Johnson & Johnson Vision Care, Inc.

CR-5930

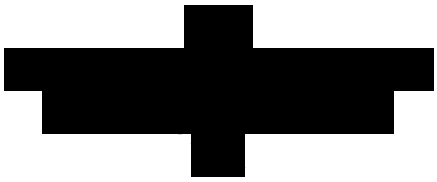
Clinical Evaluation of etafilcon A with Ketotifen

29Mar2018

Final Statistical Analysis Plan

Version 1.0

Prepared by:



SIGNATURE PAGE

Issued by: [redacted] 29 ___ 2018

Reviewed by: [redacted] Date: 29 /MAR /2018

Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

Approved by: [redacted] Date: ___/___/___

Approved by: BRIAN PALL Digitally signed by BRIAN PALL
DN: c=US, o=JNJ, ou=Subscribers, cn=BRIAN PALL, 0.9.2342.19200300.100.1.1=176727
Reason: I attest to the accuracy and integrity of this document.
Date: 2018.03.29 15:54:19 -04'00'
Adobe Reader version: 11.0.10 Date: ___/___/___

Brian Pall, O.D., M.S., F.A.A.O
Senior Principal Research Optometrist, Clinical Sciences
Johnson & Johnson Vision Care, Inc.

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CLUE	Contact Lens User Experience
CLPU	Contact Lens induced Peripheral Ulcer
CS	Compound Symmetry
[redacted]	[redacted]
D	Diopter
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FCS	Fully Conditional Specification
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRT	Item Response Theory
ISO	International Organization for Standardization
J&J	Johnson & Johnson
logMAR	Logarithm of Minimal Angle of Resolution
MI	Multiple Imputation
mITT	Modified Intention-to-Treat
OD	Right Eye
OS	Left Eye
PRO	Patient Reported Outcome
SAS	Statistical Analysis System
SEALS	Superior Epithelial Arcuate Lesions
SIE	Significant Infiltrate Event
SLF	Slit Lamp Findings
SD	Standard Deviation
VA	Visual Acuity
UN	Unstructured

1. Introduction

This statistical analysis plan (SAP) describes the analyses and data presentations for protocol CR-5930 v3.0 Amendment 2.0 dated 31 October 2017. This study is a multi-site, double-masked, randomized controlled trial.

This document will serve as the final guidance for all the statistical analysis for this study and will supersede the Statistical Method section (section 14) in the protocol if there are any discrepancies.

The etafilcon A with ketotifen contact lens is being developed as a novel drug/device combination product that incorporates the anti-allergy agent ketotifen with the same material as the 1•DAY ACUVUE® Brand disposable contact lens (etafilcon A daily disposable contact lens). This new product will be referred to hereafter as K-Lens. The control 1•DAY ACUVUE® Brand disposable contact lens will be referred to hereafter as Placebo. Ocular allergy, and the discomfort associated with its signs and symptoms, is a common cause of contact lens intolerance and of seasonal exacerbation of eye allergy symptoms in contact lens wearers. The creation of a concomitant system of an anti-allergy agent and a contact lens will offer significant advantages over existing therapies in that it allows contact lens users to continue wearing their lenses during the allergy season while preventing ocular itching associated with allergic conjunctivitis.

K-Lens has been evaluated for safety, tolerability, and efficacy (prevention of ocular itching) in previous studies[9-20]. The results of these studies have shown it to be safe, tolerable and efficacious. Two (2) pivotal Phase 3 studies have shown that K-Lens was effective in the prevention of ocular itching associated with allergic conjunctivitis at 15 minutes and 12 hours following lens insertion[16, 17]. The goal of this study is to evaluate the clinical performance of K-Lens produced on the new J&J Vision Care, Inc. manufacturing line in Limerick, Ireland, in a population of normal, healthy, habitual contact lens wearers.

