# Topical rVA576 for TReatment of AtopiC KERatoconjunctivitis: a Randomised Placebo Controlled Double Masked Parallel Trial (TRACKER)

## Akari Therapeutics Plc Study No: AK701
## Syne qua non Ltd Study No: TNS18002

# Statistical Analysis Plan

**Version: Final 4.0**

**Date: 12 July 2021**

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**For Akari Therapeutics Plc**

*If signing manually, please include: Signature + Date + Full Name + Position*

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# Modification History

| Version | Change History | Reason | Date |
|---|---|---|---|
| 1.0 | First Version | N/A | 27 FEB 2020 |
| 2.0 | 1. Clarification of outputs to be produced for Part 1<br>2. Update to baseline definition to account for non-compliance of treatment schedule<br>3. Update to derivation of post-inhillation comfort scores to account for missing data and clarification of average score derivation | Updates made following review of dry run outputs. | 15 JUN 2021 |
| 3.0 | 1. Update to medication presentation to remove separate background medication summaries and listings.<br>2. Update to the definitions of compliance calculations | Updates made following review of data cleaning. | 22 JUN 2021 |
| 4.0 | 1. Summaries of efficacy endpoints by indication group added. | Further updates made following review of dry run output and clinical consideration. | DDMMMYYYY |

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AIC | Akaike Information Criterion |
| AKC | Atopic Keratoconjunctivitis |
| ATS | All Treated Set |
| CRF | Case Report Form |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FAS | Full Analysis Set |
| LLOQ | Lower Limit of Quantification |
| LS | Least Squares |
| LTB4 | Leukotriene B4 |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMP-9 | Matrix Metalloprotease 9 |
| PAC | Perennial Allergic Conjunctivitis |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PT | Preferred Term |
| RAN | All Randomised Patients |
| SAC | Seasonal Allergic Conjunctivitis |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| TBUT | Tear Film Break Up Time |
| VKC | Vernal Keratoconjunctivitis |
| WHO Drug | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

This document details the statistical analysis of the data that will be performed for the Akari Therapeutics Plc study: Topical rVA576 for TReatment of Atopic KERatoconjunctivitis: a randomised placebo controlled double masked parallel trial (TRACKER).

The proposed analysis is based on the contents of Version 8.0 of the protocol (dated 10th February 2020). In the event of future amendments to the protocol, this statistical analysis plan (SAP) may be modified to account for changes relevant to the statistical analysis.

The table, listing and figure shells are supplied in a separate document.

Comparison of the conjunctival impression cytology results will be done for qualitative research information and will not form part of this statistical analysis plan.

# 2 STUDY OBJECTIVES AND DESIGN

## 2.1 Study Objectives

The primary objective of Part 1 and Part 2 of the study is to demonstrate the safety and tolerability of rVA576 (nomacopan) when given by topical ocular administration to patients with atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC) and severe allergic conjunctivitis (seasonal allergic conjunctivitis (SAC) or perennial allergic conjunctivitis (PAC)).

An additional objective for the first 3 patients (Part 1) is to allow the Principal Investigator (PI) and independent clinician to assess the patients' ability to use the eye dropper and vials correctly.

The secondary objective of Part 2 of the study is to demonstrate efficacy in this patient population, specifically to assess whether nomacopan 0.25% eye drops solution is effective in mitigating the signs and symptoms of AKC, VKC, and severe allergic conjunctivitis (SAC or PAC) and whether they have any effect on markers of inflammation.

## 2.2 Study Endpoints

The primary endpoint of the study is:

- Incidence of ocular treatment emergent adverse events during the treatment period. The adverse events (AEs) which have occurred during the 56 days following randomisation (Part 2 of the study only) will be considered in the analysis of the primary safety outcome.

