COVERPAGE MT-11 STATISTICAL ANALYSIS PLAN

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
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Statistical Analysis Plan (SAP)

Trial ID: MT-11

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

Sponsor: ALK-Abelló A/S
Bøge Alle 6-8
DK-2970 Hørsholm

Investigational medicinal Product: HDM SLIT-tablet

Phase: III

EudraCT No.:2016-004363-39

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ALK Approval of Statistical Analysis Plan

Please refer to the electronic signatures of the document.

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Table of abbreviations

ACQ	Asthma Control Questionnaire
ACQ-IA	Asthma Control Questionnaire - Interviewer Administered version
AE	Adverse event
ALK	ALK-Abelló A/S
AMP	Auxiliary Medicinal Product
AR	Allergic Rhinitis
AST	Aspartate aminotransferase
Covid-19	Coronavirus disease 2019
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*
DMS	Daily Medication Score
DPS	Data Point Set
DSS	Daily Symptom Score
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EMA	European Medicines Agency
EudraCT	European Union drug regulating authorities clinical trials database
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEE	Generalised Estimating Equations
GLMM	Generalised Linear Mixed Model
HDM	House Dust Mite
ICH	International Council on Harmonisation of technical requirements for registration of pharmaceuticals for human use

ICS	Inhaled corticosteroid
IgE	Specific Immunoglobulin E (specific IgE) against *D. pteronyssinus* and *D. farinae*
IgE-BF	IgE-Blocking factor
IgG4	Specific Immunoglobulin G4 (specific IgG4) against *D. pteronyssinus* and *D. farinae*
IMP	Investigational Medicinal Product
IND	Investigational New Drug
LABA	Long-Acting β_2-Agonist
LOCF	Last Observation Carried Forward
LR	Likelihood Ratio
LSMeans	Least Squared Means
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measurement
NB	Negative Binominal
OCS	Oral corticosteroid
OP	Observational Period
[redacted]	[redacted]
[redacted]	[redacted]
PDCO	Paediatric Committee under EMA
PEF	Peak Expiratory Flow
PP	Protocol Analysis Set
PT	Preferred Term
[redacted]	[redacted]
SABA	Short-Acting β_2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	SAFety analysis set
[redacted]	[redacted]
SLIT	Sublingual immunotherapy

SOC	System Organ Class
SPT	Skin Prick Test
SSR	Sample Size Reassessment
TC	Telephone Call
TCRS	Total Combined Rhinitis Score
TCS	Total Combined Score
TEAEs	Treatment-Emergent Adverse Events
[redacted]	[redacted]
UN	Unscheduled Visit
VAS	Visual Analogue Scale

Table of definitions

Background treatment	Standard of care treatment administered to all subjects in addition to the IMP, in agreement with **(EMA 2016)** The background treatment in this trial is low dose 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 date is the date of sponsor's decision to end the trial, due to the severe impact by the Covid-19 pandemic. This date was the 10th of August 2022
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 **(EMA 2016)**. 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 at the discretion and medical evaluation of the investigator at visit 4 based on the 15 pre-specified symptoms reported by a subject 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 CSR is signed

Version History

SAP Version	*Date*	*Change*	*Rationale*
3.2	*March 2022*	*Updated to include the Estimand principle*	*Original version*

1 INTRODUCTION

This SAP for trial MT-11 is based on the following three protocols:

- Protocol v10.0 dated 11-Nov-2020 (Europe)
- Protocol v12.0 dated 18-Feb-2021 (US)
- Protocol v13.0 dated 18-Feb-2021 (Bulgaria)

The SAP is a supplement to the statistical section in the protocols and provides additional details regarding estimands, analysis sets, endpoints and the statistical analyses. The SAP is written in accordance with ICH-GCP guidelines **(ICH 1998)**.

In section **7.1** (Appendix 1 'Definitions and Derivations') all definitions and derivations for the trial are detailed, and in section **7.2** (Appendix 2 'Further details pertaining to statistical analyses') a detailed description of how to code the statistical analyses is provided.

Major deviations from the protocol are documented in section **4.8**.

This SAP has been written and approved before database lock and unblinding.

1.1 Objectives, endpoints, and estimands

1.1.1 Primary objective

The primary objective of the trial is to demonstrate efficacy of the HDM SLIT-tablet versus placebo as add-on treatment in children (5-11 years) and adolescents (12-17 years) with HDM allergic asthma based on clinically relevant asthma exacerbations after at least 4 months of treatment.

1.1.2 Key secondary objectives

The key secondary objectives of the trial 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:

1. Nocturnal awakening due to asthma which require SABA rescue medication
2. Rescue medication use (SABA)
3. Lung function (FEV_1)

1.1.3 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
- Treatment of HDM AR
- Treatment of HDM allergic rhinoconjunctivitis
- Changes in immunological parameters
- Safety and tolerability

1.1.4 Other objectives

The other objectives are to evaluate:

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

1.1.5 Primary endpoint

The primary endpoint of the trial is the annualised rate of clinically relevant asthma exacerbations calculated as the number of exacerbation events 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 1 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

1.1.6 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
- Proportions of days with SABA use during the 14 days eDiary recording every 4 months after randomisation
- Percentage predicted FEV_1 assessed every 4 months after randomisation

1.1.7 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 1 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)
- Predicted FEV_1
    - Change from baseline in percentage predicted FEV_1
- Asthma symptoms
    - Average asthma DSS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
    - Asthma VAS
    - Global evaluation of allergic asthma
    - Overall ACQ/ACQ-IA measured at V5, V6, V7, V8, V9, V10 and V11
- Asthma symptomatic medication
    - The average daily dose of SABA during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11

- Rhinitis symptoms and symptomatic medication
  - The average TCRS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinitis DSS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinitis DMS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinitis CSMS during the 2-week 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 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinoconjunctivitis CSMS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinoconjunctivitis DSS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinoconjunctivitis DMS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
  - The average rhinoconjunctivitis VAS during the 2-week assessment period before V5, V6, V7, V8, V9, V10 and V11
- Immunology
  - Changes from baseline in IgE, IgE-BF and IgG4 against *D. pteronyssinus* and *D. farinae* measured at V7 and V11
- Safety and tolerability endpoints
  - Treatment-emergent AEs (TEAEs), IMP-related AEs, treatment-emergent SAEs, TEAEs leading to (IMP) discontinuation, time to discontinuation due to TEAEs, solicited AEs
  - Vital signs, FEV_1, clinical laboratory values and physical examination during treatment and at the final visit (V11)

1.1.8 Other endpoints

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

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

1.1.9 Estimands

For the primary endpoint, both a primary and a secondary estimand are defined (see sections **1.1.9.5** and **1.1.9.6**). For the key secondary endpoints, a common primary estimand is defined (see section **1.1.9.7**). No estimands are defined for neither the additional secondary endpoints, the other endpoints nor the safety endpoints.

The general definitions of Population in section **1.1.9.1** and Intercurrent Events in section **1.1.9.3** apply for the estimands considered for the trial. The definitions of "Variable" and "Population level

summary" are described individually for each estimand as found in the sections **1.1.9.5**, **1.1.9.6** and **1.1.9.7**.

1.1.9.1 Population

The population is defined by the inclusion and exclusion criteria of the trial to reflect the targeted patient population. The full analysis set (FAS) and the per protocol analysis set (PP) are used in the efficacy analyses.

1.1.9.2 Variable

See sections **1.1.9.5**, **1.1.9.6** and **1.1.9.7**.

1.1.9.3 Intercurrent events

Discontinuation of treatment, both before and during the efficacy period, is considered an intercurrent event and will be handled by the hypothetical strategy.

Different approaches for discontinuation of treatment during the efficacy period are applied for the primary and the secondary estimands (see sections **1.1.9.5**, **1.1.9.6** and **1.1.9.7**.). The difference between the primary and the secondary estimands for the primary endpoint is the inclusion or exclusion of data from subjects who discontinue treatment during period 4, respectively.

If a subject discontinues treatment prior to the efficacy period (period 4 for the primary endpoint and visit 5 to visit 11 for the key secondary endpoints), no data from the efficacy period will contribute to the analysis of the primary and secondary estimands.

As only 3 subjects discontinued treatment but did not withdraw from the trial at the time of treatment discontinuation, the discontinuation of trial is not considered with respect to the intercurrent events as it will not add information to make a separate analysis approach (treatment policy estimand) for these very few subjects.

In allergy immunotherapy clinical trials, rescue medication is dispensed to every subject. Therefore, rescue medication is expected to be used as part of the trial design, and hence use of rescue medication is not classified as an intercurrent event.

As all estimands follow the hypothetical strategy, they assess the anticipated effect of the trial product if taken as instructed.

1.1.9.4 Population level summary

See sections **1.1.9.5**, **1.1.9.6** and **1.1.9.7**.

1.1.9.5 Primary estimand for the primary endpoint

Variable: Annualised rate of clinically relevant asthma exacerbations.

Population level summary: The inter-treatment ratio of rates of clinically relevant asthma exacerbations calculated as the number of exacerbation events per subject year during the efficacy evaluation period (period 4), between treatments with HDM SLIT-tablet and placebo.

Intercurrent events (discontinuations) in period 4: Period 4 begins on September 1st after treatment initiation for all subjects and lasts until the end of trial or discontinuation of treatment.

