

## **STATISTICAL ANALYSIS PLAN**

**PROTOCOL: CP007A**

**AN OPTIONAL PROSPECTIVE FOLLOW-ON STUDY TO EVALUATE THE  
CONTINUED EFFICACY AND SAFETY OF CAT-PAD IN CAT ALLERGIC  
SUBJECTS UP TO FIVE YEARS AFTER THE ADMINISTRATION OF TREATMENT**

**AUTHOR: ROLAND KLOPPER**

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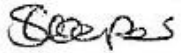
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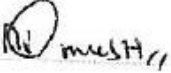
Statistical Analysis Plan V2.0 (Dated 23 FEB 2017) for Protocol CP007A.

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Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorised Version
1.0	18OCT2016	Roland Klopper	Not Applicable – First Version
2.0	23FEB2017	Roland Klopper	<p>Added frequency and percentage of subjects included in each population to Section 9.</p> <p>In Section 13.1.3 specified that all 21 days of symptom score recording is to be populated using each of the 3 methods of imputation</p> <p>Clarified in Section 13.2.1.5 how subjects are defined as asthmatic or non-asthmatic</p> <p>In Section 13.2.2.5 update the denominator used for percentage of subjects whose symptoms have been significantly worse in the past month</p> <p>In Section 13.3.2.6 added the total number of doctor visits as well as the number and percentage of subjects with any visit to the doctor</p>

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### LIST OF ABBREVIATIONS

ACQ	Asthma control questionnaire
AE	Adverse event
AIC	Akaike's information criterion
ANCOVA	Analysis of covariance
ASS	Mean Asthma Symptom Score
BOCF	Baseline Observation Carried Forward
CGM	Computer Graphics Metafile
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CS	Combined Score
ENR	Enrolled population
ePRO	Electronic Patient Reported Outcome
FAS	Full Analysis Set
GINA	Global Initiative for Asthma
LOCF	Last Observation Carried Forward
LS	Least squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
ODS	Output Delivery System
PAC3	Post Administration Collection Period 3
PSQI	Pittsburg Sleep Quality Index
PT	Preferred Term
RMS	Rescue Medication Score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SAE	Serious adverse event
SAF	Safety
SAP	Statistical analysis plan
SOC	System Organ Class
TLF	Table, Listing, Figure
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TRSS	Total Rhinoconjunctivitis Symptom Score
WHO-DD	World Health Organization-Drug Dictionary

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WOCF	Worst Observation Carried Forward
WPAI:CIQ-AS	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific

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## 1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol CP007A as set out in the latest version of the output shells. 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 5 dated 08 December 2014.

## 2. STUDY OBJECTIVES

### 2.1. PRIMARY OBJECTIVE

The primary objective is to evaluate the continued efficacy of Cat-PAD, the first in a new class of Synthetic Peptide Immuno-Regulatory Epitopes, for a total of up to 5 years after the initial administration of treatment in Protocol CP007, based on the reduction of symptoms and the use of allergy medication in subjects previously participating in Protocol CP007.

### 2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the continued safety and tolerability of Cat-PAD for up to 5 years after the administration of treatment.
- To evaluate the effect of Cat-PAD on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) for up to 5 years after the administration of treatment.
- To evaluate the effect of Cat-PAD on the onset of asthma for up to 5 years after the administration of treatment.
- To evaluate the effect of Cat-PAD on asthma progression in subjects previously enrolled in CP007 with Global Initiative for Asthma (GINA) 1 asthma for up to 5 years after the administration of treatment.

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### 2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate the effect of Cat-PAD on changes in asthma control in asthmatic subjects for up to 5 years after the administration of treatment.
- To evaluate the effect of Cat-PAD on changes in sleep quality in adults using the Pittsburg Sleep Quality Index (PSQI) for up to 5 years after the administration of treatment.
- To evaluate the effect of Cat-PAD on changes in productivity using the Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI:CIQ-AS) for up to 5 years after the administration of treatment.
- To evaluate the effect of Cat-PAD on symptomatology on unplanned exposure to a cat in normal daily life in subjects who no longer keep a cat for up to 5 years after the administration of treatment.
- To evaluate the effect of Cat-PAD on health economic outcomes for up to 5 years after the administration of treatment.

### 2.4. SAFETY OBJECTIVES

The safety and tolerability of Cat-PAD is to be assessed by measurement/recording of adverse events (AEs) and serious AEs (SAEs).

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### 3. STUDY DESIGN

#### 3.1. GENERAL DESCRIPTION

This is an optional, prospective, follow-on study to a randomised, double-blind, superiority, multiple dose, placebo-controlled, parallel group, multi-centre, field study (CP007). Subjects from participating sites who complete the final Post Administration Collection Period (PAC3) in CP007 are to be invited to participate in CP007A.

The population is to be limited to those subjects in the CP007 study and hence the maximum number to be enrolled in this study is the number of subjects randomised in CP007 which was 1408 subjects.

No additional investigational product is to be administered. Subjects will have received one of the following three study drug regimens in study CP007:

- Single course of Cat-PAD [4 doses of Cat-PAD 6 nmol (one dose administered every 4 weeks), followed by 4 doses of Placebo (one dose administered every 4 weeks), 4 x 6 nmol]
- Two courses of Cat-PAD [8 doses of Cat-PAD 6 nmol (one dose administered every 4 weeks), 8 x 6 nmol]
- Placebo [8 doses of Placebo (one dose administered every 4 weeks)]

In CP007, Cat-PAD and/or Placebo doses were administered every 4 weeks ( $\pm 2$  days) for 28 weeks (2 x 4 doses per subject).

Where possible, enrolment for CP007A is to occur at the same time as the final Follow-Up Visit as scheduled in CP007. Subjects who consent to take part in this study and who meet all inclusion/exclusion criteria are to be issued with paper diary binders and a digital pen (ePRO) or mobile phone to record the required subject reported outcomes data.

Subject reported outcomes are to comprise of monthly and annual evaluations.

On a monthly basis, subjects are to record information regarding:

- Hospital/doctor visits
- Lost work/school days
- Changes in home environment
- Exposure to cat

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- Global assessment of symptoms to cat exposure (only for subject no longer living with an indoor cat)
- Asthma progression
- Concomitant medication

The annual Allergy Evaluation Period for CO007A is defined as a 3-week (21 day) period, taking place at the same time of year as the 3-week Baseline Allergy Evaluation visit in CP007 (Visits 2A and 2B) and is to include:

- At the start of the 3-week Allergy Evaluation Period
  - o Diagnosis of asthma
- Daily recording for 3 weeks
  - o Rhinoconjunctivitis symptoms
  - o Asthma symptoms
  - o Allergy medication use
  - o Exposure to indoor cat
- At the end of the 3-week Allergy Evaluation Period
  - o Change in geographic location
  - o 6-Question asthma control questionnaire (ACQ) excluding lung function (for asthmatics only)
  - o RQLQ
  - o PSQI (if at least 18 years old at the time of assessment)
  - o WPAI:CIQ-AS

Subjects are to have up to four study visits each year, two of which may be conducted by telephone. At each visit, site staff will record any AEs and SAEs, and at the on-site visits subjects are to be provided with their next diary binder.