The secondary endpoints are:

- Post-instillation comfort, as graded on patient diary cards at the following intervals: Days 1 to 14, 15 to 28, 29 to 42 and 43 to 56
- Visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS) charts comparison from Day 1 to Day 56
- Change from Day 1 in composite clinical scores (including Symptom and Sign subcomponents) at Day 14, 28, 42 and 56

- Number and percentage of patients with Matrix metalloprotease 9 (MMP-9) < 40 ng/mL and ≥ 40 ng/mL assessed using Inflamma Dry (Quidel) device at Days 1, 28 and 56
- Change from Day 1 in Tear film break up time (TBUT) at Day 14, 28, 42 and 56

The exploratory endpoints are:

- Systemic absorption by blood sampling
- If enough tear fluid can be collected analysis of complement C3, C5 and leukotriene B4 (LTB4) will be performed
- A comparison of the number of patients requiring rescue therapy at any stage of the trial and the number on such therapy at the end of the trial

## 2.3 Study Design

This will be a multi-centre study in two parts. The target patient population comprises male and female patients above the age of 18 with moderate to severe AKC, VKC and severe allergic conjunctivitis (SAC or PAC).

Part 1: The first 3 patients selected for the study will be treated with active drug in an open-label manner. They will have weekly clinic visits for the first 2 weeks and thereafter biweekly visits. When the third of the first 3 patients has completed their first 2 weeks treatment, the PI and independent clinician will review the safety, tolerability and ease of application for each patient before deciding to proceed to the randomised, double-masked comparative phase of the study (Part 2). The 3 patients will continue on the study and complete the 8 weeks trial as open label patients.

Part 2: A randomised, double-masked, placebo controlled, parallel group trial of topical rVA576 or placebo eye drops in moderate to severe AKC, VKC and severe allergic conjunctivitis (SAC or PAC). The Part 2 trial population will comprise 16 patients who meet the inclusion and exclusion criteria (Section 4.1 and 4.2 of protocol). Patients will have a screening visit and 4 visits occurring every 2 weeks over 8 weeks.

## 2.4 Visit Structure

The visit structure and scheduled assessments are detailed in protocol section 6.7 (visit structure) and protocol section 17.2 (schedule of events and blood draws).

# 3 SAMPLE SIZE

Up to 19 patients, 3 active in Part 1 of the study and up to 16 randomised to active or placebo in Part 2, will be enrolled under this protocol. The sample size for this study was determined based on practical, and not statistical, considerations.

# 4 RANDOMISATION

Patients will only be randomised in Part 2 of the study. They will be randomised in a 1:1 fashion. There will be no stratification.

# 5 INTERIM ANALYSIS & REPORTING OF PART 1

No interim analysis is planned.

The decision to proceed to Part 2 will be determined through PI and an independent clinician review of the data for the first three patients up until the time that the third patient has completed the second week of the study. Medical History, Adverse Event, Concomitant Medication and Compliance data will be reviewed via the clinical database. A trend analysis will be carried out for the adverse events. No statistical outputs will be produced at this time, but the patients from Part 1 will be included in the same patient listings as for Part 2 as a separate group. Should the study be discontinued after Part 1, the listings described in the sections below will be produced for Part 1 only. The summary tables and figures described in the following sections relate to Part 2 only unless otherwise stated.

# 6 ANALYSIS PLAN

## 6.1 General

Summary statistics for continuous variables will consist of number of non-missing observations (n), mean, standard deviation (SD), minimum, 25$^{th}$ percentile, median, 75$^{th}$ percentile and maximum, unless specified otherwise. The precision of these variables is defined in the table, figure and listing shells document.

For categorical variables the number and percentage of patients in each category will be presented, based on the number of non-missing observations apart from disposition of patients, protocol deviations, background and demographic characteristics, prior and concomitant medications/procedures and adverse events where the percentage will be based on the number of patients in the analysis set.

Any statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. The null hypothesis at all times will be that the treatments are equivalent. All comparisons between the treatments will be reported with 95% confidence intervals for the difference.

## 6.2 General Derivations

This section provides details of general derivations. Detailed descriptions of specific parameter derivations are provided later in the SAP.