Additionally, in the previous K-Lens studies, visual acuity was assessed using Snellen visual acuity charts which are commonly used in clinical practice. The proposed clinical study will assess visual acuity using logMAR (ETDRS) charts which are more commonly used in clinical research studies. By collecting data from both types of visual acuity charts, a more comprehensive assessment of visual acuity with K-Lens will be obtained.

For additional clinical information regarding K-Lens, refer to the latest version of the Investigator's Brochure.[21]

2. Objectives

The purpose of this study is to evaluate the clinical performance of K-Lens produced on the new J&J Vision Care, Inc. manufacturing line in Limerick, Ireland.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomized, double-masked, bilateral, controlled, two-arm parallel group, multi-site, 1-week dispensing study. Approximately 132 subjects will be screened and randomly assigned to either K-Lens or Placebo using 2:1 ratio (i.e. 2/3 of subjects on the K-Lens arm and 1/3 on the Placebo arm). The goal is for a sample size of 120 (80 subjects in K-lens and 40 subjects in Placebo) after subjects who withdraw or are lost-to-follow-up.

The study begins with an Initial Visit (Visit 1). If a subject is found to meet all eligibility criteria, they will be randomized and fit with either the K-Lens or Placebo lens in both eyes based on the randomization scheme provided to the investigators; otherwise, the subject will be deemed ineligible for this study.

Successfully dispensed subjects at the initial visit will be scheduled for a follow-up visit (Visit 2). The follow-up visit will occur approximately 6 to 9 days after the Initial Visit. Unscheduled follow-up visits may occur during the study. Subjects will be advised to wear the study lenses at least 8 hours a day for a minimum of 6 days.

Both study lenses will be worn as a daily disposable modality. J&J Vision Care (JJVC) will provide the investigational sites with sufficient quantities of study lenses and supplies to complete the study.

The Investigator is responsible for ensuring that all subjects entering the study conform to subject selection criteria. The number of subjects targeted for randomization and completion are as follows:

Table 1: Target number of subjects by arm and site

	K-Lens	Placebo	Total
Randomization	88	44	132
Completion	80	40	120
Number of sites	6	6	6
Subjects/site (Min-Max)	12-16	5-9	20-24

The schedule of events is reported in section 12.1.

3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint is monocular contact lens-corrected distance visual acuity using a logMAR visual acuity scale. This will be evaluated under high luminance and high contrast conditions at 4 meters from ETDRS charts at the 1-week follow-up visit for each eye. The analysis will be conducted at subject level, so each eye evaluation will be considered as a repeated measure for the same subject.

The subject is asked to read the visual acuity chart and the investigator will report in eCRF the letters missed by the subject and the logMAR score will be derived in eCRF. In case the subject is unable to read at least 3 letters on the top line of the chart, the investigator will repeat the assessment at a closer distance: The subject starts at 4 meters, then will be moved to 3 meters then 0.5m closer at a time (e.g. 4m, 3m, 2.5m, 2.0m). If the subject correctly reads all 5 letters on the last line, the test will be stopped and 0 missing will be recorded without moving subjects further away from the chart.

The procedure is explained in the [redacted] in Appendix D of the study protocol.

3.2.2. Secondary Endpoints

FDA Biomicroscopy Scale

This secondary endpoint is a binary response measured at eye level over the post-fit period including unscheduled visits between Visit 1 and Visit 2:

- Yes = eye has at least one clinically significant (Grade 3 or Grade 4) slit lamp finding;
- No = otherwise.

An eye with multiple clinically significant slit lamp finding events will be counted only once.

The FDA Biomicroscopy Scale measures the severity of the ocular clinical findings and goes from Grade 0 (none) to Grade 4 (severe). The procedure is explained in the [redacted] in Appendix D of the study protocol. The individual ocular finding results are considered as other endpoints, these are described in section 3.2.3 Slit-lamp findings.