Subjects will have a final End of Study Visit, which will coincide with the end of the final annual Allergy Evaluation Period assessment.

The duration of this follow-up study is to be up to 4 years for each subject.

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### 3.2. SCHEDULE OF EVENTS

The schedule of events can be found in Section 6.1 of the Protocol.

## 4. PLANNED ANALYSES

There are four planned unblinded interim analyses.

The first analysis of the data is to be performed on the first year's data after all subjects have either

- Completed their year 1 annual assessment in CP007A
- Discontinued prior to their year 1 annual assessment
- Progressed beyond their year 1 annual assessment regardless of the completion of the assessment

Additional analyses of the second, third and fourth year in the study are to be performed for each relevant year based on the same criteria as above. Analysis of the later years will only be performed if there was a positive outcome in the previous years.

The Quintiles study team, including those responsible for creating the programs to produce the outputs for each analysis, will remain blinded. Once the programs have been produced by the blinded Quintiles study team, these programs are to be sent to an independent statistician at a different geographical location than the blinded team, who will apply the randomisation schedule and provide Circassia with a set of unblinded outputs each year.

Details on independent unblinded team members within Quintiles to perform the analysis and members within Circassia authorised to receive unblinded outputs are specified in a separate Unblinding Plan document.

### 4.1. FINAL ANALYSES

All final, planned analyses identified in this SAP are to be performed by Quintiles Biostatistics.

The following events are prerequisites for the production of any of the four interim analyses planned.

- Sponsor authorisation of the SAP and Table, Listing, Figure (TLF) shells
- Quintiles authorisation of final locked database snapshot

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For each interim analysis Quintiles Biostatistics will extract all data as entered in the relevant year's diary binder of each subject (there is a separate diary binder for each analysis year).

After cleaning (no outstanding data queries) of the relevant analysis year's data by DataMatica and authorisation by Quintiles Biostatistics as well as coding of all AEs and concomitant medications by Quintiles Coding, the final locked database snapshot for the relevant interim analysis (year 1, year 2, year 3 or year 4) is to be provided by DataMatica to Quintiles for the purpose of producing the interim analysis.

AEs entered in the Adverse Event Case Report Form (CRF) are to be cumulative and will not be assigned to a specific year for analysis.

- Sponsor authorisation of analysis sets

Prior to each interim analysis Quintiles Biostatistics will programmatically prepare listings of all subjects and their status with regards to inclusion or exclusion from each analysis population based on the definitions of each analysis population as described in [Section 5: Analysis Sets](#).

The listings are to be provided to Circassia for authorisation prior to each interim analysis.

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## 5. ANALYSIS SETS

Agreement and authorisation of subjects included/excluded from each analysis set is to be conducted annually prior to each year's interim analysis.

### 5.1. ENROLLED POPULATION [ENR]

The Enrolled population (ENR) will consist of all subjects who are consented into the study and subjects are to be listed and summarised by the treatment they were randomised to in study CP007.

### 5.2. FULL ANALYSIS SET [FAS]

The Full Analysis Set (FAS) will consist of all subjects who are consented into the study and have at least one day of symptom scores and rescue medication use recorded during the annual Allergy Evaluation Period of CP007A. Subjects are to be listed and summarised by the treatment they were randomised to in study CP007. The FAS population is to be re-assessed for each analysis year to account for subject drop-outs during each year.

### 5.3. MODIFIED INTENT TO TREAT POPULATION [MITT]

The modified Intent-to-Treat (mITT) population will consist of all subjects in the FAS who continue to live in a house with an indoor cat during the annual Allergy Evaluation Period. The mITT population is to be defined on an annual basis based on the subject's completion of the ePRO question as to whether the subject still lives in a house with an indoor cat. The mITT population may therefore change during the course of the study. Subjects are to be listed and summarised by the treatment they were randomised to in study CP007.

### 5.4. SAFETY POPULATION [SAF]

All subjects are to be included in the safety population. Safety data is to be listed and summarised by study medication actually received in study CP007.

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## 6. GENERAL CONSIDERATIONS

### 6.1. REFERENCE START DATE AND STUDY DAY

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

Reference start date is defined as the day of written informed consent for CP007A, (Day 1 is the day of informed consent), and will 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:

$$\text{Study Day} = (\text{date of event} - \text{reference date}) + 1.$$

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

$$\text{Study Day} = (\text{date of event} - \text{reference date}).$$

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

### 6.2. BASELINE

Subject data is to be obtained from the CP007 database and is used as Baseline data for CP007A.

Baseline for all efficacy variables listed in [Section 13.1](#): Primary Efficacy, [Section 13.2](#): Secondary Efficacy and [Section 13.3](#): Exploratory Efficacy is defined as the 3 week Baseline Allergy Evaluation period (Visit 2A to Visit 2B) before randomisation into study CP007.

For other Baseline characteristics Baseline is defined as follows:

- Age as entered on the Enrolment Visit CRF for CP007A
- Gender as collected at the CP007 Screening visit
- Ethnic group as collected at the CP007 Screening visit
- Asthma status as collected at the CP007 Screening visit

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### 6.3. STATISTICAL TESTS

All tests are two-sided, unless otherwise specified in the description of the analyses. The significance level for each analysis is specified in the relevant analysis section of the SAP.

### 6.4. COMMON CALCULATIONS

For quantitative measurements, change from Baseline is calculated as:

- Test Value at Year xx – Baseline Value

Percentage change from Baseline is calculated as:

- $[(\text{Test Value at Year xx} - \text{Baseline Value}) / \text{Baseline Value}] \times 100$

Denominator for percentages is either the total number of subjects in the analysis population or the number of subjects in the analysis population with data available for the applicable assessment and is specified in each analysis section.

### 6.5. SOFTWARE VERSION

All analyses are conducted using SAS® version 9.2 or higher.

