography tables and efficacy tables and subject listings.

The per protocol analysis set

The per protocol (PP) analysis set comprises subjects without protocol deviations that may substantially affect the primary endpoint.

Before data base lock, a list will be made that defines which subjects are excluded from the PP analysis set and the reason for exclusion. The criterias for exclusion will be based on procotol deviations such as:

1. Violation of the inclusion/exclusion criteria
2. Use of prohibited medication close to or during the efficacy evaluation period (period 4)
3. IMP compliance in the entire trial. Subjects with a compliance below 80% are excluded from the PP analysis set
4. Diary compliance. Subjects with less than 6 months of efficacy assessment in period 4 are excluded from the PP analysis set

The PP analysis set will be used for a supportive analysis of the primary endpoint.

The safety analysis set

The safety analysis set (SAF) will be used for safety analyses. The SAF will include all randomised subjects who received at least 1 dose of IMP. Subjects will be included in the treatment group corresponding to the IMP they actually received during the trial. SAF will be used for safety tables and listings.

15.4 Subject disposition

A table of subject disposition by treatment group displaying number and percentage of subjects screened, randomised, included in FAS, with observation of the primary endpoint, included in PP, included in safety set, discontinued IMP, discontinued trial, by primary reason for IMP and trial discontinuation and who completed the trial will be presented.

The overall IMP discontinuation will be displayed by a Kaplan-meier plot. Cumulative incidence plot will be used to show cause specific IMP discontinuation distribution.

15.5 Baseline characteristics

Demographic (including age, sex, race, ethnic origin, country/region, weight, height, and body mass index) and baseline characteristics (including baseline asthma medication, predicted FEV_1, duration of HDM AR and HDM allergic asthma, sensitisation type, medical history) will be summarised by treatment group.

15.6 Extent of exposure

IMP accountability (number of daily doses used) is the difference between the number of daily doses dispensed and the number of daily doses returned. IMP compliance is the number of daily doses used divided by the duration of the treatment period in days and multiplied with 100. A treatment year is the number of daily doses divided by 365. Duration of IMP treatment period in days, IMP accountability, IMP compliance and treatment years will be displayed in summary tables by treatment groups.

15.7 Concomitant therapy

Concomitant medication and illness will be summarised by means of descriptive statistics.

15.8 Efficacy analyses

Derivation of the primary efficacy endpoint

Clinically relevant asthma exacerbation endpoint

The source for deriving the clinically relevant asthma exacerbation endpoints is the AE form of the eCRF. On the AE form the clinically relevant asthma exacerbations are reported with an AE number, a start and a stop time/date and the criterion/criteria's fulfilled for the event being categorised as a clinically relevant asthma exacerbation (section 2.5) .

A clinically relevant asthma exacerbation must be separated by >7 days from a previous clinically relevant asthma exacerbation in order to be considered an individual event. I.e. the difference between the start date of an event (i) and the stop date for the previous event (i-1) must be more than 7 days:

$$AE\ Start\ data_{event=i} - AE\ Stop\ date_{event=i-1} > 7\ days$$

If there are 7 days or less between two or more successive clinically relevant asthma exacerbations the asthma exacerbations will be considered as one single event starting with the start date of the first asthma exacerbation and ending with the stop date of the last asthma exacerbation.

Annualised rate of clinically relevant asthma exacerbations in period 4

The efficacy assessment period (period 4) begins on the 1st of September for all subjects and lasts until the end of trial or discontinuation from IMP. The annualised rate of clinically relevant asthma exacerbations is calculated for each subject as the number of observed clinically relevant asthma exacerbations divided by the time in years in period 4. For the statistical analyses of clinically relevant asthma exacerbations based on a negative binomial regression model the number of clinically relevant asthma exacerbations will be the response variable and the $\log_{10}$ transformed time in years in period 4 will be the corresponding offset.

For each subject the number of clinically relevant asthma exacerbations are the sum of all clinically relevant asthma exacerbations with a start date in period 4 while the subject is still on IMP. The time in period 4 is calculated as the time in years from start in period 4 until last day of IMP intake, i.e.:

$$Time_{Years} = Years\left(date_{Last\ IMP} - date_{Start\ period\ 4}\right)$$

A subject who discontinues IMP prior to period 4 will not have any observations of the clinically relevant asthma exacerbations in period 4 and is therefore not included in the primary analysis.