- Definition of baseline

The Baseline value will be defined as the pre-dose value on Day 1, if that is missing or the first administration is not on Day 1, it will be defined from the most recent value available and recorded prior to the first administration of study treatment.

- Incomplete dates

For calculation purposes, incomplete dates will be completed using worst case, the most conservative value possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations. If day is

missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

- Methods for handling withdrawals and missing data

There will be no imputation of missing data. Screening data will be used if baseline is missing.

Statistical testing and graphical presentations will not be carried out for any given score or measurement if there are less than 5 results, for either the placebo or active group, for that score or measurement at any single time point.

## 6.3 Analysis Sets

The **Enrolled Set** includes all patients who passed screening irrespective of whether they received the study treatment.

The **All Treated Set** (ATS) includes all patients who have received study treatment.

The **Pharmacokinetic Analysis Set** (PK Analysis Set) includes all patients who take at least one dose of nomacopan and have at least one PK sample taken and analysed. This will be the primary population for assessing PK.

The **Safety Analysis Set** (SAF) includes all patients who received at least one dose of investigational product. This will be the primary population for assessing safety. Patients will be classified by the actual study medication they receive.

The following analysis sets apply to subjects in Part 2 of the study only:

- The **All Randomised Patients Set** (RAN) consists of all patients who were randomised, irrespective of the treatment they received, if any. If this analysis set coincides with the full analysis set, it will be omitted from the tables and listings.
- The **Full Analysis Set** (FAS) includes all patients randomised to treatment who received at least one dose of investigational product. This will be the primary population for assessing efficacy. Patients will be classified by the study medication they were randomised to.

The definitions for all analysis sets are sufficient to determine the patients included within these analysis sets and so do not require listing and agreeing prior to database lock. Actual study medication will be determined from the Study Drug Dispensing and Return Case Report Form (CRF) page.

## 6.4 Data presentations

The data will be summarised in tabular form by treatment group apart from disposition of patients, protocol deviations and background and demographic data which will be summarised by treatment group and overall patients.

The following treatment labels will be used “nomacopan 0.25% eye drops”, “Placebo” and “Overall” (where applicable). For disposition of patients, “All patients” will be presented combining Part 1 and Part 2.

Only scheduled post-baseline visual acuity, clinical scoring, TBUT and categorical MMP-9 estimation will be tabulated, post-baseline repeat/unscheduled assessments will be disregarded, although they will be listed.

Analysis sets and study completion/withdrawal will be summarised using the enrolled set. Background and demographic characteristics will be summarised using the FAS. The efficacy endpoints will be summarised using the FAS. Prior/concomitant medications, administration of study treatment and exposure and safety will be summarised using the SAF. Pharmacokinetics will be based on the PK Analysis Set.

Eligibility listings will be based on the screened set and sorted by patient number.

Analysis set listings will be based on the enrolled set, PK will be based on the PK Analysis Set, safety listings and all other listings will be based on the ATS set.

Listings will be sorted by treatment group, patient number and date/time of assessment. Treatment groups will be presented in the following order: “Part 1, Treatment: nomacopan 0.25% eye drops”, “Part 2, Treatment: nomacopan 0.25% eye drops”, “Part 2, Treatment: Placebo”.

Graphical presentations of the data will also be provided where appropriate.

## 6.5 Disposition of patients

For Part 1 and Part 2, the number and percentage of all patients enrolled, included in the RAN, FAS, SAF, PK Analysis Set, who completed the study and prematurely discontinued the study, who completed study treatment and prematurely discontinued study treatment and study duration, will be summarised.

The number and percentage of patients will be summarised by their reasons for withdrawal from the study and study treatment.

Study duration will be derived as the number of days between date of starting drug administration and the date of study completion or the date of early study withdrawal. The date of starting drug administration will be determined from the Comfort Diary Card CRF page.

Eligibility for each of the analysis sets along with reasons for exclusion will be listed. Study completion/withdrawal data will be listed.

## 6.6 Protocol Deviations

Details of all protocol deviations (date, deviation category, specific details and classification of major or minor) and patient eligibility will be listed.