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## 7. STATISTICAL CONSIDERATIONS

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

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

- Pooled site [Pooled Site 01,...,Pooled Site xx]
- Age group [Adolescents/Adults], assigned based on subject's age as entered on the Enrolment Visit CRF for CP007A
- Gender [Male/Female], as collected at the CP007 Screening visit
- Asthma status [Present/Absent], as collected at the CP007 Screening visit
- Baseline score [Represents the Baseline value of the relevant score being analysed], where Baseline is defined as in [Section 6.2](#): Baseline.

### 7.2. MULTICENTRE STUDIES

This study is to be conducted by multiple Investigators at multiple centres internationally.

If a centre has less than five subjects, pooling with other centre(s) is performed based on geographical region, and is to be completed and agreed with Circassia prior to unblinding.

### 7.3. MISSING DATA

Missing safety data will not be imputed.

Missing efficacy data is to be handled as described in [Section 13.1.3](#): Sensitivity Analysis of Primary Efficacy Variable.

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## 7.4. MULTIPLE COMPARISONS/MULTIPLICITY

For the primary hypothesis testing vs. Placebo a Bonferroni-Holm procedure is to be used to adjust alpha in order to compensate for multiplicity when comparing the two Cat-PAD treatment arms vs. Placebo, thereby keeping the overall type I error rate at 0.05. More detail on the procedure is described in [Section 13.1.2: Primary Analysis of Primary Efficacy Variable](#).

Multiple analyses are to be performed as specified in [Section 4: Planned Analyses](#). At each of the statistical analyses performed after one, two, three and four years, there is no adjustment to the significance level, apart from the Bonferroni-Holm correction (due to multiple treatment comparisons) stated above, because analysis of the later years will only be performed if there is a positive outcome in the previous years, and this is, therefore, a hierarchical analysis.

## 7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses are to be conducted for the primary analysis of primary efficacy variable only. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups. Subgroup analyses are only to be performed if there are at least 10 subjects in each category of the subgroup.

The following subgroups are to be assessed for the primary efficacy variable:

- Gender:
  - o Female
  - o Male
- Age (years):
  - o  $\geq 12$  to  $\leq 17$
  - o  $\geq 18$  to  $\leq 49$
  - o  $\geq 50$  to  $\leq 65$
  - o  $> 65$
- Ethnic group
  - o Caucasian
  - o Black
  - o Asian (Indian)
  - o Asian (Oriental)
  - o American Hispanic
- Asthma status

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- o Present
- o Absent

All subgroup variables above are from the same source as described in [Section 6.2](#): Baseline.

## 8. OUTPUT PRESENTATIONS

[APPENDIX 1](#): Programming conventions for outputs shows conventions for presentation of data in outputs.

The templates provided within this SAP describe the presentations for this study and therefore the format and content of the summary TLFs to be provided by Quintiles Biostatistics.

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## 9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent are to be accounted for in this study.

The number and percentage of subjects that signed informed consent to CP007A, failed any inclusion/exclusion criteria and were enrolled in the study are to be presented.

The specific inclusion/exclusion criteria not met is to be listed.

The frequency and percentage of subjects included in the FAS, mITT and SAF are to be presented.

Frequency and percentage of premature withdrawals from the study and reason for withdrawals will also be presented. Premature withdrawal from the study is defined as subjects who answered "No" to "Did the subject complete the study as planned?" on the End of Study/Withdrawal/Discontinuation Visit CRF.

## 10. PROTOCOL DEVIATIONS

Protocol deviations are to be tracked on an ongoing basis throughout the conduct of the CP007A Study. All subject deviations from the Protocol that are determined to be major are to be reported in a by subject listing.

## 11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other Baseline characteristics are to be presented for the ENR, FAS and mITT populations.

Continuous demographic and Baseline characteristic variables (e.g. Age) are to be summarised by treatment arm using descriptive statistics (n, mean, standard deviation (SD), median, minimum and maximum). Categorical variables (e.g. Gender) are to be summarised by frequency (n) and percentage (%). The denominator for the percentages is the total number of subjects in the population treatment arm with data available.

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

The following demographic and other Baseline characteristics are to be reported for this study and are from the same source as described in [Section 6.2](#): Baseline:

- Age (Years)
- Age group (Years), categorised as  $\geq 12$  to  $\leq 17$ ,  $\geq 18$  to  $\leq 49$  and  $\geq 50$  to  $\leq 65$

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- Age group, categorised as adolescents or adults, where adolescents are defined as subjects with age  $\geq 12$  and  $< 18$  years and adults are defined as subjects  $\geq 18$  years of age
- Gender [Male/Female]
- Ethnic group [Caucasian/Black/Asian (Indian)/Asian (Oriental)/American Hispanic]
- Asthma status [Absent/Present]

## 12. MEDICATIONS

Medications are to be presented by generic name and are coded using World Health Organization-Drug Dictionary (WHO-DD) Version 01-Mar-2016.

The summaries are to be sorted by descending frequency of the total number of subjects for each generic name.

Medications are to be presented separately for medications taken outside the annual Allergy Assessment Period and medications taken during the annual Allergy Assessment Period.

### 12.1. MEDICATION USE OUTSIDE ANNUAL ALLERGY ASSESSMENT PERIOD

Medication use outside of the annual Allergy Assessment Period is to be presented for the SAF population.

Medications outside of the annual Allergy Assessment Period are defined as any medications entered on the Medicines page of the monthly diary binder.

### 12.2. MEDICATION USE DURING THE ANNUAL ALLERGY ASSESSMENT PERIOD

Medication use during the annual Allergy Assessment Period is to be presented for the FAS.

Allergy medications during the annual Allergy Assessment Period are defined as any medications entered on the “Allergy Medicines that You Have Taken in the Past 21 Days” page of the annual Allergy Assessment Period diary binder.

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## 13. EFFICACY OUTCOMES

### 13.1. PRIMARY EFFICACY

#### 13.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the daily Combined Score (CS) of the 3-week annual Allergy Assessment Period completed after Year 1 to Year 4 in the subject's annual assessment diary binder.

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 the primary analysis, for each subject the mean of the daily non-missing CS during the annual Allergy Assessment Period is to be calculated as follows:

- $Sum(\text{Day 1 CS to Day 21 CS}) / \text{Number of non-missing days}$

The mean CS is to be calculated over the 21 days of the annual Allergy Assessment Period for each subject based on the data available for the non-missing days if a subject does not complete the whole annual assessment period.

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

For each symptom, the subject will rate (on a daily basis for the duration of the Allergy Assessment Period) the severity as follows:

0 = absent

1 = mild, barely noticeable

2 = moderate, annoying/troublesome

3 = severe, very annoying/very troublesome

The TRSS will 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 + Sore Eyes.