For a subject who discontinues IMP prematurely in period 4, all available data in period 4 until IMP discontinuation will be used. The number of clinically relevant asthma exacerbations is the sum of all clinically relevant asthma exacerbations with a start date in period 4 before IMP discontinuation. The time with observations in period 4 is the time in years from start of period 4 until the last point of contact for collecting asthma exacerbations or until the last day of IMP intake, depending on which date comes first, i.e.:

$$Time_{Year} = Years\left(\min\left(date_{Last\ point\ of\ contact}, date_{Last\ IMP}\right) - date_{Start\ period\ 4}\right)$$

Example 1: A subject is lost to follow up in period 4 and the last point of contact for collecting asthma exacerbations data while the subject was still on IMP treatment was telephone contact 4 (TC 4). The subject reported 1 clinically relevant asthma exacerbation with an event start date in

period 4 while the subject was still on IMP treatment, and the time from start of period 4 until TC4 is 93 days. This subject will contribute with 1 asthma exacerbation and a duration time of 93/365=0.25 years in period 4. The annualised rate for this subject is 4 events per year.

Example 2: A subject discontinues IMP due to AEs but continues in the trial. The date of last IMP intake corresponds to 250 days of treatment in period 4 and the subject did not experience any clinically relevant asthma exacerbations that started in period 4 while the subject was still on IMP. This subject will contribute with 0 asthma exacerbations and a duration time of 250/365=0.68 years in period 4. The annualised rate for this subject is 0 events per year.

Primary efficacy analysis

The primary efficacy analysis will be based on all subjects in FAS with observations of the primary endpoint. The primary endpoint will be analysed by means of a negative binominal (NB) regression model with the number of asthma exacerbations as the response variable, treatment group, age group (<12 years/≥ 12 years) and country as fixed factors and the logarithm of the duration time in years in period 4 as an offset value. The between treatment group comparison will be performed using a Log Likelihood Ratio (LR) test derived from the NB regression analysis. The null hypothesis is that the rate of clinically relevant asthma exacerbations is equal for the active group and the placebo group. The alternative hypothesis is that the rate of clinically relevant asthma exacerbations is different for the active group and the placebo group. The primary outcome is the resulting p-value from the LR test reported together with the ratio of the rates and Wald 95% confidence intervals. The result of the primary efficacy analysis is considered successful when the p-value is below 0.05.

SAS Code for primary efficacy analysis

```
proc genmod data=a;
  class treat  agegroup country;
  model y = treat agegroup country/ link=log dist = nb offset=log_time type3;
   lsmeans treat/ cl means exp diff;
run;
```

If the NB regression model fails to converge a poisson regression model with an overdispersion parameter will instead be applied for the primary efficacy analysis with the same covariates and offset as for the NB regression. If this model also fails to converge the poisson regression model without overdispersion will be used for the primary efficacy analysis.

As a supportive analysis the primary efficacy endpoint will be analysed based on the PP analysis set using the same NB regression model as for the primary efficacy analysis. Sensitivity analyses with respect to missing data of the primary efficacy endpoint are described in section 15.13.

Key secondary and secondary efficacy analysis

The key secondary and secondary efficacy analyses will be based on all subjects in FAS with observations of the key secondary/secondary efficacy endpoints.

The proportion of days with nocturnal awakening which require SABA use over the two weeks diary assessment period (before V5, V6, V7, V8, V9, V10 and V11) will be analysed by means of a generalised linear mixed effect model (GLMM) with a logit link function. Treatment, visit, age group (<12 years/≥ 12 years) and country will be included as fixed factors. Baseline proportions of nocturnal awakenings requiring SABA will be included as a covariates and subject will be included as a random effect. Parameters in the model are estimated by applying pseudo-likelihood techniques as in Wolfinger and O'Connell (**Wolfinger & O'connell 1993**) and Breslow and Clayton (**Breslow & Clayton 1993**). From the GLMM model, the odds ratio for having a day with nocturnal awakening of active treatment relative to placebo will be presented together with the coherent p-values and 95% confidence limits.

The average daily dose of SABA over the two weeks diary assessment period (before V5, V6, V7, V8, V9, V10 and V11) will be analysed by means of a mixed-effect model repeated measurement (MMRM). The model includes treatment, visit, age group (<12 years/≥ 12 years) and country as fixed factors, the baseline average daily SABA dose as a covariate and subject as a random effect. Different residual errors for each treatment group will be speficied and the within-subject correlated errors is modelled with a Toeplitz structure (TOEP). A between treatment comparison will be performed by means of a t-test with Kenward-Roger degrees of freedom approximation. The resulting p-value will be reported together with the difference in adjusted means. In addition the relative difference will be reported together with 95% confidence limits calculated based on Fieller's theorem.

Percentage predicted FEV_1 assessed every 4 month after randomisation will be analysed by means of a MMRM. The model includes treatment, visit and age group (<12 years/≥ 12 years) and country as fixed factors, the baseline percentage predicted FEV_1 as a covariate and subject as a random effect. Different residual errors for each treatment group will be speficied and the within-subject correlated errors is modelled as TOEP. A between treatment comparison will be performed by means of a t-test with Kenward-Roger degrees of freedom approximation. The resulting p-value will be reported together with the difference in adjusted means. In addition the relative difference will be reported together with 95% confidence limits calculated based on Fieller's theorem.