## 6.7 Background and Demographic Characteristics

### 6.7.1 Demography

Demographic characteristics (age, sex, ethnic origin and race) collected at Screening will be summarised along with indication (AKC, VKC, SAC, PAC), patient group (AKC/VKC and SAC/PAC) and country/site.

Age is calculated in years from the date of informed consent.

All patient demographic data including informed consent will be listed.

### 6.7.2 Medical History

Medical history events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary version. The version used will be indicated in the data summaries and listings. The number and percentage of patients will be presented for ongoing conditions and previous conditions separately by system organ class (SOC), and preferred term (PT), where SOC and PT will be presented in decreasing frequency of the total number of patients with medical history events. All events will be listed.

### 6.7.3 Ophthalmic History

The number and percentage of patients with any significant ophthalmic history will be presented for ongoing and previous conditions separately and also by condition, where conditions will be presented in the order: Cataract, Pseudophakia, Glaucoma, Glaucoma surgery, Eye lid surgery, Other surgery on the eyes, Other. All events will be listed.

## 6.8 Background Therapy and Concomitant Medications

Medications will be coded using the latest World Health Organization Drug dictionary (WHO Drug) version. The version used will be indicated in the data summaries and listings.

Prior medications are defined as those that started and ended prior to the first administration of study treatment. Medications that are ongoing at the first administration of study treatment or started after time of first administration will be deemed to be concomitant medications. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

For Part 1 and Part 2, the number and percentage of patients taking concomitant medications will be summarised by medication class and standardised medication name, where medication class and standardised medication name will be presented in decreasing frequency of the total number of patients with medications. The number of patients receiving rescue therapy will be presented similarly (see section 6.10.3.3).

In summary tables, patients taking multiple medications in the same medication class or having the same standardised medication recorded multiple times in the study will be counted only once for that specific background therapy type, medication class and standardised medication name.

Background therapy and medication data will be listed together, where concomitant medications and background therapy as identified via the eCRF will be flagged. Background therapy diary card data will be listed.

## 6.9 Administration of Study treatment and Exposure

### 6.9.1 Compliance

For Part 1 and Part 2, the number of vials dispensed, the number of used vials returned, the number of vials expected to have been used and compliance for each patient will be summarised by treatment group.

- number of vials expected to have been used = 2 x (number of days that a subject administered eye drops dependent on date of first and last dose)

where *number of days that a subject administered eye drops dependent on date of first and last dose* is derived from the Study Drug Dispensing and Return CRF page data as “date of final study drug return – date of first study drug dispensing”. If a patient does not return their final dispensed study drug vials then the date of study competition/withdrawal will be used instead of date of return.

- compliance (vial return) = 100 x (total number of used vials returned / total number of vials expected to have been used)
- compliance (exposure) = 100 x (total number of doses administered / (total number of vials expected to have been used* 2)

  The multiplication from 2 is required as each vial holds a dose per eye and the number of doses is counted per eye treated.

### 6.9.2 Exposure

For Part 1 and Part 2, the number of doses of study treatment administered (total number of occasions that a time of study drug was recorded) and the number of days of exposure to the study treatment ([last date of dosing - first day of dosing] + 1) will be summarised. These data will be obtained from the comfort diary card data.

All study drug dispensing and return data will be listed. The number of vials expected to have been used for each period will be presented. This will be calculated as 2 x (number of days that a subject administered eye drops dependent on date of first and last dose within each period)

where *number of days that a subject administered eye drops dependent on date of first and last dose within each period* is derived from the Study Drug Dispensing and Return CRF page data as “date of last study drug return for the period – date of first study drug dispensing for the period”.

## 6.10 Efficacy Evaluation

### 6.10.1 Primary Endpoint

The primary endpoint is a safety outcome and is described under section 6.14.1.1.

### 6.10.2 Secondary Endpoints

#### 6.10.2.1 Post-instillation comfort

Post-instillation comfort scores will only be available for the least comfortable eye. The eye that the scoring was recorded on will not be captured on the eCRF.