All subjects with observations in period 4 will be included in the analysis.

1.1.9.6 Secondary estimand for the primary endpoint

Variable: Annualised rate of clinically relevant asthma exacerbations.

Population level summary: The ratio of rates of clinically relevant asthma exacerbations calculated as the number of exacerbation events per subject year during the efficacy evaluation period (period 4) between treatments with HDM SLIT-tablet and placebo.

Intercurrent events (discontinuations) in period 4: For this estimand period 4 is defined to begin on September 1st for all subjects and last until the end of trial. Thus, discontinuation of treatment during period 4 is no longer captured through the definition of the primary endpoint. This means that if a subject discontinues trial treatment during period 4, no period 4 data will contribute to the analysis.

1.1.9.7 Primary estimand for the key secondary endpoints

Variable: Each key secondary endpoint defines a variable for the estimand.

Population level summary: The absolute difference in means of the endpoint between treatment with HDM SLIT-tablet and placebo or the ratio between treatment means of the endpoint between treatment with HDM SLIT-tablet and placebo (depends on the definition of each endpoint).

Intercurrent events (discontinuations) in efficacy period: Discontinuations in the efficacy period will be handled as for the primary estimand for the primary endpoint. The efficacy period for the key secondary endpoints is defined as visit 5 – visit 11.

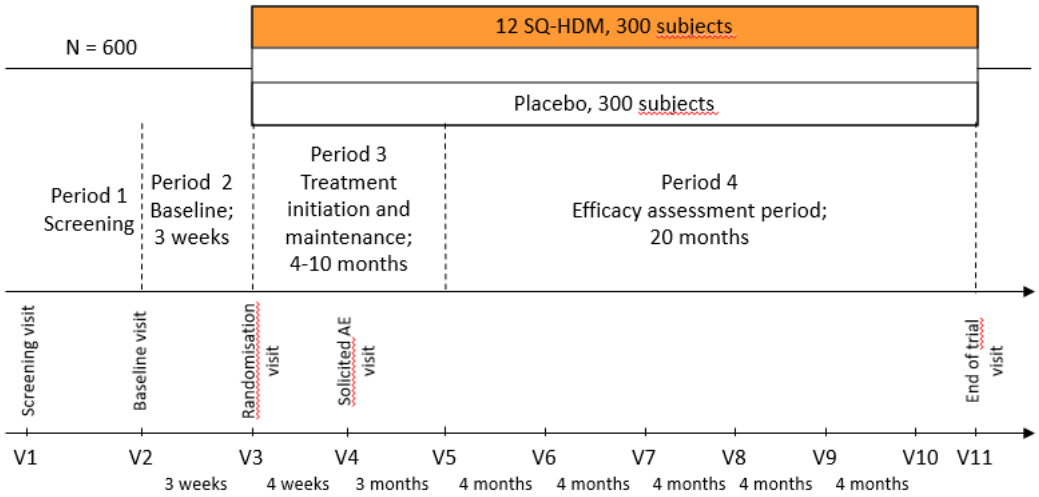
1.2 Trial design

This trial is a randomised, parallel-group, double-blind, placebo-controlled, multi-national phase III trial conducted in Europe and North America.

The trial was initiated in Q1 2018 and subjects were to receive treatment for 24-30 months consisting of a treatment initiation and maintenance period of 4-10 months followed by a 20-month efficacy assessment period.

A total of 533 subjects were randomised to receive treatment with the HDM SLIT-tablet or placebo, see **Figure 1**.

Figure 1 Overview of trial design



Period 1 is the screening period.

Period 2 is the 3-week baseline period during which eligible subjects will fill in their asthma and rhinoconjunctivitis symptoms and medication use in an electronic diary (eDiary). Only the 2 last weeks of the 3-week baseline period will be used for calculation of baseline scores. At the start of period 2 (visit 2) subjects' regular asthma rescue mediation and rhinoconjunctivitis rescue medication will be replaced with the rescue medication provided by ALK.

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 4-10 months. Period 3 ends the 31st of August. During the first 28 days of period 3, 15 prespecified symptoms occurring after IMP intake will be assessed by the subject/parent/caregiver in the eDiary. The reported symptoms will be evaluated by investigator and reported, based on the investigator's medical evaluation and discretion, in the eCRF as solicited AEs.

Period 4 is the efficacy assessment period for the primary endpoint. Period 4 begins on September 1st for all subjects and lasts until the end of trial or discontinuation from IMP. During this period, the rate of clinically relevant asthma exacerbations will be evaluated.

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 (25-29 months).

1.2.1 Flow chart

The flow chart of the trial assessments by visits are shown in **Figure 2**.

Figure 2 Flow chart

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**[1]	**TC20**[2]	**V11**[3]	**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[4] 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[5]	X																					
Demography	X																					
Medical history incl. evaluate previous asthma exacerbations	X																					
SPT[6]	X		(X)																			
Review of in-/exclusion criteria	X		X		X																	
Randomisation					X																	
Physical examination[7]	X																			X		(X)

[1] 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 subjects randomised in cohort 4 after 31-Mar-2022, if applicable.

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

[3] 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.

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

[5] 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.

[6] If medication that could interfere with the SPT 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.

7 Oropharyngeal examination is included in physical examination

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[1]	TC20[2]	V11[3]	TC21	UN
Oropharyngeal Examination			X		X[8]	X		X		X		X		X		X		X				(X)
Height and weight[9]	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 [10]	X		X		X	X		X		X		X		X		X		X		X		X
Urine pregnancy test, if applicable[11]	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[12]	X	(X)[13]																				(X)
Recording of asthma exacerbations[14]	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[15]	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
[redacted]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

[8] Oropharyngeal examinations will be done before and 60 mins after IMP administration at visit 3
[9] If applicable, adjust the Asthma Action Plan and Local and Systemic Allergic Reaction Emergency Plan
[10] Measure FEV_1 and calculate the % of predicted FEV_1 after 6 hours of SABA.
[11] For female subjects of childbearing potential, additional urine pregnancy tests should be performed during the trial, if a menstrual period is missed.
[12] IgE against *D pteronyssinus, D farinae, Cladosporium herbarum* and *Blattella germanica*
[13] Inform subjects of continued participation in trial depending on the blood sample for specific IgE against *D. pteronyssinus* and *D. farinae*
[14] In case of an asthma exacerbation the subject should be called in for an unscheduled visit.
[15] If an AE was ongoing at the previous visit, if a new AE is identified at the telephone contact or if 1 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[1]	TC20[2]	V11[3]	TC21	UN
[redacted]																						
[redacted]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Issue and review Asthma Action Plan[16]			X																			
Issue and review Local and Systemic Allergic Reaction Emergency Plan [17]			X		X																	
ACQ or ACQ-IA					X			X		X		X		X		X		X		X		X
[redacted] [18]					X			X		X				X				X		X		X
[redacted]					X					X										X		X
[redacted] [19]			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)

[16] Dispense Peak Expiratory Flow (PEF) meters.
[17] Instruct in the use of rescue medication for severe allergic reaction, in countries where it is a regulatory requirement.
[18] [redacted]
[19] [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[1]	TC20[2]	V11[3]	TC21	UN
Intake of IMP at clinic					X20																	(X)
Dispense asthma and rhinoconjunctivitis rescue medication21			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 wk22		-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		

[20] 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.
[21] Dispense rescue medication for severe allergic reaction (adrenaline/epinephrine) in countries where this is applicable.
[22] eDiary recording of prespecified symptoms

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[1]**	**TC20[2]**	**V11[3]**	**TC21**	**UN**
Collect eDiary																				X		

1.2.2 Visit windows

See the flow chart in **Figure 2**.

1.2.3 Randomisation

The randomisation list has been 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.

At least 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 and 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.

2 STATISTICAL HYPOTHESES

2.1 Multiplicity adjustment

The primary and key secondary endpoints will be controlled for multiplicity to ensure a maximum overall type I error rate of 5% in the hypothesis testing of these endpoints. The control for multiplicity is done by hierarchical testing, pre-specifying the order of the hypothesis to be tested. For all endpoints the null hypothesis to be tested is the hypothesis of no difference between treatment groups.

The order of hypothesis to be tested 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 (primary objective, section **1.1.1**). The primary estimand will be used.

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 months after randomisation (first key secondary objective, section **1.1.2**).

3. Superiority testing of the HDM SLIT-tablet over placebo with respect to the proportions of days with SABA use during the 14 days eDiary recording every 4 months after randomisation (second key secondary objective, section **1.1.2**).

4. Superiority testing of the HDM SLIT-tablet over placebo with respect to the percentage predicted FEV_1 assessed every 4 months after randomisation (third key secondary objective, section **1.1.2**).

All hypotheses in the hierarchy are tested on a 5% significance level, i.e. significance is obtained when a p-value is below 5%. If the first hypothesis is statistically significant at the 5% level, i.e. the null hypothesis of no difference is rejected, then the second hypothesis is tested, and so forth. A hypothesis is only tested if all previously tested hypothesis were statistically significant at the 5% level, i.e. all previous null hypotheses were rejected.