The average TCRS over the two week diary assessment (before V5, V6, V7, V8, V9, V10 and V11) will be analysed by means a MMRM.The analysis includes the square root transformed average TCRS as response variable; treatment, visit, and treatment-by-visit interaction, age group (<12 years/≥ 12 years) and country as fixed factors; the square root transformed baseline score as a covariate and subject as random effects. Different residual errors for each treatment group is specified. For each visit, the between treatment comparison will be performed by means of a t-test. The resulting p-value will be reported together with the difference in back-transformed adjusted means. As additional information the relative difference of the back-transformed adjusted means is reported together with 95% confidence limits. The latter is calculated based on Fieller's theorem.

The average rhinitis DSS, the average rhinitis DMS, the average total combined rhinoconjunctivitis score, the average rhinoconjunctivitis DSS, the average rhinoconjunctivitis DMS will be analysed using a similar MMRM model as described for the average TCRS.

The average asthma DSS score and ACQ/ACQ-IA will also be analysed by means of a MMRM model.

Time to first severe asthma exacerbation and time to first clinically relevant asthma exacerbation will be analysed by means of a Cox proportional hazards regression analysis. The model is stratified for country and includes treatment group as a factor.

The severe asthma exacerbations will be analysed by means of a NB regression model with treatment group, agegroup (<12 years/≥ 12 years) and country as factors and the logarithm of the duration time in years in period 4 as an offset value.

The global evaluation as binary outcomes “improved/not improved” will be analysed using a generalised linear mixed model (GLMM) model.

In addition, all efficacy endpoints will be presented in summary tables.

15.9 Safety analyses

Analyses of AEs

AEs are recorded from the subjects sign the informed consent and until the last follow-up visit.

Unless otherwise specified, AE endpoints in this protocol refer to events occurring after the first IMP administration (treatment-emergent AEs).

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

Additionally the following AEs will be summarised by treatment group

- asthma exacerbations
- asthma related hospitalisations
- worsening of asthma requiring medication
- discontinuations of treatment due to asthma related symptoms
- solicited AEs
- unsolicited adverse events

The analyses will be described further in the SAP.

Analyses of other safety parameters

Physical examination assessments, laboratory assessments, vital signs and FEV_1 will be summarised by means of descriptive statistics.

15.10 Multiplicity

The issue of multiple testing for the primary and 3 key secondary efficacy endpoints will be handled by using hierarchical testing. The order of the hierarchical tests is:

1. Superiority testing of the HDM SLIT-tablet over placebo with respect to the rate of clinically relevant asthma exacerbations during the efficacy evaluation period

2. Superiority testing of the HDM SLIT-tablet over placebo with respect to proportions of days with nocturnal awakenings due to asthma which require SABA use during the 14 days eDiary period recorded every 4 month after randomisation
3. Superiority testing of the HDM SLIT-tablet over placebo with respect to the average daily dose of SABA use during the 14 days eDiary period recorded every 4 month after randomisation
4. Superiority testing of the HDM SLIT-tablet over placebo with respect to the percentage predicted FEV_1 assessed every 4 month after randomisation

A lower test can only be evaluated when the null hypothesis in the former test has been rejected.

15.11 Interim analyses

No interim analysis is planned for efficacy. Subject safety will be monitored by a DMC, see Section 12.4. A sample size reassessment is planned based on blinded data , see section 15.2.

15.12 Subgroup analyses

Subgroup analyses of the rate of clinically relevant asthma exacerbations during the efficacy evaluation period (period 4) include age (5-11, 12-17 years), sex, race (caucasian, non-caucasian), asthma treatment, allergen sensitivity (mite only, mite + others), geographic location. The trial is not powered to detect a treatment effect within a subgroup and the subgroup analyses will thus only be descriptive in nature.

A forest plot will be provided by the above specified subgroups. The plot will display the estimated ratio of rates to placebo (and corresponding confidence interval) for each subgroup. The estimated ratio of rates is calculated using the NB regression model defined in section 15.8 and based on all observed data in FAS.

15.13 Handling of missing data

For the primary endpoint, annualised rate of clinically relevant asthma exacerbations, missing data can occur in two ways.

1) A subject who discontinues treatment or trial before period 4 will not have any observation of the primary endpoint.
2) A subject who discontinues treatment or trial during period 4 before the planned end-of-trial visit after approximately 20 months of efficacy assessment will have observations of the primary efficacy endpoint for less than 20 months.