A score of 0 to 4 will be recorded at 0.5 min, 1 min, 2 min, 3 min and 5 min each morning and evening on diary card.

The total score over two-week periods for days 1 to 14, 15 to 28, 29 to 42 and 43 to 56 will be calculated for each patient by summing the scores from the five timepoints taken each morning and evening over the 14 days, therefore the total score will have a possible range of 0 to 560. If there are 20 or more missing data points during the period, then the total score will not be calculated and set to missing.

For derived non-missing scores, an average score for the period will also be calculated as follows:

$$Average\ score = \frac{Total\ score}{Number\ of\ non-missing\ days}$$

The average score at each two week-period will be classified as follows: an average total comfort score of < 10 will be deemed to be comfortable/acceptable, 10 – 19 will be moderately uncomfortable, 20 – 29 will be very uncomfortable and ≥ 30 will be severely/unacceptably uncomfortable.

The number and percentage of missing data over the two-week period will be calculated, where 140 data points would expected to be recorded over 14 day period.

Should the five scores not be available at any morning or evening timepoint there will be no imputation, and the total score and classification will be derived for the two-week period for that patient regardless of missing data.

#### 6.10.2.1.1 Descriptive Summaries

Descriptive statistics for the total comfort score and the 14 day average comfort score will be presented along with the number and percentage of patients at each comfort classification will be presented for each treatment group for Days 1 to 14, Days 15 to 28, Days 29 to 42 and Days 43 to 56 for the recorded eye. The percentage will be out of the number of patients at each timepoint who had some data and therefore the total score could be calculated.

The percentage of missing data points will be summarised for each treatment group for Days 1 to 14, Days 15 to 28, Days 29 to 42 and Days 43 to 56.

#### 6.10.2.1.2 Analysis

The classification of the average daily post-instillation comfort score will be analysed using an ordinal logistic regression model. The model will include treatment and visit as fixed effects and a treatment-by-visit interaction.

The following variance/covariance matrix structures for the repeated visits by a patient will be assessed: Compound symmetry, 1st order autoregressive, Toeplitz and unstructured. The variance/covariance matrix structure that results in the smallest Akaike information criterion (AIC), indicating the best model fit will be selected.

Assumptions about the proportionality of odds will also be assessed by appropriate methods such as by fitting fixed and random effects at each partition and testing the equality of the effects at different partitions. Should assumptions not hold, then the treatment odds ratios for the individual cumulative levels of the variable will be presented.

The adjusted least squares (LS) estimate for the treatment odds ratio (nomacopan:Placebo) along with corresponding 95% CI will be presented for each treatment period.

A null hypothesis of no change in classification of total post-instillation comfort score at Days 43 to 56 between treatment groups (nomacopan/Placebo) will be assessed and a p-value will also be reported.

The extent of missing data will be taken into consideration when analysing the total score data. Should it be felt appropriate, alternative analysis may be carried out and/or

sensitivity analyses using imputation methods such as last observation carried forward will also be considered.

#### 6.10.2.1.3 Listing

All post-instillation comfort diary card data will be listed.

### 6.10.2.2 Visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS) charts

#### 6.10.2.2.1 Descriptive Summaries

Descriptive statistics for observed and change from baseline (Day 1) number of ETDRS letters will be presented for each treatment group at each visit for right eye, left eye and the score from worse of the two eyes at the visit. The worst eye is determined from the eye assessed on the clinical scoring CRF page at the same visit. The number and percentage of patients whose assessed eye differed from the previous assessment will be presented.

#### 6.10.2.2.2 Analysis

Change from baseline (Day 1) for the ETDRS on the worst eye at Day 14, Day 28, Day 42 and Day 56 will be analysed using a mixed-effect model for repeated measures. The model will include baseline ETDRS as a covariate, treatment group and visit as fixed factors and the treatment-by-visit interaction.

The variance/covariance matrix structure that results in best model fit will be selected using the process described in section 6.10.2.1.2.