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Allergy medications are to be provided to subjects to be used according to a pre-specified Allergy Medication Plan (Appendix 1 in Protocol). The use of allergy medications are to be scored based on Didier (Didier *et al*, 2009) as follows:

- RMS = 0; no allergy 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.

If any of the eight individual TRSS, namely sneezing, runny nose, blocked nose, itchy nose, itchy eyes, watery eyes, red eyes or sore eyes 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 will also be considered missing.

### 13.1.2. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

The primary objective of this study is to test the hypothesis that there is a difference between either or both Cat-PAD treatment arms and the Placebo arm.

The primary efficacy analysis is to be performed for the FAS.

The least squares (LS) mean difference in mean CS between treatment arms, along with 95% two-sided CIs and p-value are to be estimated by fitting an analysis of covariance (ANCOVA) model, adjusting for the stratification factors listed in [Section 7.1: Adjustments for Covariates and Factors to be Included in Analyses](#).

Additionally, the LS mean and 95% CI for the CS at the CP007 study endpoint of PAC3 is to be calculated for the CP007A FAS subjects using the same ANCOVA. The LS mean and 95% CI is to be presented by treatment arm.

The Bonferroni-Holm procedure is to be utilised to assess each of the two treatment comparisons (two courses of Cat-PAD vs. Placebo and one course of Cat-PAD vs. Placebo), whereby the smallest p-value (of the two treatment comparisons) is to be tested at the 0.05/2 (i.e.  $p < 0.025$ ) alpha level. If this first comparison is statistically significant then the remaining treatment comparison p-value is to be tested at the 0.05 alpha level. The study is to be declared a success if one or more

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treatment arms are statistically significantly different from Placebo.

The differences in LS means for each treatment comparison of active vs. Placebo together with the corresponding two-sided 95% CI and the p-values are to be presented. Additionally p-values are to be calculated and presented for all model effects.

The ratio of LS means along with its 95% CI (calculated by using Fieller's method) is to be presented for evaluation of the clinical significance of active treatment vs. Placebo comparisons.

The primary efficacy variable is also to be analysed for subgroups as specified in [Section 7.5: Examination of Subgroups](#), using a simplified ANCOVA including treatment arm as main effect and Baseline CS as covariate. Subgroup analyses are not to utilize the Bonferroni-Holm procedure to assess each of the two treatment comparisons (two courses of Cat-PAD vs. Placebo and one course of Cat-PAD vs. Placebo). Each treatment comparison p-value is to be tested at the 0.05 alpha level.

Observed and change from Baseline values are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm.

A waterfall plot of the percentage change from Baseline in CS for each individual subject is to be plotted for each treatment arm.

The analyses are to be repeated for the mITT population.

### **13.1.3. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)**

For sensitivity analyses the mean of the daily CS during the annual Allergy Assessment Period is to be calculated after imputation of the missing daily CS using the following three methods respectively:

- If valid data for any given day in the 3-week period is not available for a particular subject for a particular day, the previous day's CS (if complete) is to be carried forward by using Last Observation Carried Forward (LOCF) to impute the missing value. If the previous day's CS is not complete, the most recent complete CS is to be used.
- For a worst-case sensitivity analysis (WOCF), missing CS data for a particular day is to be imputed as the worst (highest) CS in the 3-week assessment period for that subject.
- Baseline Observation Carried Forward (BOCF) imputation of missing daily CS using the Baseline mean daily CS.

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For each annual assessment period all 21 days of symptom score recording is to be populated using each of the 3 methods detailed above, that is, if a subject has less than 21 days of valid symptom scores, the CS is to be populated for the full period of 21 days.

Using the imputed data (from each imputation method respectively) the LS mean difference in mean CS between treatment arms, along with 95% two-sided CIs and p-value are to be estimated using the same ANCOVA as for the primary efficacy variable as described in [Section 13.1.2: Primary Analysis of Primary Efficacy Variable](#).

As an additional sensitivity efficacy analysis of the primary efficacy variable the missing at random (MAR) assumption will hold for daily CS and the treatment effect is to be estimated using a Mixed Model Repeated Measures (MMRM) of the CS at each day of the annual Allergy Assessment Period, for the FAS and mITT populations.

In MAR the probability of an observation being missing depends only on observed measurements. This assumption implies that the behaviour of the missing observations can be predicted from the observed variables, and therefore a response can be estimated without bias using exclusively the observed data without any imputation of the missing days.

The MMRM will include all stratification factors as specified in [Section 7.1: Adjustments for Covariates and Factors to be Included in Analyses](#).

The following covariance structures will be used to estimate the within-patient errors in preliminary analyses:

- Unstructured
- Spatial power
- Heterogeneous Toeplitz
- Heterogeneous compound symmetric
- Simple structures with and without heterogeneous variances by visit

A different covariance structure is to be used for each treatment group if deemed appropriate. This is to be tested by fitting each of the aforementioned covariance structures, with- and without a GROUP statement where GROUP = treatment (see SAS code below). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC) (covariance structure with the lowest value), is to be selected as the covariance structure for the primary analysis. Type III sum-of-squares for the LS means is to be used.

The following SAS code is to be used:

```
PROC MIXED data=<input dataset> IC INFO METHOD = TYPE3;  
  CLASS subject treatment pooled_site age_group gender asthma_status;  
  MODEL CS = baseline treatment pooled_site age_group gender asthma_status /
```

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**DDFM** = kr;  
**ESTIMATE** 'Cat-PAD2 vs Placebo' treatment 1 0 -1 / **CL**;  
**REPEATED** day / **SUBJECT**=subject /\***GROUP**=treatment\*/  
**TYPE**= <covariance structure option>;

**RUN**;

Appropriate ESTIMATE statements will be added for the comparisons of Cat-PAD1 vs Placebo as well as Cat-PAD2 vs Cat-PAD1.

#### **13.1.4. NORMALITY AND HOMOGENEITY OF PRIMARY EFFICACY VARIABLE**

The residuals from the primary efficacy ANCOVA as well as the sensitivity analysis MMRM are to be checked for normality and homogeneity of variance. Normality is to be examined by normal probability plots, while homogeneity of variance will 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 or using an appropriate alternative transformation (such as logarithmic or power transformation) of the data.

## **13.2. SECONDARY EFFICACY**

### **13.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS**

#### **13.2.1.1. Mean Total Rhinoconjunctivitis Symptom Score (TRSS)**

The daily TRSS is to be derived as described in [Section 13.1.1: Primary Efficacy Variable & Derivation](#).

The mean of the daily TRSS for each annual Allergy Assessment Period is to be calculated over all days with complete data.

