STATISTICAL ANALYSIS PLAN

PROTOCOL: TH005

A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED, MULTI-CENTRE FIELD STUDY TO ASSESS THE EFFICACY AND SAFETY OF HDM-SPIRE IN SUBJECTS WITH A HISTORY OF HOUSE DUST MITE-INDUCED RHINOCONJUNCTIVITIS

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VERSION NUMBER AND DATE: V2.0, 24MAR2017

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 24MAR2017) for Protocol TH005.

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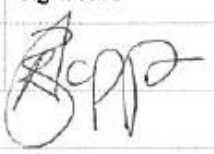
Author:	Roland Klopper		DDMMMYYYY 27MAR2017
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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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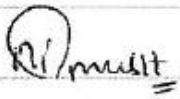
Approved By:	Alec Mushunje		DDMMMYYYY 27-MAR-2017
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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
V1.0	28SEP2016	Roland Klopper	Not applicable. First version.
V2.0	24MAR2017	Roland Klopper	Added subgroup summaries to Disposition and Demographic sections Removed baseline-by-treatment interaction from efficacy model

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol TH005. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This Statistical Analysis Plan (SAP) is based on Protocol version 4.0 dated 01 April 2015.

The rules, conventions and output presentations used for the Data Safety Monitoring Committee (DSMC) are set out in a separate DSMC SAP.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the efficacy of House Dust Mite (HDM) Synthetic Peptide Immuno-Regulatory Epitopes (HDM-SPIRE) in the reduction of symptoms and the use of allergy rescue medication associated with HDM allergy in subjects with clinically relevant symptoms.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the safety and tolerability of HDM-SPIRE
- To evaluate the effect of HDM-SPIRE on rhinoconjunctivitis-specific quality of life using the rhinoconjunctivitis quality of life questionnaire (RQLQ)
- To evaluate the effect of HDM-SPIRE on sleep quality using the Pittsburgh Sleep Quality Index (PSQI)

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate the effect of HDM-SPIRE on rhinoconjunctivitis symptom scores measured using a visual analogue scale (VAS) during the baseline allergy evaluation (BAE) period and each post-administration collection (PAC) period
- To evaluate the effect on mean combined score (CS) in the HDM-SPIRE treatment groups compared with placebo during PAC1 and PAC2 periods

- To evaluate the effect on mean total rhinoconjunctivitis symptom score (TRSS) in the HDM-SPIRE treatment groups compared with placebo during PAC1 and PAC2 periods
- To evaluate the effect on mean rescue medication score (RMS) in the HDM-SPIRE treatment groups compared with placebo during PAC1 and PAC2 periods
- To evaluate the effect on mean component scores of the TRSS (nasal and non-nasal) in the HDM-SPIRE treatment groups compared with placebo during the PAC1 and PAC2 periods
- To evaluate the effect on overall RQLQ score in the HDM-SPIRE treatment groups compared with placebo at the end of the PAC1 and PAC2 periods
- To evaluate the effect on sleep quality measured using the Pittsburgh Sleep Quality Index (PSQI) for the HDM-SPIRE treatment groups compared with placebo at the end of the PAC1 and PAC2 periods
- To evaluate the effect on asthma control for asthmatic subjects at the end of the BAE, PAC1, PAC2 and PAC3 periods
- To evaluate subject's home environment and exposure to allergens

2.4. SAFETY OBJECTIVES

The safety and tolerability of HDM-SPIRE is to be assessed by the recording of:

- Adverse Events (AEs)
- Physical examination
- Vital signs
- Laboratory values (haematology, serum biochemistry, urine tests, immunology tests)
- Forced expiratory volume in 1 second (FEV_1)
- Local reactions at the injection site

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a randomised, double-blind, placebo-controlled, parallel group, multi-centre field assessment of three dose regimens of HDM-SPIRE administered at 4 weekly intervals for 28 weeks.

A total of approximately 660 subjects are to be randomised into the study, with approximately 165 subjects in each of the three HDM-SPIRE treatment groups and 165 in the placebo group.

Subjects are to attend the investigative centre for screening. Subjects meeting the inclusion/exclusion criteria are to be randomised to either one of the following three active treatment groups or the placebo group in a 1:1:1:1 ratio:

- 8 x placebo, 4 weeks apart (placebo)
- 4 x 12 nmol HDM-SPIRE followed by 4 x placebo, 4 weeks apart
- 4 x 20 nmol HDM-SPIRE followed by 4 x placebo, 4 weeks apart
- 8 x 12 nmol HDM-SPIRE 4 weeks apart

Following randomisation a total of 8 doses of HDM-SPIRE or placebo are to be administered at the investigative centre, one dose every 4 weeks (±2 days), for a total duration of 28 weeks as shown in the Table 1 below:

Table 1: Dosing Schedule

Visit	3A	3B	3C	3D	3E	3F	3G	3H
Week (± 2 days)	0	4	8	12	16	20	24	28
Treatment Group								
Placebo	P	P	P	P	P	P	P	P
HDM-SPIRE 4 x 12 nmol	X	X	X	X	P	P	P	P
HDM-SPIRE 4 x 20 nmol	X	X	X	X	P	P	P	P
HDM-SPIRE 8 x 12 nmol	X	X	X	X	X	X	X	X
X = HDM-SPIRE doses, P = Placebo doses.								

Subjects are to complete an electronic diary (eDiary) during the following four periods for efficacy evaluation:

- Baseline allergy evaluation (BAE)

Subjects are to record Baseline Rhinoconjunctivitis symptom scores (RSS) and rescue medication score (RMS) in an eDiary during a period of approximately 3 weeks prior to randomisation.

The RSS and RMS assigned to the BAE period for a subject is to be taken as all scores entered on the subject's eDiary dated from the date of Visit 2A up to and including the date of Visit 2B.

- Post-administration collection period 1 (PAC1)

Subjects are to record RSS and RMS during weeks 18 to 20 after first administration of study medication.

The RSS and RMS assigned to the PAC1 period for a subject is to be taken as all scores entered on the subject's eDiary dated from the date of Visit 4A up to the date of Visit 4C - 1.

- Post- administration collection period 2 (PAC2)

Subjects are to record RSS and RMS during weeks 37 to 39 after first administration of study medication.

The RSS and RMS assigned to the PAC2 period for a subject is to be taken as all scores entered on the subject's eDiary dated from the date of Visit 4C up to the date of Visit 4E - 1.

- Post-administration collection period 3 (PAC3)

Subjects are to record RSS and RMS during weeks 50 to 52 after first administration of study medication.

The RSS and RMS assigned to the PAC3 period for a subject is to be taken as all scores entered on the subject's eDiary dated from the date of Visit 4E up to and including the date of the last subject visit date.

The duration (days) of the BAE, PAC1, PAC2 and PAC3 periods are defined by the Visit dates specified above. At approximately 52 weeks post first administration of study medication, subjects are to undergo a final safety assessment. The total duration of the study for each subject will be approximately 62 weeks.

3.2. SAMPLE SIZE CALCULATION

The study is to recruit approximately 660 subjects (approximately 165 per treatment group). Based on the data from observational study TH003, if a mean CS of 1.6 is observed for the placebo group, and a mean CS of 1.28 for the active group, the expected treatment difference of 0.32 is to be a 20% improvement from placebo. The statistical model is to include the baseline CS as a covariate, taking this into account a standard deviation of 0.986 is assumed, so that a sample of 150 patients is to have 80% power to detect a statistically significant difference in treatment.

3.3. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6.1 Schedule of Assessments of the Protocol.

4. PLANNED ANALYSES

The following analyses are to be performed for this study:

- Analyses for DSMC meetings
- Final analysis

4.1. DATA SAFETY MONITORING COMMITTEE (DSMC)

A Data Safety Monitoring Committee (DSMC) SAP, describing the methodology and presentation of results and access to results is to be provided by Quintiles Biostatistics as a separate document.

4.2. FINAL ANALYSIS

The final, planned analysis identified in this SAP is to be performed by Quintiles Biostatistics following:

- Sponsor authorization of this SAP and output shells
- Sponsor authorization of analysis populations
- Database lock (100% cleaned data with no outstanding data queries)
- Routine study unblinding

5. ANALYSIS POPULATIONS

Prior to the locking of the database, agreement of subjects' assignment to each of the analysis populations and identification of major protocol deviations are to be determined in collaboration with Circassia at a blind data review (BDR) meeting. The authorisation of analysis sets is required prior to the final locking of the database and routine study unblinding.

The analysis populations below are described in detail in the latest version of the BDR plan, including the criteria to be used in defining each of these analysis populations.

5.1. ALL SUBJECTS ENROLLED [ENR] POPULATION

The Enrolled [ENR] population is to consist of all subjects that signed informed consent.

5.2. RANDOMISED [RND] POPULATION

The Randomised (RND) population is to consist of all subjects in the ENR population who passed both the Screening assessments and the BAE period and are subsequently randomised to study medication.

5.3. INTENT TO TREAT [ITT] POPULATION

The Intent to Treat (ITT) population is to consist of all subjects who are randomised, who have received at least one dose of study medication. Subjects are to be reported by the treatment they were randomised to. The ITT is the primary population for the study and all the primary and secondary efficacy analyses are to be based on the ITT population.

5.4. SAFETY [SAF] POPULATION

The Safety (SAF) population is to consist of all subjects that received at least one dose of study medication (HDM-SPIRE or placebo) and have at least one post-baseline safety assessment available. Subjects are to be reported by the treatment they actually received. The Safety population is to be used for all of the safety endpoints.