Unacceptable Lens Fitting

This secondary endpoint is a binary response (yes/no) measured at eye level at fitting and post-fitting evaluations including unscheduled visits:

- Unacceptable = unacceptable fit due to meeting one of the following criteria:
    - limbal exposure at primary gaze or with extreme eye movement;
    - edge lift;
    - excessive movement in primary up gaze;

  - insufficient movement in all three of the following conditions: primary gaze, up gaze, and push up test.
- Acceptable = otherwise.

This will be recorded on the eCRF as whether the fit is unacceptable or not.

Subjects discontinued because of unacceptable fitting will also be counted as having an Unacceptable response. An eye with multiple unacceptable fitting events will be counted only once.

The procedure is explained in the [redacted] in Appendix D of the study protocol. The individual lens fitting characteristics are considered as other endpoints, these are described in section 3.2.3 Lens Fitting Characteristics.

3.2.3. Other Endpoints

Average daily wear time (in Hours):
Average daily wear time will be calculated as the number of hours between subjects reported time of insertion and time of removal of the study lenses, on an average day, at 1-Week Follow-up evaluation.

Subjective assessment of lens handling:
Lens handling will be assessed using Contact Lens User Experience™ (CLUE) questionnaire at 1-Week Follow-up evaluation. CLUE™ is a validated patient reported outcomes (PRO) questionnaire to assess patient-experience attributes of soft contact lenses (comfort, vision, handling, and packaging) in a contact-lens wearing population in the US, ages 18-65. Derived CLUE™ scores using Item Response Theory (IRT) follow a normal distribution with a population average score of 60 (SD 20), where higher scores indicate a more favorable/positive response with a range of 0-120. A 5-point increase in an average CLUE™ score translates into 10% shift in the distribution of scores for population of soft contact lens wearers.[22] The handling scores will be generated using the flexMIRT software version 3 or higher (Chapel Hill, NC).

Slit-lamp findings:
Frequency and severity by eye of slit lamp findings (SLFs) including conjunctival injection, corneal edema, corneal neovascularization, corneal staining, tarsal abnormalities or any other complications. SLFs will be evaluated at fitting and post-fitting evaluation visits including unscheduled visits.

Subject's Reported Ocular Symptoms:
Frequency and severity by eye of subject's reported ocular symptoms and problems with the study lens at fitting and post-fitting evaluation visits including unscheduled visits.

Severity of the symptoms can be:

- 0 = Not Applicable or Not Recorded;
- 1 = Mild and results in little or no interference with lens wear;
- 2 = Moderate AND/OR occasionally interferes with lens wear;
- 3 = Severe AND/OR frequently interferes with lens wear.

The related procedure is explained in [redacted] in Appendix D of the study protocol.

Lens fitting characteristics:
Frequency by eye of mechanical lens fitting characteristics at fitting and 1-Week Follow-up evaluations. Lens fitting characteristics to be reported are:

- Lens Centration Grade
- Decentered Direction
- Limbal Exposure Grade
- Edge Lift (Present or Absent)
- Primary Gaze Movement Grade
- Upgaze Movement Grade
- Lens Tightness Grade (Push-up Test)
- Acceptable Fitting (yes/no)

Additional Endpoints

- Adverse events
- Discontinuation
- Reason for discontinuation
- Unscheduled lens replacement
- Reasons for unscheduled lens replacement including lens damage.

4. General Statistical Considerations

Continuous data will be summarized descriptively by n, mean, standard deviation (SD), median, minimum (Min) and maximum (Max). Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to 1 more decimal place than the raw data, and standard deviation will be presented to 2 more decimal places than the raw data.

Categorical data will be summarized descriptively by frequency: n (%). The denominator for all percentages will be the number of subjects (or eyes as applicable) available, once pooled, within that treatment group for the analysis set of interest, unless otherwise indicated. Percentages will be presented to 1 decimal place and will not be displayed for zero frequencies. A row denoted “Missing” will be included in count tabulations where necessary to account for missing values.