3 ANALYSIS SETS

For the purposes of analysis, the following participant analysis sets are defined:

Analysis set	Description
FAS	The FAS consists of all randomised subjects, who received at least 1 dose of IMP. Subjects will be analysed as randomised, i.e. according to their randomised assignment of treatment.
SAF	The SAF consists of all randomised subjects, who received at least 1 dose of IMP. Subjects will be analysed as treated, i.e. according to the treatment they actually received.
PP	The PP will consist of all subjects in FAS without protocol deviations, which may substantially affect the primary endpoint. Subjects will be analysed as randomised, i.e. according to their randomised assignment of treatment.

Before database lock, a list will be made that defines which subjects in FAS are not included in PP and the reason for this. The criteria for not including subjects in PP are the following:

1. Violation of the inclusion/exclusion criteria that may potentially impact the primary endpoint
2. Use of prohibited medication close to or during the efficacy evaluation period (period 4) that may potentially impact the primary endpoint
3. Treatment compliance in the entire trial. Subjects with a treatment compliance below 80% are not included in the PP
4. Efficacy compliance. Subjects with less than 6 months of efficacy assessment in period 4 are not included in the PP

The list of subjects in PP is found in Appendix 4 section **7.4**.

The FAS will be used for baseline tables and efficacy output and the SAF will be used for safety tables and listings. The PP will be used for a supportive analysis of the primary endpoint.

The following data point sets are defined:

DPS	Description
DPS1	• Subjects who are treated in period 4 will be included. • Post-discontinuation data will not be included.
DPS2	• Only subjects who complete treatment in period 4 will be included.

FAS and DPS1 are used to estimate the primary estimand for the primary endpoint and the primary estimand for the key secondary endpoints.

FAS and DPS2 are used to estimate the secondary estimand for the primary endpoint.

In addition, to investigate the impact of covid-19 (see section **3.2**), the following observation periods are defined:

OP	Description
OP1	• The time period is from the start of the trial and until March 20, 2020, both dates included
OP2	• The time period is from March 20, 2020 (excluded) until the end of the trial

3.1 Issue at site 613

In Sep-2018 the CRO discovered that 2 subjects at the site had been enrolled in 2 different trials for 2 different sponsors at the same time. Evaluation from the CRO medical monitor review showed that subjects' safety was not affected. All 9 subjects at the site were discontinued from the trial in Nov-2018 and the site was terminated in Mar-2019.

Thus, efficacy data from site 613 are neither included in the PP, nor in the FAS. However, safety data from site 613 are included in the SAF.

3.2 Impact of Covid-19

Covid-19 has impacted the trial in terms of both recruitment opportunities and impact on the primary endpoint, see section **5.1**.

Additional statistical analyses of the primary endpoint (see section **4.2.6**) and the key secondary endpoints (see section **4.3.1.6**) are performed to analyse the impact of Covid-19.

4 STATISTICAL ANALYSES

Statistical analyses will be carried out by ALK, Biometrics, Hørsholm, Denmark. All computations will be performed using the statistical analysis system SAS® version 9.4 or later.

The analyses described in this section, along with the supporting information supplied in the Appendices (**7.1** and **0**), specify the statistical analyses.

4.1 General considerations

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 2-sided. The null hypothesis is the hypothesis of no difference and the alternative to the null hypothesis is the hypothesis of difference.

Descriptive statistics for numerical variables include summary tables displaying mean, SD, median, minimum and maximum and relevant quantiles. Descriptive statistics for categorical variables include frequency tables that display numbers and percentage.

When age is used as fixed effect in the statistical models, it is the age assessed at randomisation that is used.

If baseline measurements are missing for any efficacy endpoints, the last measurement before or on the date of first treatment will be used, if possible, for the given endpoint (screening observation carried forward).

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

4.1.1 Considerations regarding countries/region

Variation between countries/region in the primary endpoint is expected and may result from variation in geography and thus HDM exposure, variation in standard treatment procedures and from possible differences in conduct of the trial protocol. Variation between sites (centres) is also expected but is assumed to be small compared to the variation between countries and regions.

To ensure a balanced dataset for the primary endpoint, countries are pooled to regions. Three regions are defined (west: DEU, ESP, FRA, GBR and USA; central: POL; east: BGR, HUN and RUS). The region variable is used instead of country for all analyses, where a country/region factor is applied.

4.1.2 Model assumptions

Model checking of the models used in the test hierarchy, see section **2.1**, will be performed based on visual inspections of residual plots (for the NB models and marginal models) and by visual inspections of quantile-quantile (QQ) plots (for the MMRM model).

4.2 Primary endpoint analysis

For the primary endpoint, data collected after treatment discontinuation is only used for sensitivity analysis 2. For all other scenarios, no data collected after treatment discontinuation is used.

4.2.1 Definition of endpoint

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

Note that period 4 begins on September 1st for all subjects and lasts until the end of trial or discontinuation of IMP.

4.2.2 Overview of analyses of primary endpoint

Table 1 gives an overview of the analyses of the primary endpoint including the handling of treatment discontinuations and missing data.

In the sensitivity analysis 1, the data from the discontinuations in period 3 (number of events and exposure time) are carried forward and used in period 4 (LOCF). Data for discontinuations in period 4 are included as observed.

In the sensitivity analysis 2, subjects are not included if they discontinue in period 3. Data for discontinuation in period 4 are included as observed together with data imputed from placebo completers.

Table 1 Overview of analyses and handling of discontinuations and missing data for the primary endpoint

Analysis	Estimand	Analysis set/DPS	Impact of Covid-19 effect included	Statistical method	Treatment discontinuation approach/ Missing data approach	
					Discontinuations in period 3	Discontinuations in period 4
Primary	Primary	FAS/ DPS1	1) None 2) OP1, OP2	NB regression	Not included/ None	Included as observed/ None
	Secondary	FAS/ DPS2	1) None 2) OP1, OP2	NB regression	Not included/ None	Not included/ None
Sensitivity 1	N/A	FAS	1) None	NB regression	Included as observed/ LOCF	Included as observed/ None
Sensitivity 2	N/A	FAS	1) None	NB regression	Not included/ None	Included as observed/ Imputed from placebo completers
Supportive	Primary	PP/ DPS1	1) None	NB regression	Not included/ None	Included as observed/ None

None = no Covid-19 effect analysed, LOCF = Last Observation Carried Forward, OP1 = trial observation period before and including 20-Mar-2020 (before Covid-19), OP2 = trial observation period after 20-Mar-2020 (during Covid-19), OP1, OP2 = a Covid-19 effect is applied representing either the period before or during Covid-19. Included as observed = only observed data in the part of the period in which they are collected are used. If discontinuations occur, the observed values are included.

4.2.3 Main analytical approach

The primary endpoint, based on both the primary and secondary estimand, will be compared between treatment groups using the hypothetical estimand for the FAS population using either the DPS1 or DPS2, i.e. subjects for whom the primary endpoint is missing due to discontinuation of treatment prior to period 4 will not contribute to the analysis. This approach of using observed data only (an observed case analysis), implicitly assumes that observations are missing completely at random (MCAR), i.e. had the subjects continued treatment into the efficacy assessment period (period 4), they would have experienced the same treatment effect as subjects from the same treatment arm with observations of the primary endpoint. This assumption will be investigated in a sensitivity analysis.

The primary endpoint will be analysed by means of a negative binomial (NB) regression model with the number of asthma exacerbations as the response variable, treatment group, age group (<12 years/≥12 years) and region as fixed effects, and the logarithm of the time in period 4 (in years) 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 main outcome is the resulting p-value from the LR test reported together with the ratio of the rates and Wald 95% confidence intervals.

4.2.4 Sensitivity analyses

Two sensitivity analyses are performed. Both sensitivity analyses challenge the primary estimand.

Sensitivity analysis 1

The primary analysis relied on the assumption that discontinuation of treatment prior to period 4 occurred completely at random. A sensitivity analysis challenging this assumption will be performed as follows. For subjects in FAS who discontinue treatment prior to the efficacy assessment period (period 4), the primary endpoint will be carried forward in term of both the number of clinically relevant asthma exacerbations observed in period 3 and the actual exposure time in period 3. This dataset using an LOCF-type approach is based on FAS and will be analysed using the same model specified for the primary efficacy analysis.

No missing data approach is defined for treatment discontinuations in period 4.

The datasets specified in this sensitivity analysis will be analysed using the same model specified for the primary efficacy analysis.

Sensitivity analysis 2

Subjects who discontinue treatment in period 3 are not included in the analysis and no missing data approach is applied for these subjects.

Missing data for subjects who discontinue treatment and withdraw from trial prematurely before the planned end of study will be multiple imputed from the completers in the placebo group, i.e. it is assumed that after discontinuation of treatment subjects will experience the same treatment effect as subjects treated with placebo. Subjects that discontinue treatment and complete trial are treated as completers and all observations until the end of the trial period are used in the analysis. There will be no imputations to or from these subjects.

The datasets specified in this sensitivity analysis will be analysed using the same model specified for the primary efficacy analysis.

4.2.5 Supportive analysis

As a supportive analysis, the primary efficacy endpoint will be analysed based on the PP using the same NB regression model as for the primary efficacy analysis and the same intercurrent event approach as for the primary estimand.