Assumptions of normality will be assessed visually using diagnostic plots. Should assumptions of normality not hold, transformations such as percentage change and ratio to baseline will be considered. If there remains uncertainty regarding the assumptions, a non-parametric analysis may be considered as an alternative.

The LS means and 95% confidence interval will be presented for each visit and treatment. The adjusted LS mean difference (nomacopan - placebo) and 95% confidence interval will be presented for each visit.

A null hypothesis of no change in ETDRS at Day 56 between treatment groups (nomacopan - placebo) will be assessed and a p-value will also be reported.

#### 6.10.2.2.3 Listing

All visual acuity data will be listed, including the worst eye assessment.

### 6.10.2.3 Clinical scores

Clinical scores will only be available for the eye judged as worst affected at each visit by the patient. In the event that the patient judges both eyes to be equally affected the right eye will be assessed. The eye that the scoring was recorded on will be captured on the eCRF and presented in the listing.

The clinical score is calculated from the Symptom and Sign sub-components.

For AKC and VKC the Symptom sub-component consists of 5 items and the Sign sub-component consists of 6 items with each item being given a score between 0 and 3.

The Total and Symptom and Sign sub-components are calculated as the sum of all items, Symptom items and Sign items respectively giving a possible range of 0 to 33 on the Total score, 0 to 15 on the Symptom score, and 0 to 18 on the Sign score.

For SAC and PAC the Symptom sub-component consists of 4 items and the Sign sub-component consists of 5 items with each item being given a score between 0 and 3. The Total and Symptom and Sign sub-components are calculated as the sum of all items, Symptom items and Sign items respectively giving a possible range of 0 to 27 on the Total score, 0 to 12 on the Symptom score, and 0 to 15 on the Sign score. The sign sub-component items are different for SAC and PAC to AKC/VKC.

For all indications, should an item be missing there will be no imputation and the score will be missing for that timepoint.

#### 6.10.2.3.1 Descriptive Summaries

Descriptive statistics for the observed and change from baseline (Day 1) clinical scores for the total clinical score, the overall symptom and sign subcomponent scores and each item score will be presented for each treatment group at each visit for the recorded eye.

#### 6.10.2.3.2 Analysis

Change from baseline (Day 1) for the total score at Day 14, Day 28, Day 42 and Day 56 will be analysed using a mixed-effect model for repeated measures. The model will include baseline total clinical score as a covariate, treatment group, visit and patient group (AKC/VKC or SAC/PAC) as fixed factors and the treatment arm by visit interaction.

The variance/covariance matrix structure that results in best model fit will be selected using the process described in section 6.10.2.1.2.

Assumptions of normality will be assessed visually using diagnostic plots. Should assumptions of normality not hold, transformations such as percentage change and ratio to baseline will be considered. If there remains uncertainty regarding the assumptions an alternative analysis, for example non-parametric analysis, may be considered.

The LS means and 95% confidence interval will be presented for each visit and treatment. The adjusted LS mean difference (nomacopan - placebo) and 95% confidence interval will be presented for each visit.

A null hypothesis of no change in clinical score at Day 56 between treatment groups (nomacopan - placebo) will be assessed and a p-value will also be reported based on the relevant mixed-effect model.

Where there is sufficient data (see section 6.2) the item scores will be analysed using the same method as for the total score.

Where there is a sufficient number of patients receiving rescue therapy, additional analysis (as described above) may be conducted using the same methods as the recorded clinical scores by imputing the worst-case score for all post-rescue therapy visits.

6.10.2.3.3 Listing

All clinical score data will be listed.

### 6.10.2.4 MMP-9 positive levels

The number and percentage of patients with MMP-9 negative (< 40ng/mL) and positive (≥ 40ng/mL) assessed using the Inflamma Dry device will be presented for each treatment group at each visit for right and left eyes.

All MMP-9 data will be listed.

### 6.10.2.5 Tear film break up time

Tear film break up time (TBUT) will only be available for one eye. The eye that the test was carried out on will be captured on the eCRF and will be presented in the listing.