5.5. PER PROTOCOL [PP] POPULATION

The Per Protocol (PP) population is to consist of all subjects in the ITT population who have no major protocol deviations likely to affect the integrity of the study and who completed all study visits. Allocation of subjects to the PP population and all protocol deviations are to be fully documented in the BDR report. The PP population is to be evaluated for the primary variable to confirm results from the ITT population. Subjects are to be reported by the treatment they were randomised to.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day is to be calculated from the reference start date, and is to be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first administration of study medication, (Day 1 is the day of the first administration of study medication), and is to appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations are to appear partial or missing in the listings.

6.2. BASELINE

For all safety variables, unless otherwise specified, Baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments or retests). In the case where the last non-missing measurement and the reference start date coincide, that measurement is to be considered pre-baseline, but AEs and medications commencing on the reference start date are to be considered post-baseline.

For all efficacy variables Baseline is defined as the measurement taken during the BAE period prior to reference start date.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit is to be presented. Unscheduled measurements are not to be included in by-visit summaries, but may contribute to the Baseline value.

In the case of a retest at any post Baseline visit (same visit number assigned but a different date and/or time of assessment), the first measurement (original value) for that visit is to be used for by-visit summaries.

Listings are to include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

Windows for PAC1, PAC2 and PAC3 are to the applied based on scheduled visit dates as defined in Section 3.1 General Description.

For inclusion in the PP population a window is to be defined for the PAC3 period only. The window start date is defined as the planned Visit 4E date ± 10 days, relative to the Visit 3A date (Baseline), that is, 50 weeks after the Baseline date ± 10 days. Similarly, the window end date is defined as the planned Visit 4F date ± 10 days, that is, 52 weeks after the Baseline date ± 10 days.

Any subjects for whom being out of window doesn't affect whether or not their symptoms might have been confounded with seasonal allergies are also to be included. For this latter category, a review is to be done manually by Circassia.

Review of the PAC3 windows and decisions regarding inclusion/exclusion form the PP population is to be documented in the BDR meeting minutes.

6.5. STATISTICAL TESTS

The default significance level is to be 5%; confidence intervals are to be 95% and all tests are to be two-sided, unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

For quantitative measurements:

- Change from Baseline is to be calculated as
    - Test Value at Visit X – Baseline Value

- Percentage change from Baseline is to be calculated as
    - [(Test Value at Visit X – Baseline Value) / Baseline Value] x 100
- Descriptive statistics are to include n, mean, standard deviation (SD), median, minimum and maximum

For qualitative measurements (e.g. Gender):

- Summaries are to include frequency (n) and percentage (%) of subjects. Percentages are to be calculated as either
    - The number of subjects within a category relative to the total number of subjects in the relevant analysis population with data available. In this case a missing category is to be added to indicate the number of subjects with no data and the missing counts are not to be included in the denominator for the percentage calculation, or
    - The number of subjects in a category relative to the total number of subjects in the relevant analysis population

The applicable method of percentage calculation is indicated in each relevant analysis section.

6.7. SOFTWARE VERSION

All analyses are to be conducted using SAS Version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN EFFICACY ANALYSES

The following covariates and factors are to be used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Study period
  - PAC1
  - PAC2
  - PAC3
- Pooled region as finalised prior to the analysis during the BDR meeting
  - Pooled Region 01
  - Pooled Region 02
  - Pooled Region 03
  - Pooled Region 04
  - Pooled Region 05
  - Pooled Region 06
  - Pooled Region 07
  - Pooled Region 08
- Gender as captured on the Demographics eCRF (DEM)
  - Male
  - Female
- Asthma status as captured on the Asthma Diagnosis eCRF (ASTHMASCR)
  - No asthma
  - Controlled
  - Partly/Uncontrolled
- Baseline score
  - Represents the Baseline value of the relevant score being analysed from the BAE period

7.2. MULTI-CENTRE STUDIES

This study is to be conducted by multiple investigators at multiple centres internationally. Randomisation to treatment groups is not stratified by country/centre.

If a region has less than 5 subjects, pooling with other centre(s) is to be performed based on geographical region of the centres, providing the combination of data from small centres within a geographic region does not create a disproportionately large combined region. Distribution of subjects across pooled regions is to be assessed and pooling criteria finalised during the BDR meeting.

7.3. MISSING DATA

Missing safety data is not to be imputed. Partial start/stop dates for concomitant medications and AEs are not to be imputed. Treatment emergence of AEs and study period of medication use (prior or concomitant) is to be assigned based on available information as described in Appendix 2: Partial Date Conventions.

Daily derived efficacy scores (such as TRSS and CS) may be missing and will not be imputed as explained in Section 15.1.1 Primary Efficacy Variable & Derivation and Section 15.2.1 Secondary Efficacy Variables & Derivations.

Means of all derived daily efficacy scores during BAE, PAC1, PAC2 and PAC3 are to be calculated based on all days with non-missing scores within the respective periods defined in Section 3.1 General Description.

The primary efficacy analysis is to be performed using all available data on the assumption that the probability of missing observations is independent of unobserved measurements (missing at random). Therefore the missing values are not to be imputed for the primary analysis.

A Pattern-mixture model based on control-based imputation is to be utilised as the sensitivity analysis of the primary efficacy variable as described in Section 15.1.4 Sensitivity Analysis of Primary Efficacy Variable.

7.4. MULTIPLE COMPARISONS/MULTIPLICITY

For the primary efficacy analysis a hierarchical (step-down) approach is to be used to control the overall Type I error rate at 5%.

For declaring statistical significance, a step-down approach (first 4 x 12 nmol versus placebo, then 4 x 20 nmol versus placebo and then 8 x 12 nmol versus placebo) is to be used to control the overall Type I error at 0.05.

Thus:

- Step 1: If 4 x 12 nmol HDM-SPIRE versus placebo is significantly different at the 0.05 significance level, move to Step 2. If there is no statistical significance, no further statistical significance is to be declared

- Step 2: If 4 x 20 nmol HDM-SPIRE versus placebo is significantly different at the 0.05 significance level, move to Step 3. If there is no statistical significance, no further statistical significance is to be declared

- Step 3: If 8 x 12 nmol HDM-SPIRE versus placebo is significantly different at the 0.05 significance level, declare statistical significance.

Statistical significance is declared for each step individually if $p<0.05$ and overall statistical significance is to be declared if Step 1, Step 2 and Step 3 has $p<0.05$.

7.5. EXAMINATION OF SUBGROUPS

A treatment-by-pooled region interaction is to be added to the primary efficacy analysis as a supportive analysis as described in Section 15.1.5.2 Treatment-by-pooled region Interaction. In the event that the treatment-by-pooled region interaction term is observed to be statistically significant ($p<0.10$), the primary efficacy analysis as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable is to be analysed in subgroups of pooled region. Additionally, Baseline and Demographic Characteristics are to be summarised in subgroups of pooled region (see Section 10 Demographic and Baseline Characteristics).

8. OUTPUT PRESENTATIONS

The templates provided with this SAP describe the planned presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Quintiles Biostatistics.

9. DISPOSITION AND WITHDRAWALS

Disposition and withdrawals are to be summarised for the ENR population.

Additionally, disposition and withdrawal summaries are to be presented for the following subgroups:

- Asthma status (Absent/Present/Missing) as captured on the Randomization eCRF (RAND)
    - Where Controlled and Partly/Uncontrolled are categorised as Present and
    - No Asthma is categorised as Absent
- TRSS categorised as TRSS <16, TRSS ≥ 16 or Missing as captured on the Randomization eCRF (RAND)

The frequency (n) and percentage (%) of the following disposition and withdrawal categories are to be reported:

- Subjects screened
- Screen failures, defined as subjects where the Study Entry eCRF completed at the Screening visit indicates screening was not passed

- Subjects that initially failed Screening may have been re-screened for eligibility following modifications to eligibility criteria in protocol amendments. Re-screened subjects are to be provided with a new Screening number and a link to the previous Screening number is to be captured on the Rescreening Status eCRF. Re-screened subjects that pass Screening are not to be counted as screen failures under their previous Screening numbers and are only to be accounted for once using the newly assigned Screening number and status.

- BAE failures, defined as subjects where the Study Entry eCRF (SENTRY) completed at the end of the BAE period indicates that the BAE period was not passed

- Randomised subjects, as indicated on the Randomisation eCRF (RAND). Subjects are to be eligible for randomisation if they passed both Screening as well as BAE.

- Completed study medication, early withdrawal from treatment period as well as primary reason for termination of study medication as entered on the End of Treatment eCRF (EOT)

    - Completed study medication is defined as receiving 8 doses of study medication from Visit 3A to Visit 3H

- Completed the study, early withdrawal from the study as well as primary reason for early withdrawal from the study as entered on the End of Study eCRF (EOS)

Completed the study is defined as completing the Follow-up Period (Visit 5) without prior early withdrawal from the study as indicated on the End of Study eCRF (EOS), regardless of completion of study medication as indicated on the End of Treatment eCRF (EOT). The frequency (n) and percentage (%) of subjects assigned to each analysis population is to be provided for the Randomized, ITT, PP and SAF populations, as well the reasons for exclusion from each population.

Percentages are to be calculated relative to the total number of subjects in the analysis population.