4.2.6 Additional analyses investigating the impact of Covid-19

Additional analyses, where a Covid-19 effect is applied, are performed for the primary and secondary estimands of the primary endpoint (see **Table 1**). The Covid-19 effect is representing either the period before or during Covid-19 (20-Mar-2020).

4.3 Secondary endpoint analyses

For all secondary endpoints (key secondary and additional secondary endpoints), no data collected after treatment discontinuation is used.

4.3.1 Key secondary endpoints

4.3.1.1 Definition of endpoints

- 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 number of days with nocturnal awakenings due to asthma requiring SABA rescue medication as well as the total number of eDiary recordings are calculated, and the proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication is calculated as the number of days with nocturnal awakenings due to asthma requiring SABA rescue medication out of the total number of days recorded.

- Proportions of days with SABA use during the 14 days eDiary recording every 4 months after randomisation

The number of days with SABA use as well as the total number of eDiary recordings are calculated, and the proportion of days with SABA use is calculated as the number of days with SABA rescue medication use out of the total number of days recorded.

- Percentage predicted FEV_1 assessed every 4 months after randomisation

The calculated percentage of predicted FEV_1 (%) is analysed.

4.3.1.2 Overview of analyses of key secondary endpoints

Table 2 gives an overview of the analyses of the key secondary endpoints including the handling of treatment discontinuations.

Table 2 Overview of analyses and handling of discontinuations for the key secondary endpoints

Endpoint	Estimand	Analysis set	Impact of Covid-19 effect included	Statistical method	Treatment discontinuations in efficacy period
Nocturnal awakenings	Primary	FAS	1) None 2) OP1, OP2	Marginal logistic regression	Included as observed
SABA use	Primary	FAS	1) None 2) OP1, OP2	Marginal logistic regression	Included as observed
Pred. FEV_1	Primary	FAS	1) None 2) OP1, OP2	MMRM	Included as observed

None = no Covid-19 effect analysed, Pred. = predicted percentage, OP1 = trial observation period before and including 20-Mar-2020 (before Covid-19), OP2 = trial observation period after 20-Mar-2020 (during Covid-19), OP1, OP2 = a Covid-19 effect is applied representing either the period before or during Covid-19. Included as observed = only observed data in the part of the period in which they are collected are used. If discontinuations occur, the observed values are included.

4.3.1.3 Main analytical approach

The key secondary endpoints will be compared between treatment groups using the primary estimand for the FAS population.

The proportion of days with nocturnal awakening which require SABA rescue medication over the 14 days eDiary assessment period (before V5, V6, V7, V8, V9, V10 and V11) will be modelled by a marginal logistic regression model with an unstructured working covariance matrix. The response variable is the number of days with nocturnal awakenings due to asthma requiring SABA rescue medication out of the total number of days recorded. Treatment, visit and treatment-by-visit interaction, age group (<12 years/≥ 12 years) and region will be included as fixed effects. Baseline proportions of nocturnal awakenings requiring SABA will be included as a covariate. The marginal model will be estimated using a generalized estimating equations (GEE) approach. The treatment effect on the logit scale is an average treatment effect across all visits and will be estimated as a contrast of parameters in the marginal model. For both the overall treatment effect and the effect per visit, the corresponding odds ratio for proportions of days with nocturnal awakening requiring SABA of active treatment relative to placebo will be presented together with the coherent p-value and 95% confidence limit.

The proportion of days with SABA use over the 14 days eDiary assessment period (before V5, V6, V7, V8, V9, V10 and V11) will be analysed by means of a marginal logistic regression model and a GEE estimation approach as described for “proportion of days with nocturnal awakening which require SABA”.

Percentage predicted FEV_1 assessed every 4 months after randomisation (at V5, V6, V7, V8, V9, V10 and V11) will also be analysed by means of an MMRM model. The response variable is the percentage predicted FEV_1. Treatment, visit, treatment-by-visit interaction, age group (<12 years/≥ 12 years) and region will be included as fixed effects. Baseline percentage predicted FEV_1 (measured at visit 3) will be included as a covariate. Different residual errors for each treatment group will be specified and the within-subject correlated errors are modelled by an unstructured covariance. The treatment effect is the average treatment effect across all visits. The between treatment comparison will be performed by means of a t-test with Kenward-Roger degrees of freedom approximation **(Kenward and Roger 1997)**. For both the overall treatment effect and the effect per visit, the resulting p-value will be reported together with the difference in adjusted means.

In addition, the absolute treatment estimates by visit and 95% confidence intervals will be plotted from the MMRM model.

4.3.1.4 Sensitivity analyses

None.

4.3.1.5 Supplementary analyses

None.

4.3.1.6 Additional analyses investigating the impact of Covid-19

Additional analyses, where a Covid-19 effect is applied, are performed for each of the described analyses of the key secondary endpoints. The Covid-19 effect is representing either the period before or during Covid-19 (20-Mar-2020).

4.3.2 Additional secondary endpoints

4.3.2.1 Overview of analyses of additional secondary endpoints

Table 3 gives an overview of the analyses of the additional secondary endpoints including the handling of treatment discontinuations.

Table 3 Overview of analyses and handling of discontinuations for the additional secondary endpoints

Endpoint	Estimand	Analysis set	Statistical method	Treatment discontinuations in efficacy period
Time to first and recurrent severe asthma exacerbation	None	FAS	Cox prop. hazards regression[a]	Included as observed
Time to first and recurrent asthma exacerbation	None	FAS	Cox prop. hazards regression[a]	Included as observed
Severe asthma exacerbation rate	None	FAS	NB regression	Included as observed
Change from baseline FEV_1	None	FAS	MMRM	Included as observed
Scores[b]	None	FAS	MMRM	Included as observed
ACQ/ACQ-IA	None	FAS	MMRM	Included as observed
Global evaluations[c]	None	FAS	GLMM	Included as observed
Immunology[d]	None	FAS	MMRM	Included as observed

[a]Including the Andersen-Gill extension.

[b]Scores include endpoints of scores of asthma VAS, asthma symptoms, rhinitis and rhinoconjunctivitis symptoms and symptomatic medication.

[c]Global evaluation of allergic rhinitis and global evaluation of allergic asthma.

[d]Changes from baseline in IgE, IgE-BF and IgG4 against D. pteronyssinus and D. farinae.

4.3.2.2 Asthma exacerbations

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 includes treatment and age group (<12 years/≥ 12 years) as effects. Region is included as a random effect assumed to follow a gamma distribution. Thus, this is a shared Cox gamma frailty model. The treatment comparison is performed using a Likelihood Ratio test based on the Cox proportional hazards regression model. The estimated hazard ratio (HR) of active treatment compared to placebo will be presented together with 95% Wald's confidence limits.

The Cox proportional hazards regression analysis is supplemented by a Kaplan-Meier analysis on time to first severe asthma exacerbation and time to first clinically relevant asthma exacerbation.

Time to recurrent clinically relevant asthma exacerbation and time to recurrent severe asthma exacerbation in days from the start of the efficacy period will each be analysed by means of an Andersen-Gill (AG) extension of the Cox model for recurrent events **(Andersen and Gill 1982)**.

The Andersen-Gill model assumes that events are independent, and so robust standard errors are used to accommodate heterogeneity. A Robust Sandwich covariance matrix will be used for the regression coefficient estimators. The treatment comparison is performed using a Likelihood Ratio test based on the extension of the Cox proportional hazards regression model. The model will include treatment and age group (<12 years/ ≥12 years) as fixed effects. The estimated hazard ratio (HR) of active treatment compared to placebo will be presented together with 95% confidence limits. In case of few recurrent clinically relevant asthma exacerbations or few recurrent severe asthma exacerbations, the endpoint(s) will only be summarised descriptively.

The annualised rate of severe asthma exacerbations in period 4 will be analysed similar to the primary efficacy endpoint using a NB regression model as described in section **4.2.3**.

4.3.2.3 Predicted FEV_1

Change from baseline in percentage predicted FEV_1 will be analysed by means of an MMRM model as for the endpoint "Percentage predicted FEV_1".

4.3.2.4 Asthma symptoms

The average asthma DSS, the average asthma VAS and the average daily dose of SABA use over the 2-week diary assessment (before V5, V6, V7, V8, V9, V10 and V11) will be analysed by means a MMRM. The analysis includes a square root transformation of the response variable, treatment, visit, and treatment-by-visit interaction, age group (<12 years/≥ 12 years) and region as fixed effects and a square root transformation of the baseline score as a covariate. Different residual errors for each treatment group will be specified and the within-subject correlated errors are modelled by an unstructured covariance.

For each visit and for the overall treatment effect across all visits, the 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 back-transformed adjusted means, calculated based on a second-order Taylor series expansion. 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 **(Fieller 1954)**.

The global evaluation of allergic asthma as binary outcomes “improved/not improved” will be analysed using a GLMM with a logit link function, treatment, age group (<12 years/≥ 12 years) and region as fixed effects. From the GLMM model, the odds ratio for having an improved outcome of active treatment relative to placebo will be presented together with the coherent p-values and 95% confidence limits. Additionally, Fishers exact test will be applied to the binary response of the global evaluation.

The ACQ/ACQ-IA (see section **7.1.1.5**) will also be analysed by means of a MMRM model as for the average asthma DSS, asthma VAS and the average daily dose of SABA, but without a square root transformation of the data.