6.10.2.5.1 Descriptive Summaries

Descriptive statistics for observed and change from baseline (Day 1) TBUT will be presented for each treatment group at each visit for the recorded eye.

6.10.2.5.2 Analysis

Change from baseline (Day 1) for TBUT (in seconds) at Day 14, Day 28, Day 42 and Day 56 will be analysed using a mixed-effect model for repeated measures for the recorded eye. The model will include baseline TBUT as a covariate, treatment group and visit as fixed factors and the treatment-by-visit interaction.

The variance/covariance matrix structure that results in best model fit will be selected using the process described in section 6.10.2.1.2.

Assumptions of normality will be assessed visually using diagnostic plots. Should assumptions of normality not hold, transformations such as percentage change and ratio to baseline will be considered. If there remains uncertainty regarding the assumptions a non-parametric analysis may be considered as an alternative.

The LS means and 95% confidence interval will be presented for each visit and treatment. The adjusted LS mean difference (nomacopan - placebo) and 95% confidence interval will be presented for each visit.

A null hypothesis of no change in TBUT at Day 56 between treatment groups (nomacopan - placebo) will be assessed and a p-value will also be reported.

6.10.2.5.3 Listing

All TBUT data will be listed.

## 6.10.3 Exploratory Endpoints

### 6.10.3.1 Systemic absorption of nomacopan by blood sampling

Covered under section 6.11.

### 6.10.3.2 Tear fluid analysis of complement C3, C5 and LTB4

If sufficient data, tear fluid data will be listed.

#### 6.10.3.3 Rescue therapy

The number and percentage of patients that received a rescue medication (as indicated on the Concomitant Medications CRF page) at any stage of the trial (during Day 1 to Day 56 (last dose) and during Day 56 to Day 84 (follow-up visit) to be presented separately) and the number and percentage of patients that were receiving a rescue medication at the end of the trial (indicated as ongoing on the CRF) will be presented in a summary table by treatment group.

The number and percentage of patients that received a rescue medication will be presented for each treatment group for Days 1 to 14, Days 15 to 28, Days 29 to 42 and Days 43 to 56 to compliment the intervals for the efficacy analysis. The percentage will be out of the number of patients at each timepoint who had data for comfort scores to be calculated.

A patient is considered to have taken rescue medication during an interval where the start date (Day 1 or later) occurs during that interval, or if they continue to receive rescue medication that started in a previous interval.

### 6.10.4 Additional Summaries

Key efficacy endpoints for patients in the FAS in Part 1 and Part 2 will be listed by individual patient alongside a summary (Mean (SD)) by treatment group and by indication group (Part 2 only: AKC/VKC and SAC/PAC) at each timepoint. Details of endpoints to be presented are as follows:

- Comfort score:
    - Total and average daily score will be presented for each treatment period.
- Visual Acuity:
    - Number of ETDRS letters will be presented for right eye, left eye and the score from worse of the two eyes for each visit.
- Clinical scores:
    - The total clinical score, the overall symptom and sign subcomponent scores will be presented for each visit.
- Tear film break up time:
    - TBUT in seconds will be presented at each visit.

## 6.11 Pharmacokinetics

Serum concentrations of nomacopan will be listed and summarised over time. If < 50% of patients have data which are greater than LLOQ then table outputs with summary statistics will not be produced. Should the summary statistics be produced values below the lower limit of quantification (LLOQ) will be set to 0.5 × LLOQ for calculation of summary serum concentration statistics.

## 6.12 Pharmacodynamics

Serum terminal complement activity measured by CH50 U Eq/ml and change from baseline will be summarised by treatment group for each visit.

Summary statistics will include observed values, change from baseline and the ratio to baseline (% activity). Ratio will be calculated as:

$$Ratio\ to\ baseline = \frac{Observed\ value}{Baseline\ value} * 100$$

Given the very small amount of nomacopan being administered topically, the expectation is that active and placebo patients in Part 2 will have equivalent CH50 values and a comparison between the groups will be tabulated.