The following listings are planned for presentation:

- Subjects screening status (ENR population)

    - Includes eligibility criteria and inclusion/exclusion criteria exceptions

- Subject disposition (RND population)

- Analysis population assignment (ENR population)

- Major protocol deviations (RND population)

10. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic data and Baseline characteristics are to be presented for the ITT population.

Additionally, demographic and baseline summaries are to be presented for the following subgroups:

- Asthma status (Absent/Present/Missing) as captured on the Randomization eCRF (RAND)

  - Where Controlled and Partly/Uncontrolled are categorised as Present and
  - No Asthma is categorised as Absent

- TRSS categorised as TRSS <16, TRSS ≥ 16 or Missing as captured on the Randomization eCRF (RAND)
- Pooled region 01 to pooled region 08 as determined at the BDR meeting and documented in the BDR report

No statistical testing is to be performed for demographic or other Baseline characteristics.

Continuous demographic and Baseline characteristic variables (e.g. Age) are to be summarised using descriptive statistics. Categorical variables (e.g. Gender) are to be summarised by frequency (n) and percentage (%). Percentages are to be calculated relative to the total number of subjects in the analysis population with data available.

The following demographic and Baseline characteristics are to be reported for this study:

- Age (years) relative to date of informed consent is to be calculated using the following SAS code
  - Age = int((intck('month' , <date of birth> , <date of informed consent> - (day(<date of informed consent>) < day(date of birth>))) / 12)
  - In the event that the date of birth is incomplete, the age at informed consent is to be imputed using the age as captured on the Randomisation eCRF
- Age group
  - 18 to 49
  - 50 to 70
- Gender from the System Screening eCRF (SCR)
  - Male
  - Female
- Race from the Demographics eCRF (DEM)
  - White
  - Black or African American
  - Asian
  - American Indian or Alaska Native
  - Native Hawaiian or other Pacific Islander
  - Not Collected
  - Other
- Ethnicity from the Demographics eCRF (DEM)
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported

  - Unknown

- Height (cm) from the Vital Signs eCRF (VS) at the Screening visit
- Weight (kg) from the Vital Signs eCRF (VS) at the Screening visit
- Body mass index (BMI) (kg/m^2)
- History of asthma from the Asthma Diagnosis eCRF (ASTHMASCR)
  - Yes
  - No
- Asthma status from the Asthma Diagnosis eCRF (ASTHMASCR)
  - No Asthma
  - Controlled
  - Partly/Uncontrolled
- Asthma relationship to exposure to allergens from the Asthma Diagnosis eCRF (ASTHMASCR)
  - No Relationship
  - To HDM
  - To Other Allergens

Demographic and Baseline characteristics are to be listed.

10.1. DERIVATIONS

Height is to be converted from inches (in) to cm as follows:

- Height (cm) = Height (in) x 2.54
- Weight is to be converted from lbs to kgs as follows:
- Weight (kg) = Weight (lb) x 0.453592

BMI is to be calculated as:

- BMI (kg/m^2) = Weight (kg) / [Height (cm) ÷ 100)]^2

11. MEDICAL HISTORY

Medical History conditions are to be presented for the ITT population.

11.1. ALLERGY MEDICAL HISTORY

Allergy medical history includes all medical history conditions reported on the Allergy Medical History eCRF (AMHX).

The frequency (n) and percentage (%) of the following allergies are to be presented:

- House dust mite
- Cat
- Animal dander (other than cat)
- Cockroach
- Other additional allergies indigenous to a subject's area, under the following categories
    - Other dust mites
    - Mould
    - Grass
    - Weed
    - Tree
    - Animal dander
    - Other

Allergies specified as 'Other' category for 'Other additional allergies indigenous to the subject's geographic area' are only to be listed.

Percentages are to be calculated relative to the total number of subjects in the analysis population.

11.2. MEDICAL HISTORY OTHER THAN ASTHMA AND RHINOCONJUNCTIVITIS

Medical history other than asthma and Rhinoconjunctivitis includes all conditions captured on the Medical History – Other than Asthma and Rhinoconjunctivitis eCRF (MHX).

Medical history other than asthma and Rhinoconjunctivitis is to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0

The frequency (n) and percentage (%) of conditions is to be presented by System Organ Class (SOC) and Preferred Term (PT). The summary is to be sorted by descending total frequency for each SOC, and within each SOC by the descending total frequency per PT.

Percentages are to be calculated relative to the total number of subjects in the analysis population.

11.3. SMOKING HISTORY

The frequency (n) and (%) of subjects within the following categories are to be presented for the ITT population as captured on the Smoking History eCRF (SMOK).

- Current smokers
- Former smokers
- Have never smoked

Percentages are to be calculated relative to the total number of subjects in the analysis population with data available.

Descriptive statistics are to be presented for the following categories captured on the Smoking History eCRF (SMOK) for current smokers and former smokers:

- Average number of cigarettes per day
- Average number of cigars per day
- Average number of pipes per day
- Number of years smoked
- Number of pack years

12. MEDICATIONS

Medications are to be presented for the ITT population and coded using the World Health Organization-Drug Dictionary (WHO-DD) Version 01MAR2016.

Prior (P) and concomitant (C) medications are to be presented by generic name for Allergy Medications and Other Medications respectively.

- Allergy medications are defined as medications where the Concomitant Medications eCRF (CMDT) question, 'Is the medication used for HDM allergy?' *or* 'Is the medication used for other allergy?' are indicated as 'Yes'
- Other medications are defined as medications where the Concomitant Medications eCRF (CMDT) question, 'Is the medication used for HDM allergy?' *and* 'Is the medication used for other allergy?' are indicated as 'No'

The summaries are to be sorted by descending total frequency per generic name.

Prior and concomitant medications are defined as follows:

- 'Prior' medications are medications which started and ended prior to the first administration of study medication.

- 'Concomitant' medications are medications which:

  - Started on or after the first administration of study medication and continues during the study and/or up to the end of study, OR
  - started prior to first administration of study medication and ended on or after the date of first administration of study medication or were ongoing AND
  - are not part of the medications from the rescue medication plan as specified in protocol Appendix 3: Rescue Medication Package Description and Rescue Medication Plan

See Appendix 2 for handling of partial dates for medications.

Separate by-subject listings for allergy medications and other medications are to be presented.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days is to be presented for the ITT population.

Exposure to study medication is to be summarised by descriptive statistics and treatment group.

The date of first study medication administration is to be taken from the Study Medication Administration eCRF (SDA1). The date of last study medication administration Is to be taken as the last available administration date on the Study Medication Administration eCRF (SDA1/2).

Additionally exposure to study medication is to be summarised as the frequency (n) and percentage (%) of subjects receiving study medication at each Study Medication Administration (Visits 3A-3H) visit. Subjects are considered to have received study medication at each visit if the response to the question 'Was the study medication administered in accordance with the protocol?' is indicated as 'Yes' on the Study Medication Administration eCRF (SDA1/2).

13.1. DERIVATIONS

Duration of exposure (days) = (Date of last study medication administration – Date of first study medication administration) + 1.

14. STUDY MEDICATION COMPLIANCE

Compliance to study medication is to be presented for the ITT population.

Compliance to study medication is to be summarised by descriptive statistics and treatment group for

- Compliance over first 4 doses (Visit 3A to Visit 3D)
- Compliance over last 4 doses (Visit 3E to Visit 3H)
- Overall compliance (Visit 3A to Visit 3H)

14.1. DERIVATIONS

Compliance with double-blind study medication is to be calculated as the number of injections received (as indicated on the Study medication Administration eCRF (SDA1/2)) divided by the planned number of injections, expressed as a percentage, see calculations below:

- Compliance over first 4 doses = (Number of doses received from Visit 3A to Visit 3D / Planned number of doses [4]) X 100
- Compliance over last 4 doses = (Number of doses received from Visit 3E to Visit 3H / Planned number of doses [4]) X 100
- Overall compliance = (Total number of doses received / Planned number of doses [8]) X 100

Subjects are expected to receive one dose per visit from Visit 3A to Visit 3H for a total of 8 doses.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy analysis is to be performed for the ITT population and repeated for the PP population.

The primary efficacy variable is the mean of the daily combined score (CS) during the PAC3 period as recorded on each subject's eDiary.

The daily total rhinoconjunctivitis symptom score (TRSS) and the daily rescue medication score (RMS) are to be combined and a daily CS is to be calculated for each subject as follows:

- CS = (TRSS / 8) + RMS

For each subject the mean of the daily non-missing CS during the BAE, PAC1, PAC2 and PAC3 periods is to be calculated as follows:

- Sum(All CS in respective period) / Number of non-missing days in respective period

The TRSS is the sum of 8 individual TRSS symptom scores, namely runny nose, sneezing, blocked nose, itchy nose, itchy eyes, watery eyes, red eyes and itchy ear/palate. All symptoms are reflective over the previous 24 hours.

For each symptom, the subject is to rate (each morning) the severity as follows:

0 = absent

1 = mild, barely noticeable

2 = moderate, annoying/troublesome

3 = severe, very annoying/very troublesome

The TRSS is to have a range of 0 to 24. The TRSS on each day is to be calculated as follows:

TRSS = Runny Nose + Sneezing + Blocked Nose + Itchy Nose + Itchy Eyes + Watery Eyes + Red Eyes + Itchy Ear/Palate.