#### **13.2.1.2. Mean Component Scores of Total Rhinoconjunctivitis Symptom Score (TRSS)**

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 to 12. The TNSS is to be calculated on each day as follows:

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

Mean TNSS is to be calculated for each annual Allergy Assessment Period over all days with complete data.

- Total Ocular Symptom Score (TOSS)

The TOSS is the sum of four individual ocular symptoms: itchy eyes, watery eyes, red eyes and sore eyes. The TOSS will have a range of 0 to 12. The TOSS is to be calculated on each day as follows:

TOSS = Itchy Eyes + Watery Eyes + Red Eyes + Sore Eyes.

Mean TOSS is to be calculated for each annual Allergy Assessment Period over all days with complete data.

#### 13.2.1.3. Rescue Allergy Medication Score (RMS)

The daily RMS is to be derived as described in [Section 13.1.1: Primary Efficacy Variable & Derivation](#). The mean of the daily RMS for each annual Allergy Assessment Period is to be calculated over all days with complete data.

#### 13.2.1.4. Mean Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) Score

The self-administered RQLQ with Standardised Activities for 12 years and older (RQLQ(S)  $\geq 12$ ) is to be used in this study.

The RQLQ will be completed as a once off assessment at the end of the annual Allergy Assessment Period.

The RQLQ has 28 questions in seven domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional). Refer to [APPENDIX 2: 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.

The domains are defined as follows:

- Activities: Questions 1 to 3
- Sleep: Questions 4 to 6
- Non-nose/eye symptoms: Questions 7 to 13

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- Practical problems: Questions 14 to 16
- Nasal symptoms: Questions 17 to 20
- Eye symptoms: Questions 21 to 24
- Emotional: Questions 25 to 28

#### 13.2.1.5. Asthma evaluations

- Mean Asthma Symptom Score (ASS)

The ASS has six questions which are answered daily by the subject for each annual Allergy Assessment Period. All subjects are to indicate how they have been in the past 24 hours with regards to:

- Coughing
- Wheezing
- Shortness of breath

In addition, for subjects with asthma 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 four point scale (0 to 3) for each question. For cough, wheezing and shortness of breath symptoms the subject will 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 will rate the severity as follows:

0 = not limited

1 = very slightly limited

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2 = slightly limited

3 = moderately limited or worse

For nocturnal symptoms or awakenings due to asthma the subject will 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  $\beta_2$  agonist treatments the subjects will 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 the six relevant questions (for subjects with asthma) or the mean of the three relevant questions (for all other subjects (including subjects with asthma)) separately. For the analysis of all subjects (including subjects with asthma) only the symptoms coughing, wheezing and shortness of breath are to be used in the calculation of the ASS.

The mean of the daily ASS for each annual Allergy Assessment Period is to be calculated over all days with complete data.

Subjects are to be classified as having asthma based on the subjects Asthma Progression eDiary response to the question, 'Are you diagnosed with asthma?'. The response to the last monthly assessment prior to each year's annual allergy assessment is to be used to classify subjects as either asthmatic (response of 'Yes') or non-asthmatic (response of 'No').

- Asthma onset and progression

On a monthly basis subjects will enter in their diary binders the following three questions related to asthma onset and progression:

- o Are you diagnosed with asthma
- o If yes, has your doctor prescribed stronger medicine
- o Have your symptoms have been significantly worse in the last month

Additionally, at the start of each annual Allergy Assessment Period subjects will indicate whether

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they have been diagnosed with asthma during the last year.

### 13.2.2. ANALYSIS OF SECONDARY EFFICACY VARIABLES

The secondary efficacy analysis is to be performed for the FAS.

#### 13.2.2.1. Mean Total Rhinoconjunctivitis Symptom Score (TRSS)

The LS mean difference in mean TRSS between treatment arms, along with 95% two-sided CIs and p-value are to be estimated using the same ANCOVA as for the primary efficacy variable as described in [Section 13.1.2: Primary Analysis of Primary Efficacy Variable](#) and presented in a similar manner, excluding the ratio of LS means and 95% Fieller's CI.

Additionally, the LS mean and 95% CI for the TRSS at the CP007 study endpoint of PAC3 is to be calculated for the CP007A FAS subjects using the same ANCOVA. The LS mean and 95% CI is to be presented by treatment arm.

The TRSS analysis is not to utilize the Bonferroni-Holm procedure to assess each of the two treatment comparisons (two courses of Cat-PAD vs. Placebo and one course of Cat-PAD vs. Placebo). Each treatment comparison p-value is to be tested at the 0.05 alpha level.

Observed and change from Baseline values are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm.

The analyses are to be repeated for the mITT population.

#### 13.2.2.2. Mean Component Scores of Total Rhinoconjunctivitis Symptom Score (TRSS)

The LS mean difference in mean TOSS and TNSS between treatment arms, along with 95% two-sided CIs and p-value are to be estimated using the same ANCOVA as for the primary efficacy variable as described in [Section 13.1.2: Primary Analysis of Primary Efficacy Variable](#) and presented in a similar manner, excluding the ratio of LS means and 95% Fieller's CI.

Additionally, the LS mean and 95% CI for the TOSS and TNSS at the CP007 study endpoint of PAC3 is to be calculated for the CP007A FAS subjects using the same ANCOVA. The LS mean and 95% CI is to be presented by treatment arm.

The TOSS and TNSS analyses are not to utilize the Bonferroni-Holm procedure to assess each of the two treatment comparisons (two courses of Cat-PAD vs. Placebo and one course of Cat-PAD vs. Placebo). Each treatment comparison p-value is to be tested at the 0.05 alpha level.

Observed and change from Baseline values are to be summarised by descriptive statistics (n,

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mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm.

The analyses are to be repeated for the mITT population.

#### 13.2.2.3. Rescue Allergy Medication Score (RMS)

The LS mean difference in mean RMS between treatment arms, along with 95% two-sided CIs and p-value are to be estimated using the same ANCOVA as for the primary efficacy variable as described in [Section 13.1.2: Primary Analysis of Primary Efficacy Variable](#) and presented in a similar manner, excluding the ratio of LS means and 95% Fieller's CI.

Additionally, the LS mean and 95% CI for the RMS at the CP007 study endpoint of PAC3 is to be calculated for the CP007A FAS subjects using the same ANCOVA. The LS mean and 95% CI is to be presented by treatment arm.

The RMS analysis is not to utilize the Bonferroni-Holm procedure to assess each of the two treatment comparisons (two courses of Cat-PAD vs. Placebo and one course of Cat-PAD vs. Placebo). Each treatment comparison p-value is to be tested at the 0.05 alpha level.

Observed and change from Baseline values are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm.

The analyses are to be repeated for the mITT population.