4.3.2.5 Rhinitis symptoms and symptomatic medication

The average TCRS, the average rhinitis DSS, the average rhinitis DMS and the average rhinitis CSMS will be analysed using a similar MMRM model as described for the average asthma DSS and asthma VAS.

The global evaluation of allergic rhinitis will be analysed using a similar GLMM model as described for the global evaluation of allergic asthma.

4.3.2.6 Rhinoconjunctivitis symptoms and symptomatic medication

The average total rhinoconjunctivitis TCS, the average rhinoconjunctivitis DSS, the average rhinoconjunctivitis DMS, the average rhinoconjunctivitis CSMS and the average rhinoconjunctivitis VAS will be analysed using a similar MMRM model as described for the average asthma DSS.

4.3.2.7 Immunology

Summary tables by treatment group and visit will be produced for raw data and $\log_{10}$-transformed data of specific IgE and IgG_4 and for raw data of IgE-BF against *D. pteronyssinus* and *D. farinae* by visit. Also, the change from baseline in the immunological data (IgE, IgG_4, IgE-BF, $\log_{10}$(IgE) and $\log_{10}(IgG_4)$) will be summarised.

Change from baseline in $\log_{10}$(IgE) and $\log_{10}(IgG_4)$ (against *D. pteronyssinus* and *D. farinae*) at visit 7 and 11 will be analysed using a MMRM model. For IgE and IgG_4, change from baseline of the $\log_{10}$-transformed immunological parameter is the response variable. Treatment, visit and treatment-by-visit interaction will be included as fixed effects, the $\log_{10}$-transformed immunological parameter at baseline is a covariate. Different residual errors for each treatment group will be specified in the MMRM model. The correlation structure of the repeated measure is an unstructured covariance. The active dose group will be compared to placebo at each visit using a t-test in the MMRM model and an overall treatment ratio across all visits will be estimated together with a p-value based on the MMRM model. The corresponding difference in adjusted means reported on the $\log_{10}$ scale, will be calculated together with the associated p-value and 95% confidence intervals.

Change from baseline in IgE-BF will be analysed using a similar MMRM model as described for specific IgE and IgG_4. However, IgE-BF data will not be $\log_{10}$-transformed.

The estimated mean change from baseline in the immunological parameters ($\log_{10}$(IgE), $\log_{10}$(IgG4)) and IgE-BF with 95% confidence limits will be plotted by time (visit) and treatment.

If IgE values are recorded as "0" or "<0.70" the value 0.69 will be used. If the value is recorded as ">800", 801 will be used. If IgG_4 values are recorded as "<0.15" the value 0.14 will be used. If the value is recorded as ">30", 31 will be used. Otherwise, data are used as measured.

Additional analyses are performed for all immunology endpoints using the above-described models, but where the age-group is divided into sub-age-groups: 5-7 years, 8-11 years and at least 12 years. Estimates are presented by sub-age-group.

4.4 Other endpoints analyses

For the other endpoints, no data collected after treatment discontinuation are used.

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted].

[redacted] [redacted].

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

4.5 Safety analyses

All safety tables and listings will be for the safety analysis set unless otherwise specified.

4.5.1 Extent of exposure

4.5.1.1 Tablets taken

The number of tablets taken is calculated as the difference between the number of tablets dispensed and the number of tablets returned or lost.

The number of tablets taken will be summarised by treatment group.

4.5.1.2 Treatment duration

The duration of treatment for each subject is calculated from the date of randomisation up until (and including) the date of last IMP intake. The period may include interruptions.

Treatment duration will be summarised by treatment group.

4.5.1.3 Treatment days and treatment year

Treatment days is the number of tablets taken. A treatment year is the number of tablets taken divided by 365.

Treatment days and treatment years will be displayed in summary tables by treatment groups.

4.5.1.4 Compliance

Compliance will be calculated for each subject as the number of tables taken divided by the treatment duration in days and multiplied with 100.

Percentage compliance will be summary by treatment group.

4.5.2 AEs

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

Treatment-emergent adverse events (TEAEs) are defined as AEs with start time on or after the time of first IMP administration and no later than 7 days after the last day of IMP administration. If, due to partial time/dates, there is any doubt whether an AE is treatment-emergent, the event will conservatively be assessed as treatment-emergent.

Non-TEAEs are AEs that occur prior to first IMP administration or more than 7 days after last IMP administration.

IMP-related AEs are TEAEs that are assessed ‘possibly related’ or with missing assessment.

Severe and clinically relevant asthma exacerbations reported during the trial are expected as a result of subjects' background disease and will be evaluated as part of the primary endpoint. Adverse events are separated into three groups: solicited AEs, clinically relevant asthma exacerbations and other events including events synonymous with solicited terms and present after the soicitation period.

All TEAEs and all IMP-related 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.

All TEAEs and IMP-related AEs will be broken down by intensity (mild, moderate, severe), seriousness, action taken and outcome and summarised by treatment group displaying number of subjects in treatment group, number and percentage of subjects having the event as well as number of events.

Number of events and number and percentage of subjects having TEAEs of special interest will be displayed in summary tables. The events of special interest will be based on the investigator's assessment of an event being "an anaphylactic reaction, an anaphylaxis and/or a systemic allergic reaction"; "an event treated with adrenaline/epinephrine"; "severe local swelling or oedema of the mouth and/or throat" or "an eosinophilic oesophagitis" along with SAEs of severe asthma exacerbations and clinically relevant asthma exacerbations.

Number of events and number and percentage of subjects having local application site TEAEs; medication error; drug abuse, misuse and overdose based on investigators assessments in the eCRF, will also be displayed in summary tables.

TEAEs leading to IMP interruptions, serious TEAEs (SAEs) and TEAEs leading to IMP discontinuations will be summarised by SOC, PT and treatment group in separate tables. A cumulative incidence plot will be used to show the cause specific distribution of IMP discontinuation due to TEAEs.

Most frequent TEAEs are those AEs (defined as MedDRA PTs) that are present in at least 2% of subjects with active treatment. Most frequent TEAEs and most frequent IMP-related AEs will be summarised by SOC, PT and treatment group in separate tables.

Additionally, the following TEAEs will be summarised by treatment group displaying the number and frequency of subjects having the event as well as number of events, see **0** (Appendix 3: Preferred Terms):

- asthma related events
- asthma related hospitalisations

- worsening of asthma requiring medication
- asthma related symptoms leading to IMP discontinuation
- solicited TEAEs
- TEAEs excluding solicited events and clinically relevant asthma exacerbations

Onset of a TEAE is defined as time (e.g. minutes or days) from first IMP intake to start of the first TEAE of a given PT. An onset of 1 day means that the TEAE has started on the day of first IMP intake.

Resolution time of a TEAE is defined as days from start of the TEAE until the TEAE is resolved, e.g., recurrent TEAEs like oral pruritus that occurs every day for 1 minute on 5 days in a row will have a resolution time of 5 days.

Resolution time and onset in minutes/hours/days will be summarised by treatment group for most frequent TEAEs and for local application site TEAEs displaying mean, SD, median, 5% percentile, 95% percentile, minimum and maximum.

For solicited TEAEs the duration in minutes on the first day of IMP intake will be summarised.

All AEs will be listed including non-TEAEs.

4.5.3 Additional safety assessments

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

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

Physical examination assessments will be presented as shift tables from baseline (visit 2) to the end-of-treatment visit (visit 11) and will be summarised by visit. Laboratory assessments will also be presented as shift tables from baseline (visit 1) to the end-of-treatment visit (visit 11).

Vital signs and FEV_1 will be summarised by treatment as mean, SD, median, 5%-percentile and 95%-percentile minimum and maximum by visit.

4.6 Other analyses

4.6.1 Other variables and/or parameters

Not applicable.

4.6.2 Subgroup analyses

Subgroup analyses are performed to evaluate the consistency of the primary efficacy result across different relevant subgroups. Subgroup analyses of the rate of clinically relevant asthma exacerbations during the efficacy evaluation period (period 4) include:

- age group at randomisation (5-11,12-17 years)
- sex
- race (caucasian, non-caucasian)

- asthma background treatment (ICS, ICS plus LABA)
- allergen sensitivity (HDM only, HDM + others)
- geographic region (US, Europe)

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 same NB regression model as in the primary efficacy analysis will be applied for the subgroup analyses based on all observed data in FAS corresponding to the primary estimand. The subgroup analyses will be performed using the statistical model for the primary analysis with the inclusion of the subgroup analysed and an interaction with treatment.

4.7 Interim analysis

No interim analysis will be performed.

4.8 Changes to the protocol-planned analyses

Changes to the protocol are described in this section.

Impact of Covid-19

- Due to the Covid-19 pandemic that has impacted the MT-11 trial from Q1 2020, it has been decided not to perform the planned 2nd blinded sample size reassessment (SSR) with a data cut-off point closest to but not before 1st of March 2021.
- As a consequence of the ongoing Covid-19 pandemic, it has been decided to analyse the impact of Covid-19 on the primary and key secondary endpoints by repeating the analyses including an Covid-19 effect on two levels: before and during Covid-19.
- The end of trial date has been changed to be the date of the sponsor's decision to end the trial, due to the trial's severe impact by the Covid-19 pandemic. This date was 10th of August 2022.