Rescue medications are to be provided to subjects to be used according to a pre-specified Rescue Medication Plan as specified in protocol Appendix 3: Rescue Medication Package Description and Rescue Medication Plan. The use of allergy rescue medications is to be scored based on Didier (Didier *et al,* 2009) as follows:

- RMS = 0; no allergy rescue medication used per day
- RMS = 0.5; at least one dose of antihistamine eye drops used per day
- RMS = 1; at least one dose of oral antihistamine used per day
- RMS = 2; at least one dose of intranasal corticosteroid used per day

- RMS = 3; at least one dose of systemic corticosteroid used per day

The RMS score is not additive, the maximum value per day is used and therefore the maximum RMS per day is 3. The maximum CS per day is therefore 6.

The CS ranges from 0-6 and provides equal weighting (a maximum score of 3 each) for the contribution of the symptoms and for the rescue medication use.

If any of the 8 individual TRSS, namely sneezing, runny nose, blocked nose, itchy nose, itchy eyes, watery eyes, red eyes or itchy ear/palate for a given day is missing, the TRSS for that day is to be considered missing. If either the TRSS or the RMS is missing for a particular day then the CS is to be considered missing.

15.1.2. Missing Data Methods for Primary Efficacy Variable

The primary analysis is to be performed using all available data on the assumption that the probability of missing observations is independent of unobserved measurements (missing at random). Therefore the missing values will not be imputed for the primary analysis.

A sensitivity analysis is to be performed to check the robustness of the primary results, assuming a missing not at random (MNAR) process. A pattern-mixture model based on control-based imputation is to be utilised for the sensitivity analysis.

The sensitivity analysis is described in Section 15.1.4 Sensitivity Analysis of Primary Efficacy Variable.

15.1.3. Primary Analysis of Primary Efficacy Variable

The primary objective of this study is to test the hypothesis that there is no significant difference in adjusted mean CS between the active HDM-SPIRE treatment groups and placebo.

The null and alternative hypothesis is given by:

$$H_0: \mu_A = \mu_P$$
$$H_1: \mu_A \neq \mu_P$$

Where μ_A is the adjusted mean for the active treatment groups and μ_P is the adjusted mean for the placebo treatment group.

A point estimate and two-sided 95% confidence interval for the difference in adjusted mean between the active treatment groups and placebo is to be calculated using a Mixed Model Repeated Measures (MMRM) analysis for the PAC1, PAC2 and PAC3 period mean CS.

The MMRM is to include treatment, period and pooled region as main effects, gender, asthma status and Baseline CS as covariate, treatment-by-period and baseline-by-period interaction. An unstructured covariance matrix is to be used to assess within-subject dependence of the 3 observations (PAC1, PAC2 and PAC3) of mean CS per subject.

The following SAS®code is to be used:

PROC MIXED data=<input dataset> **IC INFO**;

CLASS subject treatment period pooled_region gender asthma_status;
MODEL CS=baseline treatment period pooled_region gender asthma_status treatment*period baseline*period / **DDFM**=KR;
ESTIMATE '4 x 12 nmol HDM-SPIRE vs Placebo at PAC3**'** treatment 1 0 0 -1
treatment*period 0 0 1 0 0 0 0 0 0 0 0 -1 / CL;
REPEATED period / **SUBJECT**=subject **TYPE**=UN;

RUN;

Appropriate estimate statements are to be added for the contrasts of each HDM-SPIRE treatment group vs placebo for the PAC1, PAC2 and PAC3 periods.

- The treatment difference corresponding to the PAC3 period is to be utilised for the primary analysis
- The treatment difference corresponding to the PAC1 and PAC2 periods are to be utilised as exploratory analyses

Statistical significance is to be declared as set out in Section 7.4 Multiple Comparisons/Multiplicity.

Observed and change from Baseline values are to be summarised by descriptive statistics for the BAE, PAC1, PAC2 and PAC3 periods by treatment group.

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The sensitivity analysis is to be performed for the ITT population.

A pattern-mixture model based on non-ignorable missing observations, i.e. missing not at random (MNAR) is to be used where the conditional distribution of missing data, given the observed data, can be used to create multiple imputations for the missing values of subjects randomised to active treatment groups under the assumption that those subjects behave similar to those in the placebo treatment group after discontinuation, that is, the drug effect diminishes after subjects discontinue from the study. The approach is to be implemented by multiple imputations, where missing values are multiply replaced by sampling from the Bayesian posterior predictive distribution based on the model. The data is then analysed using the same primary analysis method as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable.

For imputation the following programming steps are to be performed using the SAS® procedures MI, MIXED and MIANALYZE:

Step 1) Impute non monotone missing data using the MCMC option of SAS PROC MI to obtain a monotone missing data pattern for all subjects

The following SAS code is to be used:

PROC MI data=<input data> **OUT**=imp1 **NIMPUTE**=100 **SEED**=<seed>;
BY trtn;
MCMC CHAIN=multiple **IMPUTE**=monotone;
VAR BAE PAC1 PAC2 PAC3;
RUN;

Where **trtn** refers to the treatment group and BAE, PAC1, PAC2 and PAC3 refers to the mean score of each respective period.

The resulting output dataset **imp1** is to have 100 copies of the original dataset of subjects where each copy is to have a monotone missing pattern.

Step 2) The missing values for each pattern is to be imputed via the chained equation method, using SAS PROC MI option MONOTONE REG. The MNAR imputation is achieved by using only appropriate study data for each pattern. For example, to impute for period PAC3 assuming that the active arm missing data has the trajectory of placebo only placebo observations up to and including PAC3 is to be used.

The following SAS code is to be used:

```
PROC MI data=imp1 SEED=<> NIMPUTE=1 OUT=imp2;
        BY _Imputation_;
        CLASS trt;
        VAR BAE0 PAC1 PAC2 PAC3;
        MONOTONE REG;

        MNAR MODEL (PAC1 / MODELOBS =(trt='Placebo'));
        MNAR MODEL (PAC2 / MODELOBS =(trt='Placebo'));
        MNAR MODEL (PAC3 / MODELOBS =(trt='Placebo'));
RUN;
```

Step 3) Analyse the resulting dataset using the same method as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable for each of the 100 imputed datasets resulting in 100 estimates of the difference in adjusted mean CS between the active HDM-SPIRE treatment groups and placebo.

Step 4) An overall result is to be obtained by combining the estimates and using SAS PROC MIANALIZE to obtain the overall result.

The following SAS code is to be used:

```
PROC MIANALYZE data = imp2;
        MODELEFFECTS estimate;
        STDERR stderr;
        BY trt period;
RUN;
```

Where **estimate** refers to each estimate of the difference in adjusted mean CS between HDM-SPIRE and placebo and **stderr** refers to the standard error of each estimate.

15.1.5. SUPPORTIVE ANALYSES OF PRIMARY EFFICACY VARIABLE

15.1.5.1. Responder Analysis

The primary analysis is to be supported by a responder analysis identifying the number of subjects who show a reduction from Baseline CS at PAC3 at each 10^{th} percentile of the percentage reduction from Baseline in CS for each HDM-SPIRE treatment and placebo. The percentage reduction can only range from 0% to 100% and a subject with an increase from Baseline is not considered a responder in any percentile.

A subject is considered a responder at the 10th percentile if they show a reduction in mean CS at PAC3 of ≥10%. In general, a subject is considered a responder at the ith percentile if they show a reduction in mean CS at PAC3 ≥i%. Where i = 10, 20 ,30…,100. The rate of subjects with a reduction from Baseline of < 10% is to be included in the analysis under the following categories:

- < 0% reduction
- < 0% to < 10% reduction

Only subjects with both a Baseline and PAC3 CS are to be included in the analysis.

The response rate (%) at each 10th percentile is to be calculated as follows

- Response rate at PAC3 (%) = Number of responders / Total number of subjects with data at BAE and PAC3 * 100

The response rate is to be presented for each 10th percentile and treatment group. The response rate is to be cumulative, meaning, if a subject is regarded as a responder in the highest percentile the same subject will also be counted as a responder in all other (lower) percentiles.

The responder status (yes or no) is to be analysed using a logistic regression model with treatment, pooled region, gender, asthma status as main effects and Baseline CS as covariate to compare the response rates of HDM-SPIRE treatment groups against placebo. Odds ratio of HDM-SPIRE/placebo with 95% confidence interval and p-value is to be presented.

The following SAS code is to be used for the logistic regression:

PROC LOGISTIC data=<input dataset>;

CLASS treatment (ref = 'Placebo') period pooled_region gender asthma_status / **PARAM** = ref;

MODEL resp (ref = 'Y') = baseline treatment period pooled_region gender asthma_status;

RUN;

Where **resp** refers to the derived response variable of 'Yes' or 'No' per subject.

A waterfall plot of the clinical response showing percentage change in CS from Baseline to PAC3 for each individual subject is to be plotted by treatment group.

15.1.5.2. Treatment-by-pooled Region Interaction

The effect of pooled region on the primary efficacy variable for the ITT population is to be investigated using the same MMRM as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable with the addition of a treatment-by-pooled region interaction effect.

The interaction is to be further explored by doing subgroup analysis for each pooled region if the effect is found to be statistically significant.

15.1.5.3. Alternative Combined Score Weighting

The CS provides equal weighting (a maximum score of 3 each) for the contribution of the symptoms and the rescue medication use.