#### 13.2.2.4. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) Score

The LS mean difference in RQLQ total score between treatment arms, along with 95% two-sided CIs and p-value are to be estimated using the same ANCOVA as for the primary efficacy variable as described in [Section 13.1.2: Primary Analysis of Primary Efficacy Variable](#) and presented in a similar manner, excluding the ratio of LS means and 95% Fieller's CI.

Additionally, the LS mean and 95% CI for the RQLQ at the CP007 study endpoint of PAC3 is to be calculated for the CP007A FAS subjects using the same ANCOVA. The LS mean and 95% CI is to be presented by treatment arm.

The RQLQ analysis is not to utilize the Bonferroni-Holm procedure to assess each of the two treatment comparisons (two courses of Cat-PAD vs. Placebo and one course of Cat-PAD vs. Placebo). Each treatment comparison p-value is to be tested at the 0.05 alpha level. Observed and change from Baseline values are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm, for the total score as well as each domain.

The analyses are to be repeated for the mITT population.

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### 13.2.2.5. Asthma Evaluations

- Mean Asthma Symptom Score (ASS)

Mean ASS is to be summarised separately for:

- Subjects with asthma
- All subjects (including subjects with asthma)

Observed and change from Baseline values are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm.

- Asthma Onset and Progression

The number and percentage of subjects that answer “Yes” or “No” to each asthma progression question are to be presented for each monthly assessment and treatment arm.

The denominator for the percentage of subjects diagnosed with asthma as recorded at each month’s asthma assessment is the total number of subjects in the population treatment arm with data available.

The denominator for the percentage of subjects whose doctor has prescribed stronger medicine and whose symptoms have been significantly worse in the past month is the total number of subjects in the population treatment arm that are diagnosed with asthma at each relevant month’s asthma assessment.

The number and percentage of subjects that have been diagnosed with asthma in the past year are to be presented for each annual assessment and treatment arm.

The percentage of subjects diagnosed with asthma in the past year are to be compared between the two active treatments and Placebo by using a logistic regression model with pooled site, treatment as main effect and age group (adolescents, adults), gender, asthma status (present, absent) and Baseline CS as covariates. Odds ratios with 95% CI and p-values are to be presented for the individual treatment comparisons vs. Placebo.

The analysis is to be repeated for the mITT population.

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### 13.3. EXPLORATORY EFFICACY

#### 13.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

##### 13.3.1.1. The Pittsburgh Sleep Quality Index (PSQI)

The PSQI assesses sleep quality during the past month and is to be completed as a once off assessment by subjects at the end of each annual Allergy Assessment Period. It consists of 19 self-rated questions and five completed by a bed-partner/roommate. Refer to [APPENDIX 2: Complete Questionnaires](#), for the complete questionnaire. For the self-rated questions there are four questions about bed and sleep times and 15 questions (each scored in one of four categories) that elicit the quality of sleep.

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

Questions one through nine 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 one through nine have been answered.

In the event that a range is given for an answer (for example, '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 below:

Table 1 : Scoring Instructions		
Domain	Question (Q) Result or Algorithm	Analysis Value
Duration of Sleep	$Q4 > 7$	0
	$6 < Q4 \leq 7$	1
	$5 \leq Q4 \leq 6$	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
	$Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j \geq 1 \text{ and } \leq 9$	1
	$Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j \geq 10 \text{ and } \leq 18$	2
	$Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j \geq 19 \text{ and } \leq 27$	3
Sleep Latency	Step 1:	

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	If $0 \leq Q2 \leq 15$ then set $Q2 = 0$	
	If $15 < Q2 \leq 30$ then set $Q2 = 1$	
	If $30 < Q2 \leq 60$ then set $Q2 = 2$	
	If $Q2 > 60$ then set $Q2 = 3$	
	Step 2:	
	$Q5a + Q2 = 0$	0
	$1 \leq Q5a + Q2 \leq 2$	1
	$3 \leq Q5a + Q2 \leq 4$	2
	$5 \leq Q5a + Q2 \leq 6$	3
Day Dysfunction Due to Sleepiness	$Q8 + Q9 = 0$	0
	$1 \leq Q8 + Q9 \leq 2$	1
	$3 \leq Q8 + Q9 \leq 4$	2
	$5 \leq Q8 + Q9 \leq 6$	3

### 13.3.1.2. 6-Question Asthma Control Questionnaire (ACQ) Score

Asthmatic subjects are to complete the 6-Question ACQ at the end of each annual Allergy Assessment Period as a one off assessment. Refer to [APPENDIX 2: Complete Questionnaires](#), for the complete questionnaire.

The six ACQ questions are answered by the subject, stating how they have been in the past week with regards to five symptoms and the average daily use (the number of puffs/inhalations) of short-acting bronchodilator in the past week.

There is a 7 point scale (0 to 6) for each question where 0 represents optimum control and six represents the poorest control. The questions are equally weighted and the ACQ score is the mean of the six questions and therefore between 0 (totally controlled) and six (severely uncontrolled).

### 13.3.1.3. Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI:CIQ-AS)

The WPAI:CIQ-AS is to be completed at the end of each annual Allergy Assessment Period and consists of nine questions. Refer to [APPENDIX 2: Complete Questionnaires](#), for the complete questionnaire.

The WPAI:CIQ-AS consists of seven domains calculated as follows:

- Percent work time missed due to allergy;  $Q3/Q2 \times 100$

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- Percent impairment while working due to allergy;  $Q4/10 \times 100$
- Percent overall work impairment due to allergy;  $((Q3/Q2) + [(1 - (Q3/Q2)) \times (Q4/10)]) \times 100$
- Percent class time missed due to allergy;  $Q7/Q6 \times 100$
- Percent impairment in the classroom due to allergy;  $Q8/10 \times 100$
- Percent overall classroom impairment due to allergy;  $((Q7/Q6) + [(1 - (Q7/Q6)) \times (Q8/10)]) \times 100$
- Percent activity impairment due to allergy;  $Q9/10 \times 100$

The outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. If any questions within a domain are missing, the domain value will also be missing.

#### 13.3.1.4. Environmental Changes and Global Assessment of Symptom Severity

On a monthly basis subjects will provide information on changes to their home environment via six questions in the diary binder:

- Any changes to number of cats in your home?
- Have you been to a house in the last month where there is a cat?
- Significant change to the number of hours spent in a house with a cat?
- Have the cats in your home been spending more time outside?
- Any significant changes in your exposure to cat(s)?
- Any significant changes to your home furnishings?