AEs

- The list of PTs defining the solicited AEs has been expanded.
- Treatment-emergent AEs (TEAEs) have been redefined to exclude AEs with a start day more than 7 days after last IMP administration. In addition, the term non-TEAE has been introduced and specified.

Statistical models

- The model for the key secondary endpoints “proportion of days with nocturnal awakening which require SABA” is changed from a generalized linear mixed effect model to a marginal logistic regression model estimated by a GEE approach. GEE estimation has fewer model assumptions and hence reduces the risk of wrong model assumption. In addition, the treatment effect has an interpretation as a population average estimate in the GEE approach.
- All MMRM analyses have been aligned and updated to include the following fixed factors: treatment, visit, treatment-by-visit interaction, age group and region. Baseline values at visit

3 will be included as a covariate. The default within-subject correlation structure has been changed from a Toeplitz covariance to an unstructured covariance.

- The model for the 2 additional secondary endpoints "Time to first severe asthma exacerbation" and "Time to first clinically relevant asthma exacerbation" has been changed to a Cox proportional hazards regression analysis including treatment and age group (<12 years/≥ 12 years) as effects. Region is included as a random effect assumed to follow a gamma distribution.

Endpoints

- A new additional secondary endpoint has been added: "Change from baseline in percentage predicted FEV_1".
- The key secondary endpoint for SABA use has been changed from a continuous endpoint (average daily doses) to a binary endpoint (proportion of days). The reason is that many subjects do not use any SABA and the resulting excessive number of zeros are challenging to model as a continuous variable. The continuous endpoint “Average daily dose of SABA" will instead be analysed as an additional secondary endpoint.
- Explorative endpoints have been renamed to Other endpoints.
- [redacted]
- [redacted]
- If any subject exceeds the recommended daily dose of a symptomatic medication for rhinitis or rhinoconjunctivitis, the maximal daily score will be used and not the actual score as specified in the protocol.
- Additional description of how safety endpoints are summarised are added:
    - Duration in minutes of the solicited AEs occurring on first day of IMP intake, treatment-emergent anaphylactic reactions, anaphylaxis and/or systemic allergic reactions, TEAEs treated with adrenaline/epinephrine, treatment-emergent severe local swelling or oedema of the mouth and/or throat, treatment-emergent eosinophilic oesophagitis, medication error, local application site TEAEs, onset and resolution time in days for most frequent TEAEs (≥2% of subjects in active group), onset and resolution time in days for local application site TEAEs, drug abuse, misuse and overdose.

5 SAMPLE SIZE DETERMINATION

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 5 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 subjects 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 time interval for the active group, $1-\beta$ is the power, alpha is the level of significance and k is the dispersion parameter.

Table 5 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 months (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 5**. 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%.

5.1 Sample size reassessment

A blinded sample size reassessment (SSR) has been performed according to the protocol section 15.2.1. For each subject, the data cut-off-point for the SSR was the visit (including TCs) closest to but not before the 1st of February 2020.

The conclusion of the SSR was that the reassessed sample size is 900 subjects, corresponding to a power of 81%. However, it was decided not to recruit for a new cohort as it was assessed that the SSR may not be accurate as the exacerbation rate was uncertain due to a very limited number of observations and due to the fact that the Covid-19 situation with rules of social distancing was likely to reduce transmission of respiratory infections, and thus also the number of exacerbations.

It was decided to perform a new SSR based on data sets from Cohort 1-3, however the SSR was not performed. Details are provided in section **4.8**.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries of numerical variables will display the descriptive statistics mean, SD, median, minimum and maximum and relevant quantiles.

Summaries of categorical variables will be frequency tables displaying numbers and percentages.

6.1 Subject disposition

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

Table(s) of subject disposition by treatment group displaying number and percentage of subjects screened, randomised, included in FAS, with observation of the primary endpoint (at least 1 observation in period 4), included in PP, included in SAF, discontinued treatment, withdrawn from trial, by primary reason for discontinuation of treatment or withdrawal from trial and who completed the trial will be presented.

The overall treatment discontinuation and treatment discontinuation due to AEs will be displayed by a Kaplan-Meier plot.

6.2 Baseline characteristics

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

Baseline characteristics (e.g. baseline asthma status, inhaled corticosteroid use, duration of HDM AR/C and asthma, and HDM wheal size from SPT, allergen sensitivity (HDM only, HDM + others)) will be summarised by treatment group.

6.3 Medical history

Medical history will be summarised by treatment group.

6.4 Prior and concomitant therapy

Prior and concomitant medication will be summarised separately by treatment group.

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

7 SUPPORTING DOCUMENTATION

7.1 Appendix 1: Definitions and derivations

7.1.1 Derivation of endpoints from eCRF data

7.1.1.1 Clinically relevant and severe asthma exacerbation endpoints

The source for deriving the clinically relevant asthma exacerbation and the severe 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 fulfilled for the event being categorised as a clinically relevant or severe asthma exacerbation. If at least 1 of the 4 criteria listed in section **1.1.5** is fulfilled, the event is considered a clinically relevant asthma exacerbation. If at least 1 of last 3 criteria listed in section **1.1.5** is fulfilled, the event is additionally considered to be a severe asthma exacerbation.

A clinically relevant asthma exacerbation must be separated by more than 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/events (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 2 or more successive clinically relevant asthma exacerbations, the asthma exacerbations will be considered 1 single event starting with the start date of the first asthma exacerbation and ending with the stop date of the last asthma exacerbation. If either clinically relevant asthma exacerbation fulfils 1 of the criteria for being a severe asthma exacerbation the entire event is considered to fulfil that criterion.

7.1.1.2 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 visit 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 is 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.:

$$Time_{Years} = Years\left(date_{Last\ IMP} - date_{Start\ period\ 4} + 1\right).$$

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 efficacy 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 day of IMP intake, if this date is a partial date, it is imputed. If the last day of IMP intake is unknown, the date of last contact is used instead.

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

7.1.1.3 Annualised rate of severe asthma exacerbations in period 4

The annualised rate of severe asthma exacerbations in period 4 is calculated in the same way as the annualised rate of clinically relevant asthma exacerbations in period 4 as described in section **7.1.1.2**. IMP discontinuation is handled in the same way as described in section **7.1.1.2**.

[redacted]

7.1.1.5 ACQ/ACQ-IA

Subjects aged at least 11 years will self-complete the asthma control questionnaire (ACQ) when possible. Otherwise, an interviewer administered version (ACQ-IA) will be used. For subjects aged 5-10 years (both inclusive) the ACQ-IA will be used. ACQ/ACQ-IA will be completed by all subjects during the trial at V3, V5, V6, V7, V8, V9, V10 and V11.

The questionnaire contains a total of 7 items: 5 questions are related to asthma symptoms, 1 question is related to SABA medication use and 1 item is related to FEV_1, the latter being calculated based on the FEV_1 measurement. Subjects are asked to recall their experiences during the previous 7 days and respond to each question using a 7-point scale which is translated into a scale ranging from 0 to 6. The items are equally weighted and the ACQ/ACQ-IA score is the average of the 7 items and therefore between 0 (well controlled) and 6 (extremely poorly controlled).

[redacted]

7.1.1.8 Global evaluation of rhinitis and asthma

At the final visit the subjects will be asked about their perception of the treatment efficacy during the treatment period answering the following question regarding rhinitis: “Compared to your rhinitis symptoms before starting treatment with the IMP, how are you feeling overall now?”.

Subjects will additionally be asked about their perception of the treatment efficacy during the treatment period answering the following question regarding asthma: “Compared to your asthma symptoms before starting treatment with the IMP, how are you feeling overall now?”.

A subject answering ”better” or “much better” will be categorised as “improved”. A subject answering “much worse”, “worse” or “the same” will be categorised as “not-improved”.

7.1.2 Derivation of endpoints from eDiary data

The eDiary data are filled in by the subject on a daily basis during a 3-week baseline period (starting at V2) and every 4 months after randomisation 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).

Only days where diary data has been entered are considered for calculating scores. For baseline data, only data collected before the date of first dose will be considered.

When calculating the baseline scores, if a subject has at least 14 days of diary data, the first 7 days are disregarded, and the following 14 days of data are used to calculate the scores. This means that a subject with 22 days of data will have baseline scores based on the data collected from day 8 to day 21 both days included. If instead the subject had 20 days of diary data, the baseline scores would be based on the 13 days of data collected from day 8 to day 20, both included.

When calculating baseline scores, if a subject has less than 14 days of diary data, the last 7 of these are used for calculating baseline scores, if the subject has less than 7 days of diary data, all data will be used.

For non-baseline periods the last 14 days of diary data are used.

The 14 days of diary records prior to visit 5, 6, 7, 8, 9, 10, and 11 will define the 14 days eDiary assesment period used for calculating the endpoints.

Average rhinitis, [redacted] and rhinoconjunctivitis DSS

Rhinoconjunctivitis symptoms are recorded on a daily basis during the periods of eDiary recording. The rhinoconjunctivitis symptoms consist of 4 rhinitis symptoms (runny nose, blocked nose, sneezing, itchy nose) and 2 conjunctivitis symptoms (gritty feeling/red/itchy eyes and watery eyes) which are scored from 0 to 3 as shown in **Table 6**.