Two alternative CS are to be calculated for sensitivity testing of the impact of different weighting of TRSS and RMS as follows:

The TRSS (0 to 24) and the RMS (0 to 3) is to be combined for analysis of the alternative primary variable as follows:

- Alternative 1 CS (ALT1 CS) = (4/3 * TRSS/8)+ (2/3* RMS)

Mean ALT1 CS is to be calculated in BAE, PAC1, PAC2 and PAC3 by taking the mean ALT1 CS over all the days with complete data for the BAE and each PAC period.

- Alternative 2 CS (ALT2 CS) = (2/3 * TRSS/8) + (4/3* RMS)

Mean ALT2 CS is to be calculated in BAE, PAC1, PAC2 and PAC3 by taking the mean ALT2 CS over all the days with complete data for the BAE and each PAC period.

A third and fourth alternative CS is to be calculated for sensitivity testing of the impact of increased weighting of oral corticosteroid use.

An alternative RMS (ALT RMS) for the purpose of testing the impact of oral corticosteroid use is to be evaluated as follows:

- ALT RMS = 0; no allergy rescue medication used per day
- ALT RMS = 0.5; at least one dose of antihistamine eye drops used per day
- ALT RMS = 1; at least one dose of oral antihistamine used per day
- ALT RMS = 2; at least one dose of intranasal corticosteroid used per day
- ALT RMS = 6; at least one dose of systemic corticosteroid used per day

The TRSS (0 to 24) and the ALT RMS (0 to 6) is to be combined for analysis of the alternative primary variable as follows:

- Alternative 3 CS (ALT3 CS) = TRSS/8 + ALT RMS/2

This formula maintains equal weighting (a maximum score of 3 each) for the contribution of the symptoms and the rescue medication use and maintains the maximum score of 6.

Mean ALT3 CS is to be calculated in BAE, PAC1, PAC2 and PAC3 by taking the mean ALT3 CS over all the days with complete data for the BAE each PAC period.

- Alternative 4 (ALT4 CS) = TRSS/8 + ALT RMS

This formula ensures that the use of oral corticosteroids results in a combined score of at least 6 even if no symptoms are present; the maximum score is 9.

Mean ALT4 CS is to be calculated in BAE, PAC1, PAC2 and PAC3 by taking the mean ALT4 CS over all the days with complete data for the BAE and each PAC period.

A point estimate and two-sided 95% confidence interval for the difference in adjusted means of ALT1 CS, ALT2

CS, ALT3 CS and ALT4 CS between the active treatment groups and placebo is to be calculated using the same MMRM as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable.

15.1.6. NORMALITY AND HOMOGENEITY OF PRIMARY EFFICACY VARIABLE

The residuals from the primary efficacy MMRM, sensitivity analysis MMRM as well as supportive primary efficacy analysis MMRM are to be visually checked for normality and homogeneity of variance. Normality is to be examined by normal probability plots, while homogeneity of variance is to be assessed by plotting the residuals against the predicted values for the model. Any deviation from either assumption may result in further analysis using non-parametric analysis of the primary efficacy variable.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses are to be performed for the ITT population.

The secondary efficacy analyses are to be prioritised in order of importance as outlined below.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Mean Total Rhinoconjunctivitis Symptom Score

The daily TRSS is to be derived as described in Section 15.1.1: Primary Efficacy Variable & Derivation.

The means of the daily TRSS for the BAE, PAC1, PAC2 and PAC3 periods are to be calculated over all days with complete data.

Analysis of Mean Total Rhinoconjunctivitis Symptom Score

A point estimate and two-sided 95% confidence interval for the difference in adjusted means between the active treatment groups and placebo is to be calculated using the same MMRM as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable.

- The treatment difference corresponding to the PAC3 period is to be utilised for the secondary analysis
- The treatment difference corresponding to the PAC1 and PAC2 periods are to be utilised as exploratory analyses

Observed and change from Baseline values are to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

15.2.1.2. Mean Component Scores of Total Rhinoconjunctivitis Symptom Score

The TRSS consists of two components:

- Total Nasal Symptom Score (TNSS)

The TNSS is the sum of four individual nasal symptoms: runny nose, sneezing, blocked nose, and itchy nose. The TNSS will have a range of 0-12. The TNSS is to be calculated on each day as follows:

TNSS = Runny Nose + Sneezing + Blocked Nose + Itchy Nose.

Mean TNSS is to be calculated for the BAE, PAC1, PAC2 and PAC3 periods over all days with complete data.

- Total Non-nasal Symptom Score (TNNSS)

The TNNSS is the sum of four individual non-nasal symptoms: itchy eyes, watery eyes, red eyes and itchy ear/palate.

The TNNSS will have a range of 0-12. The TNNSS is to be calculated on each day as follows:

TNNSS = Itchy Eyes + Watery Eyes + Red Eyes + Itchy Ear/Palate.

Mean TNNSS is to be calculated for the BAE, PAC1, PAC2 and PAC3 periods over all days with complete data.

Analysis of Mean Component Scores of Total Rhinoconjunctivitis Symptom Score

For both the TNSS and TNNSS a point estimate and two-sided 95% confidence interval for the difference in adjusted means between the active treatment groups and placebo is to be calculated using the same MMRM as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable.

- The treatment difference corresponding to the PAC3 period is to be utilised for the secondary analysis
- The treatment difference corresponding to the PAC1 and PAC2 periods are to be utilised as exploratory analyses

Observed and change from Baseline values are to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

15.2.1.3. Mean Rescue Medication Score

The daily RMS is to be derived as described in Section 15.1.1: Primary Efficacy Variable & Derivation.

The means of the daily RMS for the BAE, PAC1, PAC2 and PAC3 periods are to be calculated over all days with complete data.

Analysis of Rescue Medication Score

A point estimate and two-sided 95% confidence interval for the difference in adjusted means between the active treatment groups and placebo is to be calculated using the same MMRM as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable.

- The treatment difference corresponding to the PAC3 period is to be utilised for the secondary analysis
- The treatment difference corresponding to the PAC1 and PAC2 periods are to be utilised as exploratory analyses

Observed and change from Baseline values are to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

15.2.1.4. Clinical Global Impression of Change in Rhinoconjunctivitis Symptoms

During the Follow-up Visit (Visit 5) subjects are to complete a Clinical Global Impression (CGI) of change in Rhinoconjunctivitis symptoms.

Subjects are to rate their overall allergy symptoms at the end of the study relative to Baseline on a 7-point scale as follows:

0 = Very much better

1 = Moderately better

2 = A little better

3 = Unchanged

4 = A little worse

5 = Moderately worse

6 = Very much worse

The following additional categories of global impression are to be derived:

- Moderately or very much better
- Any improvement (a little better, moderately better or very much better)
- No change (unchanged)
- Any worsening (a little worse, moderately worse or very much worse)

Analysis of Clinical Global Impression of Change

The frequency (n) and percentage (%) of subjects in each category of CGI is to be presented.

A p-value for the difference in CGI between each HDM-SPIRE treatment group and placebo across all 7 categories is to be calculated using the Cochran-Mantel-Haenszel (CMH) row mean score differ.

The frequency (n) and percentage (%) of subjects in each of the following derived categories is to be presented

- Moderately or very much better
- Any improvement
- No change
- Any worsening

A Chi-square test is to be used to calculate a p-value for the difference in each derived CGI category between each HDM-SPIRE treatment group and placebo.

15.2.1.5. Proportion of Well Days

A well day is defined as any day where a subject has no moderate or severe RSS without the use of rescue medication. If any of the 8 RSS or the RMS is missing for a specific day the day is not to be considered as a well day.

The proportion of well days is to be calculated as the sum of days where all 8 RSS are non-missing and less than or equal to 1 and RMS is equal to 0, divided by the total number of days in the relevant assessment period (BAE, PAC1, PAC2 or PAC3) as follows:

- Proportion of well days (%) = Number of well days / Total number of days in the relevant assessment period * 100
- The total number of days in each assessment period (denominator) refers to the total number of days with complete RSS and RMS as required to define a well day.

Analysis of Proportion of Well Days

A point estimate and two-sided 95% confidence interval for the difference in adjusted means between the active treatment groups and placebo is to be calculated using the same MMRM as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable.

The treatment difference corresponding to the mean proportion of symptom free days of the PAC1, PAC2 and PAC3 periods is to be utilised for the secondary analysis.

Observed and change from Baseline values are to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

15.2.1.6. Rhinoconjunctivitis Quality of Life Questionnaire

The rhinoconjunctivitis quality of life questionnaire (RQLQ) is to be completed as a one off assessment at the end of the BAE, PAC1, PAC2 and PAC3 periods.

The RQLQ has 28 questions in the following seven domains:

- Activities
- Sleep
- Non-nose/eye symptoms
- Practical problems
- Nasal symptoms
- Eye symptoms
- Emotional
- Overall RQLQ

The domains consist of the following individual questions:

- Activities: Questions 1 to 3
- Sleep: Questions 4 to 6
- Non-nose/eye symptoms: Questions 7 to 13
- Practical problems: Questions 14 to 16
- Nasal symptoms: Questions 17 to 20
- Eye symptoms: Questions 21 to 24
- Emotional: Questions 25 to 28

Refer to Appendix 3: Complete Questionnaires for the complete questionnaire. For each question subjects record how troubled they have been during the last week on a 7-point scale. For all domains, except Emotional, the scores are (0 = Not troubled to 6 = Extremely troubled). For the Emotional domain the 7-point scale is (0 = None of the Time to 6 = All of the Time).