The global assessment of symptoms is only applicable to subjects that no longer keep a cat. On a monthly basis, if these subjects had some unplanned exposure to a cat in normal daily life, the subject will rate his/her symptoms in the following categories:

- Absent
- Mild, Barely noticeable
- Moderate, Annoying/troublesome

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- Severe, Very annoying/Very troublesome

#### 13.3.1.5. Monthly Days Off School/Work

On a monthly basis subjects will enter in their dairy binders the total number of days that either school or work was missed due to allergic Rhinoconjunctivitis symptoms during the past month.

#### 13.3.1.6. Hospital/Doctor Office Visits

On a monthly basis subjects will enter in their dairy binders the dates of doctor/hospital visits as well as the date of entry and discharge from the hospital, if applicable, during the past month.

The length of stay in hospital per hospital visit is to be calculated as follows:

- Length of Stay (weeks) = [(Date of discharge – Date of entry + 1)] / 7.

### 13.3.2. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

The exploratory efficacy analysis is to be performed for the FAS.

#### 13.3.2.1. The Pittsburgh Sleep Quality Index (PSQI)

Observed and change from Baseline values for the overall and component scores of the PSQI are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm.

#### 13.3.2.2. 6-Question Asthma Control Questionnaire (ACQ) Score

Observed and change from Baseline values for the ACQ score are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm for subjects with a history of asthma as assessed at the Screening visit of the CP007 study.

#### 13.3.2.3. Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI:CIQ-AS)

Observed values for the seven WPAI:CIQ-AS component scores are to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each annual Allergy Assessment Period and treatment arm.

The number and percentage of subjects that are either currently working (question 1) or currently students (question 5) are to be presented. The denominator for the percentages is the total number of subjects in the population treatment arm with data available.

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#### 13.3.2.4. Environmental Changes and Global Assessment of Symptom Severity

The number and percentage of subjects that answer “Yes” or “No” to each home environment question and fall within each of the symptom severity categories are to be presented for each monthly assessment and treatment arm.

The percentages for global assessment of symptom severity categories are to be calculated relative to the number of subjects in the relevant population that answered “Yes” to “Have you been to a house in the last month where there is a cat?” at each month.

A p-value for the difference in global assessment of symptom severity between treatment arms is to be calculated using the Cochran-Mantel-Haenszel (CMH) row mean score difference for all subjects that no longer keep a cat and presented for each treatment arm vs. Placebo.

#### 13.3.2.5. Monthly Days Off School/Work

The number of days that either school or work was missed due to allergic Rhinoconjunctivitis symptoms is to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each month and treatment arm.

#### 13.3.2.6. Hospital/Doctor Office Visits

The total number of hospitalisations as well as the number and percentage of subjects hospitalised are to be presented for each monthly assessment and treatment arm.

The length of stay of visits is to be summarised by descriptive statistics (n, mean, SD, median, minimum and maximum) for each monthly assessment and treatment arm.

Similarly, the total number of doctor visits as well as the number and percentage of subjects with any visit to the doctor are to be presented for each monthly assessment and treatment arm.

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## 14. SAFETY OUTCOMES

All outputs for AEs are to be based on the Safety population.

There are to be no statistical comparisons between the treatment arms for safety data, unless otherwise specified with the relevant section.

### 14.1. ADVERSE EVENTS

AEs are to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

AE reporting begins from signed informed consent and ends when the subject completes the study or withdraws.

An AE is any untoward medical occurrence. An AE can therefore be any unfavourable and unintended sign, symptom or disease.

An overall summary of number of subjects (n), percentage of subjects (%) and total number of mentions (m) within each of the following categories is to be presented:

- Any AE
- Any AE by maximum severity
- Any AE by strongest relationship
- Any AE leading to premature withdrawal from the study
- Any serious AE
- Any AE leading to death

Listings will include all AEs.

#### 14.1.1. ALL AEs

Incidences of AEs are to be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and strongest relationship to study medication.

##### 14.1.1.1. Severity

Severity is classed as mild/moderate/severe (increasing severity). AEs with a missing severity are

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to be classified as severe. If a subject reports an AE more than once within that SOC/PT, the AE with the worst-case severity is to be used in the corresponding severity summaries.

#### 14.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as not related/ unlikely to be related/ related (increasing severity of relationship). AEs 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 strongest relationship to study medication is to be used in the corresponding relationship summaries.

#### 14.1.2. AEs LEADING TO WITHDRAWAL FROM STUDY

AEs leading to withdrawal from the study are to be identified on the Adverse Events CRF as events with an action taken of “Subject withdrawn because of this event”.

For AEs leading to withdrawal from study, summaries of incidence rates (frequencies and percentages) by SOC and PT are to be presented.

#### 14.1.3. SERIOUS ADVERSE EVENTS

SAEs are those events recorded as “Serious” on the Adverse Events CRF. A summary of SAEs by SOC and PT is to be presented.

#### 14.1.4. ADVERSE EVENTS LEADING TO DEATH

AEs leading to Death are those events with a recorded outcome of “Death” on the Adverse Events CRF. A summary of AEs leading to death by SOC and PT is to be presented.

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## 15. REFERENCES

*CP007A Protocol Version 5 (Incorporating Protocol Amendment 01, 02, 03 and 04) dated 08 Dec 2014.*

*CP007 Statistical Analysis Plan Final Version dated 08 June 2016.*

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:

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

Hogan, J., & Laird, N. (1997). Mixture models for the joint distribution of repeated measures and event times. *Statistics in Medicine* , 239-258.

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## APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

### QUINTILES OUTPUT CONVENTIONS

#### OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (eg T14\_3\_01\_1.RTF)

#### PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.

The page orientation should be landscape.

Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

The number of columns per page (linesize) should be 145 for A4.

The number of rows per page (pagesize) should be 49 for A4.

#### FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No **bolding**, underlining *italics* or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.

Figures should have a default font of "Times Roman".

This can be achieved by using the following options in SAS:

```
goptions
```

```
gunit = pct
```

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cback = white

colors = (black)

hby = 2.4

ftext = "TimesRoman"

htext = 2.5

device = cgmof97l

gaccess = gsasfile;

filename gsasfile "....cgm";

#### HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
- The customer name and protocol number should appear in row 1 and 2, left-aligned
- The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in row 2, right aligned
- The output identification number should appear in row 3, centered
- The output title should start in row 4, centered
- The output population should appear in row 5, centered. The population should be spelled out in full, e.g. Intention-to-Treat in preference to ITT.
- Row 6 should be a continuous row of underscores (‘\_’) (the number of underscores should equal the linesize)
- Row 7 should be a blank line
- Mixed case should be used for titles
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (eg Vital Signs) followed by metric (eg Change from Baseline) e.g. Vital Signs – Change from Baseline.