All pharmacodynamic data will be listed.

## 6.13 Anti-drug Antibodies

. All anti-drug antibody data will be listed.

## 6.14 Safety Evaluation

### 6.14.1 Adverse Events

AEs will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings.

Ocular AEs will be identified using SOC “Eye disorders”.

A treatment-emergent adverse event (TEAE) is defined as an AE that started on or after the start of the administration of study treatment. If AE dates are incomplete and it is not clear whether the AE was treatment-emergent, it will be assumed to be treatment-emergent. When the AE occurs on the same day as start of administration of study treatment a separate file will be transferred from data management to indicate whether they are treatment emergent or not (see Data Management Plan section 6).

If it is not confirmed via Data Management, the start date will be imputed as the date of the first dose of study drug. AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

Any AE commencing after the last administration of study treatment (Day 56) plus 30 days will not be considered treatment emergent.

A treatment-related TEAE is defined as a TEAE that is possibly related or related to the study treatment. If the TEAE has a missing relationship it is assumed to be related to the study treatment for analysis purposes.

#### 6.14.1.1 Primary Endpoint

The number and percentage of patients who experienced ocular TEAEs will be presented for each treatment group. Treatment groups will be presented in the following order: “Part 1, Treatment: nomacopan 0.25% eye drops”, “Part 2, Treatment: nomacopan 0.25% eye drops”, “Part 2, Treatment: Placebo”.

The difference in the percentage of patients (nomacopan -placebo) and exact 95% confidence interval for the difference, using Chan and Zhang method (1999), will be presented for those in part 2 of the study (nomacopan-placebo) and for those in both parts of the study combined (nomacopan-placebo).

#### 6.14.1.2 Other Summary Tables

A summary table will present the following for Part 1 and Part 2,:

- TEAEs (events and patients).
- Serious TEAEs (events and patients).
- Serious study treatment related TEAEs (events and patients).
- TEAEs by severity (mild/moderate/severe) (events and patients).
- TEAEs by relationship to study treatment and the pooled study treatment related category (events and patients).
- TEAEs leading to discontinuation of study treatment (patients only).
- Study treatment related TEAEs leading to discontinuation of study treatment (patients only).
- TEAEs leading to death (patients only).

In the above summaries, if a patient experienced more than one TEAE, the patient will be counted once using the most related event for the “by relationship to study treatment” and “related to study treatment” summaries and at the worst severity for the “by severity” summary.

The following tables will be presented:

- TEAEs by system Organ Class (SOC) and Preferred Term (PT).
- TEAEs by PT.
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and relationship to study treatment and the pooled related categories (related).

For all of the above, SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs.

Further details of the above four tables are given below:

1. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT.
2. If a patient experienced more than one TEAE, the patient will be counted once for each PT.
3. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT at the worst severity.
4. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT using the most related event.

AE data will be listed in full and this will also include a treatment emergent flag, cessation of event relative to first dosing of study treatment and duration of AE. The listing will be reported by events during “Days 1-56” (treatment period) and “Days 57-84” (follow-up period).

This listing will be repeated presenting only serious TEAEs.

## 6.15 Pregnancy Test

All pregnancy test details will be listed.

## 6.16 Eye Swab

All eye swab data will be listed.

## 6.17 Changes from the Protocol Planned Analysis

- Section 11.1 of the protocol states that the baseline value will be defined as the pre-dose value on Day 1, if that is missing, it will be defined from the most recent value available. This has been updated to take account of any patients who do not take their first dose on Day 1.
- Section 11.3 of the protocol states that the weekly comfort scores for post-instillation comfort, as graded on patient diary cards will be compared. To be in-line with the secondary endpoint, the scores over the two-weekly period will be compared.
- Section 11.8 of the protocol states that the Safety Analysis Set will include only randomized subjects from Part 2 of the study. To be in line with ICH E9 guidelines section 6.3 we will include all treated subjects regardless of the part of the study they are enrolled into.

# 7 REFERENCES

Chan ISF, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics. 1999;55:1202–1209