Table 6 Subjects' symptom scoring[1]

Scored by subject	Definition of score	Numerical Score
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

The rhinitis DSS is the total of the 4 individual rhinitis symptom scores and ranges from 0 to 12.

[redacted].

The rhinoconjunctivitis DSS is the total of all 6 individual rhinoconjunctivitis symptom scores and ranges from 0 to 18.

Table 7 shows the construction of the DSS.

Table 7 Construction of DSS

Symptoms	Rhinitis DSS	[redacted]	Rhinoconjunctivitis DSS
Rhinitis symptoms			
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
Total range	0-12		0-18

The average symptom scores (average rhinoconjunctivitis DSS, average rhinitis DSS, [redacted] are for each subject and each visit (V2, V5, V6, V7, V8, V9, V10, V11) calculated as the average of non-missing records during the 14 days of eDiary assessment.

7.1.2.1 Average rhinitis, [redacted] and rhinoconjunctivitis daily medication score (DMS)

Use of rhinoconjunctivitis symptomatic medication is recorded daily during the periods of eDiary recording.

The total daily medication score for each symptomatic medication is calculated as the unit score multiplied by the number of units entered in the daily diary, see **Table 8**.

The rhinitis DMS: the sum of the total daily scores for all rhinitis symptomatic medication ranges from 0 to 12.

[redacted]

The rhinoconjunctivitis DMS: the sum of the total daily scores for all rhinitis/conjunctivitis symptomatic medication ranges from 0 to 20.

The average daily medication scores (average rhinoconjuntivitis DMS, average rhinitis DMS, [redacted]) are for each subject and each visit (V2, V5, V6, V7, V8, V9, V10, V11) calculated as the average of non-missing records during the 14 days of eDiary record period.

Table 8 Daily medication score

Rescue medication	Subject dosing instruction[1]	Score/ Dose unit[2]	Maximum daily score
Rhinitis medication score			
Desloratadine tablets[3], 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		
	At least 12 years: 1 tablet once daily		
Mometasone furoate nasal spray, 50 µg/dose	<12 years old: 1 puff in each nostril once daily	4/PUFF	8
	At least 12 years: 2 puffs in each nostril once daily	2/PUFF	
Maximum daily rhinitis DMS[4]			12
Conjunctivitis DMS[4]			
Desloratadine tablets[3], 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		
	At least 12 years: 1 tablet once daily		
Azelastine eye drops, 0.5 mg/ml	1 drop in each eye twice daily	1.5/drop	6
[redacted]			
Maximum daily rhinoconjunctivitis DMS[4]			20

[1] When calculating scores that depend on the age of the subject, the age attained at the start of the diary period is used. This age is calculated from the partial birthdate.

[2] Scoring scales are not seen by the subjects.

[3] 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 and Lorber 2002)**.

When calculating the desloratadine score, the amount of desloratadine used in mg is calculated regardless of it being syrup or tablets, and that amount is used to calculate a fraction of the associated score for the subject.

[4] If any subject exceeds the recommended daily dose of symptomatic medication, the maximal daily score will be used.

7.1.2.2 Average TCRS [redacted] and rhinoconjunctivitis TCS

TCRS: the sum of the rhinitis DSS and the rhinitis DMS and ranges from 0-24.

[redacted]

The rhinoconjunctivitis TCS: the sum of the rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS and ranges from 0-38.

The average total combined scores (average rhinoconjunctivitis TCS, average TCRS, average conjunctivitis TCS) are for each subject and each visit (V2, V5, V6, V7, V8, V9, V10, V11) calculated as the average of non-missing records during the 14 days of eDiary.

7.1.2.3 The average rhinitis and rhinoconjunctivitis CSMS recommended by EAACI task force

The rhinitis and the rhinoconjunctivitis CSMS are based on the daily rhinoconjunctivitis symptoms and medication use reported in the eDiary.

The rhinitis DSS and the rhinoconjunctivitis DSS according to the EAACI task force **(Pfaar et al. 2014)** are the sum of each individual DSS divided by the number of symptoms.

The rhinoconjunctivitis DMS according to EAACI task force **(Pfaar et al. 2014)** is a stepwise scoring method as shown in **Table 9**.

Table 9 Stepwise scoring of rhinitis/conjunctivitis medication use according to the EAACI task force

Step	Rhinitis/Conjunctivitis Medication	Score
1	oral and/or topical (eyes or nose) nonsedative H1 antihistamines	1
2	intranasal corticosteroids	2
3	oral corticosteroids	3

The CSMS according to the EAACI task force is applied to the data in the current trial even though rhinitis/conjunctivitis rescue mediation is not taken in a stepwise manner and even though oral corticosteroids are not supplied as rhinitis/rhinoconjunctivitis rescue medication and are thus not assessed in the eDiary in MT-11. The CSMS scoring applied in the current trial is shown in **Table 10**.

The average rhinoconjunctivitis CSMS and average rhinitis CSMS is for each subject and each visit (V2, V5, V6, V7, V8, V9, V10, V11) calculated as the average of non-missing records during the 14 days of eDiary assessment.

Table 10 Construction of rhinitis/rhinoconjunctivitis CSMS in MT-11

	Rhinitis score	Rhinoconjunctivitis score
Symptom Scores		
Rhinitis symptoms		
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		
Red/itchy eyes		0-3
Watery eyes		0-3
Daily symptom score (DSS)[1]	0-3	0-3
Medication score		
Step 1: Azelastine eye drops		1
Step 1: Desloratadine tablets or Desloratadine oral solution	1	1
Step 2: Mometasone furoate nasal spray	2	2
Daily medication score (DMS)[2]	0-2	0-2
Combined symptom and medication score (CSMS), DSS (0-3) + DMS (0-2)	0-5	0-5

[1] The DSS is calculated as the sum of the individual symptom scores divided by the number of symptoms and ranges from 0-3.

[2] The DMS is the score of highest medication step used. No medication use means a score of 0. The DMS range from 0-2.

7.1.2.4 Average daily asthma VAS and average daily rhinoconjunctivitis VAS

The average daily asthma VAS and the average daily rhinoconjunctivitis VAS is for each subject and each visit (V2, V5, V6, V7, V8, V9, V10, V11) calculated as the average of non-missing records during the 14 days of eDiary assessment.

7.1.2.5 The proportion of days with nocturnal awakening

Nocturnal awakenings due to asthma requiring SABA is recorded daily during the periods of eDiary recording.

The proportion of days with nocturnal awakenings due to asthma requiring SABA rescue medication is for each subject and each visit (V2 (baseline), 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 (25-29 months)) calculated as the number of events divided by the number of Diary records.

7.1.2.6 The proportion of days with SABA use

SABA use is recorded daily during the periods of eDiary recording.

The proportion of days with SABA use is for each subject and each visit (V2 (baseline), 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 (25-29 months)) calculated as the number of events divided by the number of Diary records.

7.1.2.7 The average asthma DSS

Asthma symptoms are recorded daily during the periods with eDiary recording.

The asthma symptoms consist of 4 asthma symptoms (cough, wheezing, chest tightness and shortness of breath) which are scored from 0 to 3 as follows:

0 = no symptoms

1 = mild symptoms

2 = moderate symptoms

3 = severe symptoms

The asthma DSS is the sum of all 4 individual asthma symptom scores and ranges from 0 to 12.

The average asthma DSS is for each subject and each visit (V2, V5, V6, V7, V8, V9, V10, V11) calculated as the average of non-missing records during the 14 days of eDiary assessment.

7.1.2.8 Daily SABA usage

SABA usage is recorded daily during the periods with eDiary recording.

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

The recommended daily dose for children (5-11 years) is 200 µg. The recommended daily dose for adolescent (12-17 years) is 800 µg.

The number of daily recommended SABA doses used is calculated each day as the dose used divided by the recommended daily dose.

The average daily number of (recommended) doses of SABA is for each subject and each visit (V2, V5, V6, V7, V8, V9, V10, V11) is calculated as the average of non-missing records during the 14 days of eDiary assessment.

[redacted]

7.1.3 Pharmacodynamics endpoints

Changes from baseline in log_{10} transformed specific IgE, IgE-BF and log_{10} transformed IgG_4 against *D. pteronyssinus* and *D. farinae* measured at V7 and V11.

7.1.4 Imputation of dates

When establishing how many historical asthma exacerbations a subject has within a given period, a partial end date is imputed to be as late as possible but no later than the date of informed consent.

When calculating the duration of medical history of asthma or rhinitis, a partial start date is imputed to be as early as possible.

For the purpose of defining which adverse events are treatment emergent or calculating a duration, any partial start date is imputed of the adverse event is imputed to be as early as possible, if the start date could possibly be the date of first dose of IMP given the partial date and the end date if any, it is instead imputed to be the date of first dose.

Any partial date of last dose is imputed to as late as possible but no later than the date of last contact. Missing dates of last dose are imputed as the date of last contact.

To be able to calculate the age at the start of a given diary period, the partial date of birth of each subject is imputed to be as late as possible taking the age at screening, the date of screening, the age recorded for pulmonary function tests at baseline, and the corresponding date into consideration.