The efficacy assessment period (period 4) begins on the 1st of September for all subjects and lasts until the end of trial or discontinuation from IMP. For a subject who discontinues treatment prematurely in period 4, all available data in period 4 until IMP discontinuation will be used for the primary efficacy analysis. The negative binomial regression model applied for the primary efficacy analysis is a Generalized Linear Mixed Effect Model (GLMM) and under a missing at random (MAR) assumption, the method provides an unbiased estimate of the treatment effect that would have been observed if all subjects had continued on treatment for the full trial duration.

Subjects who discontinue IMP prior to period 4 will not contribute to the primary efficacy analysis.

Data from 2 previous phase II/III trials (MT-02, MT-04) with the HDM SLIT-tablet in adult subjects with HDM allergic asthma suggest that up to 10% of all subjects are expected to discontinue treatment or trial prior to entering period 4.

To evaluate the sensitivity of the results of the primary efficacy analysis with respect to missing data, including the MAR assumption, the following sensitivity analysis will be performed:

1) Subjects who discontinue IMP treatment prior to the efficacy assessment period (period 4) will be imputed by the rate of clinically relevant asthma exacerbations observed in the treatment initiation and maintenance period (period 3) until IMP/trial discontinuation, i.e., the number of asthma exacerbations in period 3 per time in years in period 3. This imputation conservatively assumes a treatment effect similar to the treatment effect obtained in period 3 had the subjects continued on IMP for the same length of time in period 4. This imputed dataset is based on all randomised subjects and will be analysed using the negative binomial regression model (GLMM) specified for the primary efficacy analysis.
2) Missing data for subjects who discontinue IMP/trial prematurely in period 4 will be imputed using a conditional “jump to reference” approach. Subjects are assumed to be switched to the placebo arm after discontinuation in period 4 and for the rest of the planned duration of the trial. Multiple copies of the imputed dataset will be generated by imputing missing values based on estimated parameters for the placebo group. Each copy will then be analysed using the negative binomial regression model (GLMM) specified for the primary efficacy analysis. The resulting estimates and standard deviations for the multiple data sets are finally pooled to one single estimate and associated standard deviation using the method of Rubin **(Rubin D.B 1987)**.

16 Quality assurance and control

16.1 Monitoring

Regular monitoring visits will be performed according to International Conference on Harmonisation (ICH) GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. In accordance with written SOP, 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:

- Date of informed consent

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

Documentation of 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

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

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

- Option 1
  If an audit trail is available, the CRA may choose either to perform source data verification through a direct comparison of the eCRF and the electronic medical record or may choose to work according to option 2
- Option 2
  If no audit trail is available. Relevant source data from electronic medical records should be printed out by the investigator or delegate preferably at the day of the monitoring visit. The investigator or delegate must sign and date the print-out to confirm that the print and the electronic source data are identical. The CRA must verify the original source data at least once during the trial.

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

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

16.3 Investigator site file – and other trial documentation

The investigator must maintain source documents for each subject in the trial in accordance with local legislation and at least for 25 years following the trial whichever is longest.

The investigator must retain the subject identification log and subject information sheet and consent forms for at least 25 years.

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

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

16.4 Protocol compliance

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

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 World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects **(World Medical Association 2013)**

- International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6(R2) (**ICH 2016**)
- 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 GCP 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 GCP as regards IMPs 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, Protection of Human Subjects (21 CFR Part 50)

17.2 Disclosure and confidentiality

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

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

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

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

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

17.3 Subject confidentiality

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

17.4 Data protection

By signing this protocol, the investigator recognises that certain personal identifying information with respect to the investigator and all subinvestigators 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 the ALK, affiliates and ALK representative, in the investigators 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.

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

17.5 IEC/IRB/regulatory authorities

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

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

17.6 Inspections

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

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

17.7 Protocol amendment and other changes in trial conduct

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

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

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

18 Reporting and publication

18.1 Integrated clinical trial report

Data will be reported in an ICTR in compliance with the requirements of the current version of ICH E3: Structure and Content of Clinical Trial Report (**ICH 1995**), ICH GCP Guidelines (**ICH 2016**), and ALK SOPs.

The signatory investigator will review and sign the ICTR. The trial is completed once the integrated clinical trial report (ICTR) is signed.

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. For multi-site trials, it is mandatory that the primary publication is based on data from all trial sites, analysed as stipulated in the protocol and in the SAP. Authorship is based on the International Committee of the Medical Journal Editors' Uniform Requirements (Vancouver Declaration). If the number of authors is restricted, selection will be based on fulfilment of 1) involvement in the development of the protocol and 2) being coordinating investigators.

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 publication 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, 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 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's).

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 procedures 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 telephone numbers and fax numbers of relevant ALK staff are listed in the investigator's site file.

The title, name, address and contact details of investigators and clinical research organisations e.g. subcontractors for project management, clinical trial packaging, monitoring, central laboratory etc. are listed in Appendix 4: Trial organisation.

21 Reference list

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