All data summaries and statistical analyses will be performed using the SAS software version 9.3 or higher (SAS Institute, Cary, NC).

All planned analysis will be conducted with an overall type I error rate of 5%. Unless otherwise specified, all statistical tests will be 2-sided.

P-values will be rounded to 3 decimal places. P-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'.

Study day of an event that occurred after or on the first Fitting date will be calculated as Event Date – First Fitting Date + 1.

Study day of an event that occurred before the first dose date will be calculated as Event Date – First Fitting Date.

Baseline is last assessment obtained prior to the insertion of the test or control lenses, unless otherwise specified. Some subjects may have up to four baseline evaluations if a damaged lens needs to be replaced and/or due to failure to fulfil inclusion criteria and/or due to fulfilment of exclusion criteria. In this case, the last baseline evaluation will be considered in the descriptive summary and analysis. For subjects enrolled but not randomized the last non-missing assessment will be taken as baseline.

Some subjects may have up to two Visit 1 evaluations, if a damaged lens needs to be replaced and/or due to failure to fulfil inclusion criteria and/or due to fulfilment of exclusion criteria. In this instance, the last Visit 1 evaluation will be considered in the descriptive summary and analysis.

Missing or spurious values will not be imputed as the number of missing values is expected to be low. The count of missing values will be included in the summary tables and listings.

Subject dropout is expected to be one of the main reasons for missing data in this clinical trial. Past clinical trials don't provide the evidence that subject dropout is systematic or not-at-random. To evaluate the impact of missing data, a sensitivity analysis will be conducted using multiple imputation methods.

All listings will be sorted for presentation in order of study center and subject. Key variables to be displayed on each listing will be: Center, subject id, age, sex and race.

4.1. Sample Size

Assuming a perfect correlation between left eye visual acuity and the right eye visual acuity (worst case scenario), the total sample size (n) required to achieve 85% power with two-

sided type I error of 0.05 was calculated for different scenarios of mean difference (Δ = K-Lens – Placebo) and common standard deviation (σ) in the two arms. The results are summarized in the Table below:

Table 2: Sample size for different scenarios of mean Δ and σ

Δ	σ	n
0	0.05	15
0	0.01	45
0.04	0.05	33
0.04	0.1	117

The sample size calculation was conducted using the PROC POWER Procedure (SAS/STAT 14.1, SAS Institute, 2015) for two-sample means with allocation weight of 2:1.
The sample size of 120 subjects is considered sufficiently large to test for non-inferiority with a minimum statistical power of 85% and two-sided type I error of 0.05.

The plan is to enroll 132 eligible subjects with a target completion of 120 subjects (80 subjects in K-Lens and 40 subjects in Placebo).

4.2. Randomization, Stratification, and Blinding

Subjects will be randomly assigned to either K-Lens or Placebo arm based on a computer-generated randomization schedule prepared before the start of the study. The randomization will be stratified by investigational site and randomly permuted blocks of 3 assignments will be used to achieve 2:1 K-Lens versus Placebo ratio within each study site.

Randomization must be performed at the initial visit. The following must have occurred prior to randomization:

- Informed consent has been obtained
- It has been determined that the subject meets all the inclusion / exclusion criteria
- Subject history and baseline information has been collected

This is a double-masked study where subjects, investigators are masked to the identity of the study lenses during the study period. Every attempt will be made to keep the other clinical trial personnel involved in the study (e.g. Data management, Biostatistician and Clinical Operations) unaware of the identity of the study lenses. The identity of the study lenses will be masked by over labeling the blister packs with a label containing the study number, lot number, sphere power, expiration date and the randomization codes. Only the personnel involved in the over labeling and the Statistician generating the randomization scheme will have access to the decode information translating the randomization codes into K-Lens and Placebo arms. The medical monitor will also have access to the decode information in case breaking the mask is necessary for the urgent medical treatment of a subject.

Subjects who have had their treatment assignment unmasked are expected to return for all remaining scheduled evaluations.