The overall RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items within those domains.

If any individual item within a domain is missing the domain score is to be set to missing.

Analysis of Rhinoconjunctivitis Quality of Life Questionnaire

A point estimate and two-sided 95% confidence interval for the difference in adjusted means between the active treatment groups and placebo during the PAC1, PAC2 and PAC3 periods are to be calculated using an analysis of covariance (ANCOVA) with treatment, period and pooled region as main effects, gender, asthma status and Baseline RQLQ as covariate and a treatment by-period interaction for the Overall RQLQ score as well as each of the 7 domains individually.

- The treatment difference corresponding to the PAC3 period is to be utilised for the secondary analysis
- The treatment difference corresponding to the PAC1 and PAC2 periods are to be utilised as exploratory analyses

Observed and change from Baseline values are to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group, for the Overall RQLQ score as we all each of the 7 domains individually.

15.2.1.7. Mean Asthma Symptom Score

The asthma symptom scores (ASS) has six questions which are answered daily by the subject for each assessment period (BAE, PAC1, PAC2 and PAC3), describing their condition in the past 24 hours. All subjects (including non asthmatic subjects) are to describe their condition with regards to:

- Coughing

- Wheezing
- Shortness of breath

In addition for asthmatic subjects only, the ASS is to include the following questions:

- Limitation of activities
- Nocturnal symptoms or awakenings due to asthma
- Need for short-acting inhaled $\beta_2$agonist treatment

There is a 4 point scale (0 to 3) for each question. For cough, wheezing and shortness of breath symptoms the subject is to rate the severity as follows:

0 = absent

1 = Mild, barely noticeable

2 = Moderate, annoying/troublesome

3 = Severe, very annoying/ very troublesome

For limitations of activities the subject is to rate the severity as follows:

0 = Not limited

1 = Very slightly limited

2 = Slightly limited

3 = Moderately limited or worse

For nocturnal symptoms or awakenings due to asthma the subject is to rate how asthma has affected them overnight (last night) as follows:

0 = Not at all

1 = Hardly at all

2 = A few minutes disturbance

3 = Several times or more

For use of short-acting inhaled β2 agonist treatment the subjects are to record how many puffs of reliever medication (e.g. albuterol or salbutamol) they have used as follows:

0 = None

1 = One

2 = Two

3 = Three or more

The questions are equally weighted and the ASS for each day is to be calculated as the mean of all six questions (for asthmatic subjects) as well as the mean using only the 3 symptoms (for all subjects including asthmatics)

separately. The ASS is therefore between 0 and 3. The mean of the daily ASS for each assessment period is to be calculated over all days with complete data.

Subjects are to be classified as asthmatic or non asthmatic based on the System Screening eCRF. Asthmatic subjects are defined as subjects with either 'Controlled' or 'Partially/Uncontrolled' asthma status and non asthmatic subjects are defined as subjects with 'No asthma'.

Analysis of Mean Asthma Symptom Score

The ASS is to be analised for asthmatic subjects only, as well as all subjects (including asthmatics) separately.

A point estimate and two-sided 95% confidence interval for the difference in adjusted means between the active treatment groups and placebo is to be calculated using the same MMRM as described in Section 15.1.3 Primary Analysis of Primary Efficacy Variable.

- The treatment difference corresponding to the PAC3 period is to be utilised for the secondary analysis
- The treatment difference corresponding to the PAC1 and PAC2 periods are to be utilised as exploratory analyses

Observed and change from Baseline values are to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

15.3. OTHER EXPLORATORY EFFICACY

Other exploratory efficacy analyses are to be performed for the ITT population.

15.3.1. OTHER EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

15.3.1.1. Rhinoconjunctivitis Symptom Scores Measured Using Visual Analogue Scale

At start of the BAE period and the start of each PAC period subjects are to record their RSS symptoms using a Visual Analogue Scale (VAS) in their eDiaries.

Subjects are to rate their allergy symptoms on a visual scale where 0 = no allergy symptom and 10 = my allergy symptom is the worst it could possibly be with respect to the following categories:

- Runny nose
- Sneezing
- Blocked nose
- Itchy nose
- Itchy eyes
- Watery eyes
- Red eyes
- Itchy ear/palate symptoms

Analysis of Rhinoconjunctivitis Symptom Scores Measured Using Visual Analogue Scale

Observed and change from Baseline values for each symptom's VAS score individually is to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

15.3.1.2. The Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) assesses sleep quality during the past month and is to be completed as a once off assessment by subjects at the end of the BAE, PAC1, PAC2 and PAC3 periods. It consists of 19 self-rated questions and five completed by a bed-partner/roommate. Refer to Appendix 3: Complete Questionnaires for the complete questionnaire. For the self-rated questions there are four questions about bed and sleep times and fifteen questions (each scored in one of four categories) that elicit the quality of sleep.

The range of values for questions 5 through 10 are all 0 to 3.

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing then any scores calculated using missing questions are also missing. Thus it is important to make sure that all

questions 1 through 9 have been answered.

In the event that a range is given for an answer (e.g., '30 to 60' is written as the answer to Q2, minutes to fall asleep), split the difference and enter 45.

The total PSQI and component scores (duration of sleep, sleep disturbance, sleep latency, day dysfunction due to sleepiness, sleep efficiency, overall sleep quality and need medications to sleep) are calculated from the questionnaire and the scoring instructions in Table 2 below:

Table 2 : Scoring Instructions

Domain	Question (Q) Result or Algorithm	Analysis Value
Duration of Sleep	Q4 > 7	0
	6 < Q4 <= 7	1
	5 <= Q4 <= 6	2
	Q4 < 5	3
Sleep Disturbance	Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j = 0 NOTE: If Q5j-Other reason(s), is null or Q5j is null, set the value of Q5j to 0	0
	Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j >= 1 and <= 9	1
	Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j >=10 and <= 18	2
	Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j >= 19 and <= 27	3
Sleep Latency	Step 1:	
	If 0 <= Q2 <= 15 then set Q2 = 0	
	If 15 < Q2 <= 30 then set Q2 = 1	
	If 30 < Q2 <= 60 then set Q2 = 2	
	If Q2 > 60 then set Q2 = 3	
	Step 2:	
	Q5a + Q2 = 0	0
	1 <= Q5a + Q2 <= 2	1
	3 <= Q5a + Q2 <= 4	2
	5 <= Q5a + Q2 <= 6	3
Day Dysfunction Due to Sleepiness	Q8 + Q9 = 0	0
	1 <= Q8 + Q9 <= 2	1
	3 <= Q8 + Q9 <= 4	2
	5 <= Q8 + Q9 <= 6	3

Domain	Question (Q) Result or Algorithm	Analysis Value
Sleep Efficiency	Step 1:	
	Get difference in seconds between day and time of day Q1 and day Q3 (DIFFSEC)	
	Step 2:	
	Convert to hours (DIFFHOUR): Absolute value of DIFFSEC / 3600	
	Step 3:	
	Calculate the hours between GMT (Q1) AND GMT (Q3) (NEWTIB): If DIFFHOUR > 24 then NEWTIB = DIFFHOUR – 24 If DIFFHOUR <= 24 then NEWTIB = DIFFHOUR	
	Step 4:	
	Get Q4 as a percentage of NEWTIB (TMPHSE): THPHSE = (Q4 / NEWTIB) * 100	
	Step 5:	
	85 <= TMPHSE	0
	75 <= TMPHSE < 85	1
	65 <= TMPHSE < 75	2
	TMPHSE < 65	3
Overall Sleep Quality	Q6	Value of Q6
Need Meds to Sleep	Q7	Value of Q7
PSQI Total	Step 1:	
	Calculate total score (TOTAL) Duration of Sleep + Sleep Disturbance + Sleep Latency + Day Dysfunction Due to Sleepiness + Sleep Efficiency + Overall Sleep Quality + Need Meds to Sleep	TOTAL
	Step 2:	
	TOTAL <= 5	Good
	TOTAL > 5	Poor

Analysis of the Pittsburgh Sleep Quality Index

Observed and change from Baseline values for the overall and component scores of the PSQI are to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

The frequency (n) and percentage (%) of subjects in each category (good or poor) of PSQI Total Score is to be presented by treatment group for BAE, PAC1, PAC2 and PAC3.

A point estimate and exact 95% confidence interval for the difference in proportion of subjects that had a good response is to be calculated for each treatment group vs placebo using the following SAS code:

PROC FREQ;

TABLES treatment*outcome / **CMH**;

EXACT OR RISKDIFF RELRISK(METHOD=SCORE);

RUN;

15.3.1.3. Asthma Control Test

The Asthma Control Test (ACT) consists of 5 questions and is to be completed by all asthmatic subjects at the clinical Visits at the end of BAE, PAC1, PAC2 and PAC3. The questions are to be completed by the subjects stating how they have been over the last 4 weeks with regards the following:

- How much of the time did your asthma keep you from getting as much done at work, school or at home?
- How often have you had shortness of breath?
- How often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?
- How often have you used your rescue inhaler or nebulizer medication?
- How would you rate your asthma control?

Each question has a 5 point scale (1 to 5) where 1 represents the least control and 5 represents optimal control. The ACT score is the mean of the 5 questions and therefore also between 1 (severely uncontrolled) and 5 (totally controlled).

Analysis of the Asthma Control Test

Observed and change from Baseline values for the ACT score is to be summarised by descriptive statistics for the PAC1, PAC2 and PAC3 periods by treatment group.