7.2 Appendix 2: Further details pertaining to statistical analyses

7.2.1 Primary endpoint analysis

If the NB regression model fails to converge, a Poisson regression model with an overdispersion parameter will be applied instead 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.

The 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.

7.2.2 Multiple imputation

Imputation will be done using the method of unrestricted random sampling with replacement (seed=686), and 500 multiple imputed datasets will be created. For subjects discontinuing treatment in period 4 (both treatment and placebo arms), the number of clinically relevant asthma exacerbations for the remaining time of period 4 (from the treatment discontinuation to end of period 4) will be calculated based on the imputed rate (imputed events by imputed exposure time) from the completers in the placebo group. For a subject who discontinues treatment, the number of events up until discontinuation is calculated. For the rest of the observation period, the number of events is calculated from the imputed rate as follows:

Imputed events = $\frac{imputed\ number\ of\ exents}{imputed\ exposure\ time} \cdot (time_{planned\ exposure} - time_{exposure})$

where:

$time_{planned\ exposure} = planned\ end\ date - actual\ start\ date$

$planned\ end\ date = 30th\ of\ April\ 2020, 2021, 2022\ depending\ on\ cohort$

$time_{exposure} = the\ individual\ exposure\ time\ for\ the\ subject$

Then the total number of events is calculated as the sum of the events prior to discontinuation of treatment and the number of imputed events. The total exposure time is planned exposure time.

In the sensitivity analysis (sensitivity analysis 2 in Error! Reference source not found.), each of the 500 multiple imputed datasets will then be analysed using the negative binomial regression model specified for the primary efficacy analysis. The resulting estimates and standard errors for the multiple data sets are finally pooled to 1 single estimate and associated standard error using the method of Rubin **(Rubin D. B 1987)**. If a substantial number of the 500 analyses fails to converge (>1%), a Poisson regression model with an overdispersion parameter will additionally be applied in the analysis of the 500 imputed datasets using the strategy described in section **7.2.1**. If 1% or less of the 500 analyses fails to converge, additional imputed datasets will be created and analysed until in total 500 analyses converge.

7.2.3 Secondary endpoints analysis

In the analysis of the first and second key secondary endpoints, the marginal model will be estimated using a GEE- approach. The treatment effect on the logit scale is an average treatment effect across all visits and will be estimated as a contrast of parameters in the marginal model. The corresponding odds ratio for proportions of days with nocturnal awakening requiring SABA of active treatment relative to placebo will be presented together with the coherent p-value and 95% confidence limit. If convergence issues are encountered for the marginal logistic regression model, other working covariance structures will be considered (e.g. an independence structure (IND)).

In the analysis of the third key secondary endpoint and the additional secondary endpoints, the treatment effect is the average of the treatment effect across all visits and will be estimated as a contrast of the parameter estimates in the MMRM model. The corresponding p-value will be calculated by means of a t-test with Kenward-Roger degrees of freedom approximation. LSMeans by treatment group will be displayed. In addition, the relative difference will be reported together with 95% confidence limits calculated based on Fieller's theorem for non-transformed data. In models where data is square-root transformed, the absolute difference will be calculated based on a second-order Taylor series expansion.

If an MMRM model with an unstructured covariance matrix fails to converge, unstructured correlations (UNR), Toeplitz (Toep) or compound symmetry (CS) will be used instead, prioritized in the listed order. If the MMRM model still fails to converge, a reduced model is used to estimate starting values for the type of covariance structure mentioned above. If the use of starting values will still not lead to convergence, the model is reduced by eliminating effects backwards (i.e. first region then age group).

If a Cox proportional hazards regression models fails to converge in the analysis of time to events, e.g. due to few events, then Firth's penalized maximum likelihood estimation is used.

7.2.4 Additional secondary endpoints analyses

In MMRM analyses of square root transformed endpoints, the resulting means, difference and corresponding standard errors are back-transformed to the original scale using a second-order Taylor series expansion.

Let mean_p, mean_a, var_p, and var_a be the resulting means and variances for placebo and active treatment and cov be the covariance. Then the back-transformed means are given by

- mean_placebo=(mean_p)^2
- mean_active=(mean_a)^2
- mean_difference=(mean_a)^2-(mean_p)^2,

and the back-transformed standard errors are given by

- stderr_difference=sqrt(4*act**2*var_act + 4*pla**2*var_pla + var_act**2 + var_pla**2 - 2*(4*act*pla*cov_ACT + var_act*var_pla));

7.2.5 SAS code for the analysis

SAS Code for the Primary Efficacy Endpoint

The term region in the code below refers to the definition of region in section **4.1.1**.

SAS Code

proc genmod data=a;
class treat agegroup region;
model aval = treat agegroup region/ link=log dist=negbin offset=log_time;
lsmeans treat/ cl means exp diff ;
run;

7.3 Appendix 3: Preferred terms

7.3.1 Asthma

PTs to identify asthma exacerbations, asthma related hospitalisations, worsening of asthma requiring medication and asthma related symptoms leading to IMP discontinuation have been selected by using the following criteria (MedDRA version 20.1):

Standardised MedDRA Query (SMQ) Asthma/bronchospasm

PTs for identification of asthma
Aspirin-exacerbated respiratory disease
Asthma
Asthma exercise induced
Asthma late onset
Asthma-chronic obstructive pulmonary disease overlap syndrome
Asthmatic crisis
Bronchial hyperreactivity
Bronchospasm
Infantile asthma
Occupational asthma
Reactive airways dysfunction syndrome
Severe asthma with fungal sensitisation
Status asthmaticus
Airway remodelling
Allergic bronchitis
Allergic cough
Allergic eosinophilia
Allergic respiratory disease
Allergic respiratory symptom
Alveolitis allergic
Bronchial obstruction
Bronchospasm paradoxical
Charcot-Leyden crystals
Forced expiratory flow decreased
Forced expiratory volume decreased

PTs for identification of asthma
Fractional exhaled nitric oxide abnormal
Fractional exhaled nitric oxide increased
Functional residual capacity increased
Hyperventilation
Hypocapnia
Hypoxia
Lung hyperinflation
Lung hypoinflation
Obstructive airways disorder
PCO2 decreased
Peak expiratory flow rate abnormal
Peak expiratory flow rate decreased
PO2 decreased
Prolonged expiration
Pulmonary sensitisation
Respiratory alkalosis
Reversible airways obstruction
Tachypnoea
Wheezing

7.3.2 Local application site TEAEs

PTs related to local application site TEAEs have been selected by using the following criteria (MedDRA version 20.1):

High-Level Group Terms (HLGTs)
Oral soft tissue conditions
Salivary gland conditions
Tongue conditions
High-Level Terms (HLTs)
Gingival disorders NEC
Gingival discolourations
Gingival haemorrhages
Gingival pains

Gingival infections
Standardised MedDRA Query (SMQ)
Oropharyngeal allergic conditions
Additional PTs
Laryngeal discomfort
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Oropharyngeal spasm
Upper airway obstruction
Suffocation feeling
Tracheal oedema
Laryngeal obstruction
Oropharyngeal discomfort
Sensation of foreign body
Throat irritation
Throat tightness
Dysphonia
Dysphagia
Oropharyngeal pain
Hypoaesthesia oral
Oral discomfort
Aphonia
Larynx irritation
Palatal oedema
Paraesthesia oral
Pharyngeal hypoaesthesia
Pharyngeal oedema
Pharyngeal paraesthesia

7.3.3 Solicited adverse events

PTs related to solicited TEAEs are listed below

PTs for identification of solicited TEAEs
Dysgeusia
Taste disorder
Mouth ulceration
Enlarged uvula
Oedema uvula
Palatal swelling
Palatal oedema
Mouth swelling
Oedema mouth
Oral pruritus
Ear pruritus
Lip swelling
Lip oedema
Swollen tongue
Tongue oedema
Glossodynia
Tongue ulceration
Throat irritation
Pharyngeal oedema
Pharyngeal swelling
Abdominal pain upper
Abdominal pain
Nausea
Vomiting
Diarrhoea

7.4 Appendix 4: PP data set

Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
[redacted]	Y	Y	Y	Y	Y
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	Y	Y			Y

Page 1 of 16

Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
[redacted]	Y	Y			Y
[redacted]	Y	Y		N	N
[redacted]	Y	Y			Y
[redacted]	Y	Y		N	N
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Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
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Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
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Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
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Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
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Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
[redacted]	Y	Y			Y
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Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
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Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
[redacted]	Y	Y			Y
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	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y		Y	Y
	N	N			N
	Y	Y			Y
	Y	N	Y		N
	N	N			N
	N	Y			N
	Y	N			N
	Y	Y			Y

Unique Subject Identifier	Treatment compliance (>= 80%)	Efficacy compliance (>=6 mth)	Included in PP based on Inclusion/Exclusion criteria met	Subjects included in PP based on Disallowed medications	Subject included in PP
[redacted]	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	N	Y			N
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y			Y
	Y	Y	N		N
	Y	Y			Y

Role	Initials	Date	Signature
Clinical Trial manager	[redacted]	[redacted]	[redacted]
Medical Writer	[redacted]		
Trial Statistician	[redacted]		

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Approval Task	[redacted] 11-Aug-2022 08:11:17 GMT+0000

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