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- Titles should not contain quotation marks or footnote references
- The column headings should be underlined with a row of underscores (‘\_’)
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered
- Column headings containing numbers should be centered
- Column headings should be in sentence case
- In general, the population count should appear in the column header in the form “(N=XXX)”
- “Statistic” should be the column header over n, Mean, SE, n (%) etc.
- As a rule, all columns should have column headings.

#### TABLE AND LISTING OUTPUT CONVENTIONS

##### General:

- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of AEs, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest AE, medication or history coming first.

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- The study drug should appear first in tables with treatment as columns
- In general, only present totals (across treatment arms) at Baseline/randomization, and do not present them post randomization, unless the customer specifically requests it.
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Pooled Site, Treatment, and Subject Number).
- Do not use superscripts and subscripts
- Exponentiation is to be expressed using a double asterisk, i.e., mm<sup>3</sup> is to be written as mm\*\*3.
- All variables that are output in the CRF (which have data present) should appear in the listings, along with all derived data appearing in the corresponding tables
- The width of the entire output should match the linesize

#### Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  - o Minimum and maximum: N
  - o Mean, median and CV%: N + 1
  - o SD: N + 2

#### Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

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- o 77 (100.0%)
- o 50 ( 64.9%)
- o 0 ( 0.0%)

Missing category for categorical data is only to be presented if there is missing data for a specific category and percentage will not 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

- Percentages are to be reported to one decimal place, except percents <100.0% but >99.9% is to be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% is to be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding is applied after the <0.1% and >99.9% rule.

- o Eg (<0.1%)
- o ( 6.8%)
- o (>99.9%)

Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).

- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals (CIs):

- As a rule CIs are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- CIs should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence CIs should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

- o (-0.12, -0.10)

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o ( 9.54, 12.91)

#### P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 are to be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 are to be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding is applied after the <0.001 and >0.999 rule

#### Ratios:

- Ratios should be reported to one more decimal place than the original data.

#### Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

#### Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

#### Missing values

- A "0" should be used to indicate a zero frequency.
- A blank is to be used to indicate missing data in an end-of-text table or subject listing.

#### FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
- The CGM file itself should contain the title or footer.
- The image should be clear and of high quality when viewed in the Word document, and when printed.
- In general, boxes around the figures should be used.

#### FOOTNOTE INFORMATION

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Footers should be defined as follows:

- A continuous line of underscores ('\_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
- Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
- The program path and name and version number (if applicable) should appear as footnote 1 at the bottom of the page
- The date/time stamp should appear as footnote 2 at the bottom of the page
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only “typewriter” symbols are permitted – eg “\*”, “\$”, “#”, “@”, “&” and “+”.
- The choice of footnote symbols should be consistent. E.g. if you have the footnote “# indicates last observation carried forward” for one table, the same symbol and footnote should indicate LOCF for all tables.

Ordering of footnotes should be as follows:

- 1.) Source data listing reference, if necessary
- 2.) Abbreviations and definitions
- 3.) Formulae
- 4.) P-value significance footnote
- 5.) Symbols
- 6.) Specific notes

- Common notes from table to table should appear in the same order.
- The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

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## DATES

Depending on data available, dates will take the form DDMMYYYY.

## SPELLING FORMAT

English UK.

## PRESENTATION OF TREATMENT GROUPS

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

Treatment Group	For Tables, Graphs and Listings
Placebo [8 doses of Placebo (one dose administered every 4 weeks)]	Placebo
Single course of Cat-PAD [4 doses of Cat-PAD 6 nmol (one dose administered every 4 weeks), followed by 4 doses of Placebo (one dose administered every 4 weeks) ]	Cat-PAD 4x6 nmol
Two courses of Cat-PAD [8 doses of Cat-PAD 6 nmol (one dose administered every 4 weeks)]	Cat-PAD 8x6 nmol

## PRESENTATION OF VISITS

For outputs, visits are to be represented as follows:

<b>Annual Assessment</b>
Year xx, where xx = 01 to 04
<b>Monthly Assessment</b>
Month xx, where xx = 01 to 12

## LISTINGS

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

- Pooled Site

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- Randomised treatment group (or treatment received if it's a safety output), first by control/placebo and then by dose group (Cat-PAD 4x6 nmol, Cat-PAD 8x6 nmol).
- Subject ID
- Date (where applicable)

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## APPENDIX 2. COMPLETE QUESTIONNAIRES

### Rhinoconjunctivitis Quality of Life Questionnaire (S) Self-administered $\geq 12$

01. REGULAR ACTIVITIES AT HOME AND AT WORK/ SCHOOL (tasks that you have to do regularly at work/school 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

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23. Sore eyes
24. Swollen eyes
25. Frustrated
26. Impatient or restless
27. Irritable
28. Embarrassed by your symptoms

#### Asthma Control Questionnaire

01. On average, during the past week, how often were you woken by your asthma during the night?
02. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?
03. In general, during the past week, how limited were you in your activities because of your asthma?
04. In general, during the past week, how much shortness of breath did you experience because of your asthma?
05. In general, during the past week, how much of the time did you wheeze?
06. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator (eg. Ventolin/Bricanyl) have you used each day?

#### 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

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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

Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions:  
Allergy Specific

01. Are you currently employed (working for pay)? (If NO, check “NO” and skip to question 5.)

02. In general, how many hours per week do you usually work?

03. During the past seven days, how many hours did you miss from work because of problems associated with your allergies? Include hours you missed because you were sick, times you went in late, left early, etc. because you were experiencing problems with your allergies. (Do not include time you missed to participate in this study.)

04. During the past seven days, how much did allergies affect your productivity while you were

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working? Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If allergies affected your work only a little, choose a low number. Choose a high number if allergies affected your work a great deal.

05. Do you currently attend classes in an academic setting (middle school, high school, college, graduate school, additional course work, etc.)? (If NO, check “NO” and skip to question 9.)

06. In general, how many hours per week do you usually attend classes?

07. During the past seven days, how many hours did you miss from class or school because of problems associated with your allergies? (Do not include time you missed to participate in this study.)

08. During the past seven days, how much did allergies affect your productivity while in school or attending classes in an academic setting? Think about days your attention span was limited, you had trouble with comprehension or days in which you could not take tests as effectively as usual. If allergies affected your productivity at school or in class only a little, choose a low number. Choose a high number if allergies affected your productivity a great deal. (Cross a number.)

09. During the past seven days, how much did your allergies affect your ability to do your regular daily activities, other than work at a job or attend classes? By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If allergies affected your activities only a little, choose a low number. Choose a high number if allergies affected your activities a great deal. (Cross a number.)

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