15.3.1.4. Use of Concomitant Medications Associated with Rhinoconjunctivitis or Related Conditions

Concomitant medication use associated with rhinoconjunctivitis or related conditions are to be analysed for the SAF population.

Medications associated with rhinoconjunctivitis or related conditions are defined as medications where the Concomitant Medications eCRF (CMDT) question 'Is the medication used for HDM allergy?' or 'Is the medication used for other allergy?' are indicated as 'Yes'. Concomitant medications are defined as in Section 12 Medications.

Subjects are to be categorised as either 'used' or 'not used' any concomitant medications associated with rhinoconjunctivitis or related conditions.

Analysis of the Concomitant Medication Use

The frequency (n) and percentage (%) of subjects in each category is to be presented per treatment group.

A point estimate and exact 95% confidence interval for the difference in proportion of subjects that used concomitant medication for rhinoconjunctivitis or related conditions is to be calculated for each treatment group

vs placebo using the following SAS code:

```
PROC FREQ;
        TABLES treatment*outcome / CMH;
        EXACT OR RISKDIFF RELRISK(METHOD=SCORE);
RUN;
```

15.3.1.5. Home Environment Exposure and Control Measures

Control Measures

The frequency (n) and percentage (%) of subjects implementing the following control measures are to the presented for BAE, PAC1, PAC2 and PAC3 by treatment group, as captured on the House Dust Mite Control Measures eCRF (HDM1/2).

- Allergy-proof coverings for mattresses, pillows or quilts
- Sprays or chemicals to kill house dust mites
- Air filters
- Air management equipment
- Curtains

All additional information on control measures is to be listed only.

Home Environment Exposure

Subjects are to be issued with home dust collection kits on Consent Visit 1A and PAC3 Visit 4E.

House dust samples are to be collected following Consent Visit 1A and prior to the end of PAC3 Visit 4F/5. In the event that multiple samples are collected on different dates prior to Visit 4F/5 the last sample collected is to be analysed as the Visit 4F/5 sample.

Dust samples are to be tested for the following allergens and reported in mg/kg:

- Mite allergens der p 1
- Mite allergens der f 1
- Cat allergens fel d 1
- Dog allergens can f 1
- Mouse allergens mus m 1
- Rat allergens rat n 1
- Cockroach allergens bla g 2

- Alternaria allergens alt a 1

Observed and change from Baseline values for each allergen is to be summarised by descriptive statistics for Baseline and Visit 4F/5 by treatment group.

Assessments reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), are to be converted to X for the purpose of quantitative summaries, but are to be presented as recorded, i.e. as "< X" or "> X" in the listings.

All allergens identified as entered on the Issue dust Collection Pack eCRF (DMKIT) is to be listed.

16. SAFETY OUTCOMES

All outputs for safety outcomes are to be based on the SAF population.

There is to be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

16.1. ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a subject administered study treatment that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (i.e, an abnormal laboratory finding), symptom (i.e., rash, pain, discomfort, fever, dizziness, etc.), disease (i.e., peritonitis, bacteraemia, etc.) or outcome of death temporally associated with the use of study treatment, whether or not considered causally related to the study medication.

Adverse Events (AEs) are to be coded using MedDRA Version 19.0.

Adverse events are to be classified as either pre-treatment AEs or treatment-emergent adverse events (TEAEs) based on the start date of the event as follows:

- Pre-treatment AEs: Defined as any AE which started or worsened on or after informed consent and before study medication administration
- TEAE: Defined as any AE which started or worsened on or after first study medication administration.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment-emergent or not, the AE is to be classified as the worst case; i.e. treatment-emergent.

An overview of the frequency (n) and percentage (%) of subjects is to be provided for the following TEAEs together with the actual number of mentions (m) of the event per category:

- Any TEAE
- Serious TEAEs
- TEAEs leading to death

- Life-threatening TEAEs
- TEAEs leading to premature study and treatment discontinuation
- Treatment related TEAEs leading to premature treatment discontinuation
- Severe TEAEs
- TEAEs related to study medication
- TEAEs of special interest
- TEAEs within 24 hours of any dose of study medication

In addition to the overview of TEAEs, incidence of all TEAEs in the sub-sections below is to be presented by System Organ Class (SOC) and Preferred Term (PT). If an AE occurs more than once the subject is to be counted once per SOC and PT as relevant.

16.1.1. ALL TEAEs

16.1.1.1. Severity

Severity is classed as mild/moderate/severe (increasing severity). TEAEs with a missing severity are to be classified as severe. If a subject reports a TEAE more than once within that SOC/PT, the AE with the worst case severity is to be used in the corresponding severity summaries.

16.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as 'Not related', 'Unlikely to be related' or 'Related' (increasing severity of relationship). TEAEs with a missing relationship to study medication are to be regarded as 'Related' to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to the study medication is to be used in the corresponding relationship summaries.

16.1.2. SERIOUS TEAEs

Serious TEAEs are those events recorded as 'Serious' on the Adverse Events Details eCRF (AEDT).

16.1.3. TEAEs LEADING TO DEATH

Treatment-emergent AEs leading to Death are those events for which the Outcome is recorded as 'Death' or the reason for seriousness of the event is indicated as 'Death' on the Adverse Events Details eCRF (AEDT).

16.1.4. LIFE-THREATENING TEAEs

Life-threatening TEAEs are those events where the reason for seriousness of the event is specified as "Life-threatening" on the Adverse Events Details eCRF (AEDT).

16.1.5. TEAEs LEADING TO PREMATURE STUDY OR TREATMENT DISCONTINUATION

Treatment-emergent AEs leading to premature study discontinuation are to be identified as TEAEs where the Outcome on the Adverse Events Detail eCRF (AEDT) is indicated as "Subject withdrawn because of this event".

16.1.6. TREATMENT RELATED TEAEs LEADING TO PREMATURE TREATMENT DISCONTINUATION

Treatment related TEAEs leading to premature treatment discontinuation are to be identified as TEAEs where the Outcome on the Adverse Events Detail eCRF (AEDT) is indicated as "Subject withdrawn because of this event" and the Causality is indicated as "Related" and the primary reason for treatment termination on the End of Treatment eCRF (EOT) is indicated "Adverse Event".

16.1.7. TEAEs OF SPECIAL INTEREST

TEAEs of special interest are defined as TEAEs for which "Adverse Event of Special Interest (AESI)" is indicated as "Yes" on the Adverse Events Detail eCRF (AEDT).

16.1.8. TEAEs WITHIN 24 HOURS OF ANY DOSE

TEAEs within 24 Hours of any dose are defined as any AE that has a start date within 24 Hours of any dose, not only the first study drug administration date and time. If the AE onset time is missing and the start date of the TEAE is on or one day after any dosing date, the AE is to be assumed to have occurred within 24 hours of the dose.

16.2. DEATHS

If any subjects die during the study as recorded on the Death eCRF (DTH), the information is to be presented in a data listing.

16.3. LABORATORY EVALUATIONS

Results from the central laboratory are to be included in the reporting of this study for Haematology, Biochemistry, Urine dipstick and Immunology. Quantitative laboratory assessments are to be summarised by descriptive statistics and presented in International System of Units (SI). Categorical assessments are to be presented by frequency (n) and percentage (%) of subjects.

Quantitative laboratory assessments reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), are to be converted to X for the purpose of quantitative summaries, but are to be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries are to be provided for laboratory data:

- Actual and change from Baseline by visit (for quantitative measurements)
- Shift from Baseline according to normal reference range criteria (for quantitative measurements and categorical measurements) by visit
- Listings of all laboratory assessments

The following assessments are to be measured and presented:

- Haematology: Haematocrit, haemoglobin, red blood cells, white blood cells (WBC), WBC differentials (neutrophils, eosinophils, basophils, lymphocytes, monocytes) and platelets
- Biochemistry: Sodium, potassium, chloride, urea, creatinine, calcium, phosphorus, total protein, albumin, uric acid, total bilirubin, glucose (random), lactate dehydrogenase, creatine phosphokinase, alanine transaminase, aspartate transaminase, gamma glutamyltransferase and alkaline phosphatase
- Urine dipstick: pH, protein, ketones, blood and glucose
- Immunology: All relevant perennial allergen specific IgE
- Tryptase for anaphylactic response

  Blood sample for tryptase is only to be taken in the event of a suspected anaphylactic reaction. The initial sample should be taken approximately 1 hour after the reaction, with a further sample at approximately 3 hours and then repeated every 3 hours until the Investigator is satisfied that the subject may be discharged. Tryptase laboratory results are to be listed separately.

16.3.1. LABORATORY REFERENCE RANGES AND ABNORMAL CRITERIA

Quantitative laboratory assessments are to be compared with the relevant laboratory reference ranges in SI units and categorised as:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range
- Normal/Abnormal results and clinical significance as reported by the investigator is only to be presented in data listings.

16.4. ANTIBODIES TO PANEL OF DER P ALLERGES

At Consent Visit 1A a blood sample is to be taken for measurement of levels of IgE antibodies to a fixed panel of Der p allergens, using an immune-affinity based analysis technology such as ImmunoCAP®.

Observed values are to be summarised by descriptive statistics and treatment group for each panel.

Specific IgE for allergen components will be summarised as number of subjects with positive (three grade categories) vs negative (<0.3 kU/L) results for all allergen components.

Positive results will be divided in the three grade categories as described below for specific IgE values.

- Low: ≥ 0.3 - < 1 kU/L
- Moderate/high: ≥ 1 - < 15 kU/L
- Very high: >= 15 values kU/L

16.5. VITAL SIGNS

The following vital signs assessments are to be taken rested and in the sitting or semi-recumbent position and reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Oral body temperature (^{o}C)
- At each medication administration visit (Visit 3A to Visit 3H), vital signs are to be taken pre-dose as well as 30 minutes post-dose.

The following summaries are to be provided for vital signs data by descriptive statistics and treatment group for each visit:

- Actual and change from Baseline/pre-dose observation by visit
    - For medication administration visits (Visit 3A to Visit 3H), change from pre-dose to 30 minutes post-dose observation is to be presented
    - For all other visit assessments (including the pre-dose assessment at Visit 3A to Visit 3H), change from Baseline is to be presented

- Listing of all vital signs data

16.5.1. VITAL SIGNS SPECIFIC DERIVATIONS

Body temperature assessments recorded in Fahrenheit (^{0}F) are to be converted to Celsius (^{0}C) as follows:

- $^0\mathrm{C} = (^0\mathrm{F} - 32) \times \frac{5}{9}$

16.6. PHYSICAL EXAMINATION

At Screening subjects are to undergo a full examination comprising of:

- Eye, ears, nose, throat, neck, including a check for nasal polyps
- Respiratory system
- Central and peripheral nervous system
- Cardiovascular system
- Gastrointestinal system (including the mouth)
- Musculoskeletal system
- Skin
- Lymph node palpation
- Other systems if abnormality is suspected

At Visit 3I and Visit 5 targeted physical examinations are to be performed with organ systems examined if the medical history or AEs of a subject indicate a reason for examination.

Shift from Screening to Visit 3I and Visit 5 in physical examination finding (Normal, Abnormal, Not Done) is to be presented by organ system and treatment group.

Abnormal physical examination findings are to be listed.

16.7. OTHER SAFETY ASSESSMENTS

16.7.1. FORCED EXPIRATORY VOLUME IN 1 SECOND (FEV_1)

The FEV_1 is to be measured at Screening, prior to and 30 minutes post study medication administration (Visits

3A-3H), at the End of Dosing Assessment (Visit 3I), and at the end of the PAC1 (Visit 4B), PAC2 (Visit 4D) and PAC3 (Visit 4F) periods.

At each assessment FEV_1 is to be measured according to the American Thoracic Society guidelines with the subject sitting and the highest reading is to be recorded in the eCRF.

Absolute and change from Baseline/pre-dose values of FEV_1 is to be summarised by descriptive statistics and treatment group for each visit.

- For medication administration visits (Visit 3A to Visit 3H), change from pre-dose to 30 minutes post-dose observation is to be presented
- For all other visit assessments (including the pre-dose assessment at Visit 3A to Visit 3H), change from Baseline is to be presented
- FEV_1 data is to be listed
- An additional listing is to be created for any reduction in FEV_1 of more than 20% from Baseline/pre-dose, as well as a reduction of more than 30% from Baseline/pre-dose
    - The frequency (n) and percentage (%) of subjects with a reduction of more than 20% from Baseline/pre-dose as well as a reduction of more than 30% from Baseline/pre-dose is to be presented by treatment group at each applicable visit.
      Percentages are to be calculated relative to the total number of subjects in the analysis population with data available.

16.7.2. LOCAL REACTION AT INJECTION SITE

Grading of each of the four components of an injection site reaction (pain, tenderness, induration/swelling and erythema/redness) is to be categorised as 'Grade 0', 'Grade 1', 'Grade 2', 'Grade 3' or 'Grade 4' in accordance with the severity of the reactions as specified in Table 7, Section 6.2.2.1 of the protocol.

Frequency (n) and percentage (%) of subjects with local reactions at the injection site are to be summarised by reaction grade and visit for each treatment group.

All injection site reactions are to be listed.

16.7.3. PREGNANCY

A pregnancy test is to be performed for women of childbearing potential at Screening, each Study Drug Administration visit, End of Treatment and Follow-up Visit.

Pregnancy test results as captured on the Pregnancy eCRF (PREG) per Visit is to be listed only.

17. REFERENCES

Dobson, A. J. (2002). *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC.

EMA. (n.d.). *Guideline on Missing Data in Confirmatory Clinical Trials.* Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. *Biometrics* , vol 52, 1324-1333.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

- Depending on data available, dates and times are to take the form ddMMMyyyy HH:MM.

SPELLING FORMAT

- The spelling format to be used is English UK.

UNIVARIATE STATISTICS

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum and maximum: N
    - Mean, median and CV%: N + 1
    - SD: N + 2
    - Missing statistic: N

FREQUENCIES AND PERCENTAGES (N AND %):

- Percent values should be reported inside parentheses and reported to one decimal place

- Missing category for categorical data is only to be presented if there is missing data for a specific category and percentage is not to be calculated for missing category counts. An example is given below:

```
Gender
 Male            n (%)                    xxx (xxx.x)
 Female          n (%)                    xxx (xxx.x)
 Total           n (%)                    xxx (100.0)
 Missing         n                        xxx
```

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups are to be represented as follows and in that order:

Treatment Group	For Tables, Listings and Graphs
Placebo	Placebo
HDM-SPIRE 4 x 12 nmol	HDM-SPIRE 4x12 nmol
HDM-SPIRE 4 x 20 nmol	HDM-SPIRE 4x20 nmol
HDM-SPIRE 8 x 12 nmol	HDM-SPIRE 8x12 nmol

PRESENTATION OF VISITS

For outputs, visits are to be represented as follows and in that order:

Long Name (default)	Short Name
Visit 1A	1A
Screening	1B/C
Visit 2A	2A
Visit 2B	2B
. . .	. . .
Visit 4F	4F
End of Dosing	3I
Follow-up	5

LISTINGS

All listings are to be ordered by the following (unless otherwise indicated in the template):

- Randomised treatment group (or treatment received for safety output), first by placebo then active dose [by ascending dose group].
- Centre-subject ID,
- Date (where applicable),

For listings where non-randomised subjects are included, these are to appear in a category after the randomised treatment groups labelled 'Not Randomised'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

Adverse events (AEs) are allocated to study periods (pre-treatment or treatment-emergent) based on their start dates as specified in Section 16.1 Adverse Events.

Incomplete dates are to be handled as follows:

Partial start or stop dates:

- The events are allocated to the study periods using the available partial information on start and end date, no imputation is to be done. If, for instance, for the AE start date only month and year are available, these data are compared with the month and year information of the first and last study medication administration.

Completely missing start date:

- The event is allocated as treatment-emergent, except if the end date of the AE falls before the date of first study medication administration then it is classified as pre-treatment.

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

Concomitant medications (CMs) are allocated to study periods (prior or concomitant) based on their start or end dates as specified in Section 12 Medications.

Partial start or stop dates:

- In case of a partial start and/or stop date, the medication is allocated to each possible study period using the available partial information, no imputation is done. If, for a medication start and/or stop date, only month and year is available, this date is compared with the month and year information of the first and last dose of study medication administration for assignment.

- In case of a completely missing start date, the medication is considered as having started before the study. In case of a completely missing stop date, the medication is considered as ongoing at the end of the study.

APPENDIX 3. COMPLETE QUESTIONNAIRES

Rhinoconjunctivitis Quality of Life Questionnaire

01. REGULAR ACTIVITIES AT HOME AND AT WORK (tasks that you have to do regularly at work and around your home)

02. SOCIAL ACTIVITIES (e.g., activities with your family and friends, playing with children and pets, sex, hobbies)

03. OUTDOORS ACTIVITIES (e.g., gardening, mowing the lawn, sitting outdoors, sports, going for a walk)

04. Difficulty getting to sleep

05. Wake up during night

06. Lack of a good night's sleep

07. Fatigue

08. Thirst

09. Reduced productivity

10. Tiredness

11. Poor concentration

12. Headache

13. Worn out

14. Inconvenience of having to carry tissues or handkerchief

15. Need to rub nose/eyes

16. Need to blow nose repeatedly

17. Stuffy/blocked

18. Runny

19. Sneezing

20. Post nasal drip

21. Itchy eyes

22. Watery eyes

23. Sore eyes

24. Swollen eyes

25. Frustrated

26. Impatient or restless

27. Irritable

28. Embarrassed by your symptoms

Pittsburgh Sleep Quality Index

01. During the past month, what time have you usually gone to bed at night?

02. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

03. During the past month, what time have you usually gotten up in the morning?

04. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

05. During the past month, how often have you had trouble sleeping because you…

a) Cannot get to sleep within 30 minutes

b) Wake up in the middle of the night or early morning

c) Have to get up to use the bathroom

d) Cannot breathe comfortably

e) Cough or snore loudly

f) Feel too cold

g) Feel too hot

h) Had bad dreams

i) Have pain

j) Other reason(s), please describe How often during the past month have you had trouble sleeping because of this?

06. During the past month, how would you rate your sleep quality overall?

07. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

08. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

09. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

10. Do you have a bed partner or room mate?

If you have a room mate or bed partner, ask him/her how often in the past month you have had

a) Loud snoring

b) Long pauses between breaths while asleep

c) Legs twitching or jerking while you sleep

d) Episodes of disorientation or confusion during sleep

e) Other restlessness while you sleep; please describe