4.3. Analysis Set

The study population will be healthy normal habitual contact lens wearers that are at least 18 years old and less than 40 years old.

In this study, the following five populations will be defined and used in the analysis and presentation of the data.

4.3.1. All Enrolled

All Enrolled Population includes all subjects with recorded data in the electronic Case Report Form (eCRF) database.

4.3.2. Randomized

All enrolled subjects who are randomized to either the K-Lens or Placebo treatment group.

Subject will be analyzed as per randomized treatment.

4.3.3. Modified Intention-to-Treat (mITT)

The Modified Intention-to-Treat population will include all the subjects who were administered any test or control article and will exclude subjects who drop out prior to administering any test or control article.

Subject will be analyzed as per randomized treatment.

4.3.4. Per Protocol (PP)

Per Protocol Analysis set will be the primary analysis population. It will include all subjects who have successfully completed all visits and did not substantially deviate from the protocol as determined by the trial cohort review committee prior to database hard lock. Justification of excluding subjects with protocol deviations in the per-protocol population set will be documented in a memo to file.

Subject will be analyzed as per randomized treatment.

4.3.5. Safety

All subjects who were administered any test article excluding subjects who drop out prior to administering any test article. At least one observation for safety endpoints should be recorded (e.g. ocular symptom, slit-lamp finding, etc.) or on after treatment start date.

Subjects will be analyzed as per treatment received.

4.4. Handling of Missing Data

For the primary endpoint (visual acuity logMAR score), a sensitivity analysis will be conducted to explore the impact of missing data. This sensitivity analysis rely on an assumption that the missing data are missing at random (MAR) i.e., that the probability that an observation is missing can depend on observed data but is unrelated to the data not observed.

The sensitivity analysis will be based on multiple imputation analysis explained in section 8. Observed missing data are detailed in Appendix 12.2: Missing data pattern.

5. Subject Disposition

A disposition of subjects including the number and percentage of subjects enrolled, subjects adhering to protocol (PP population), subjects treated (safety population), subjects completed, subjects discontinued from the study and subjects enrolled but not dispensed will be summarized by the 2 treatment groups. In addition subjects enrolled but not randomized will be also included (where relevant).

Subjects will be allocated to one of the three mutually exclusive groups:

- Completed: Subjects are considered to have completed the study if (1) they are eligible, (2) not discontinued, (3) they have completed all visits including the final visit (Visit 2).

- Discontinued: Subjects are considered to have discontinued from the study if (1) test article administered and (2) discontinued because of one of the following reasons:
    - Adverse Event;
    - Unsatisfactory Visual Response due to test article;
    - Unsatisfactory Lens Fitting due to test article;
    - Lens Discomfort;
    - Lens Handling Difficulties;
    - Withdrew Consent during study;
    - Lost to Follow Up;
    - Subject no longer meets Eligibility Criteria;
    - Subject Withdrawn by PI due to non-compliance to protocol;

- Test Article No Longer Available;
- Other.

- Enrolled but Not Dispensed: Subjects are considered Enrolled but Not Dispensed if they provide informed consent but (1) failed to satisfy the eligibility criteria (inclusion/exclusion criteria) or (2) were randomized but test article was not administered for any reason.

Total Enrolled = Completed + Discontinued + Enrolled Not Dispensed.

The reasons for study discontinuation and study withdrawal will also be summarized.

All percentages will be based on the number of total enrolled subjects.

5.1. Protocol Deviations

Any protocol deviation that could impact the primary endpoints will result in the subject being excluded from the Per-Protocol analysis population. No analysis on protocol deviations will be performed. Protocol deviations that lead to exclusion from PP population will be listed.

6. Demographics and Baseline Characteristics

The demographic characteristics and the baseline characteristics will be summarized for All Enrolled subjects and for PP analysis set.

Individual subject listings will be provided for all the enrolled subjects to support the summary tables.

6.1. Demographics

Demographic characteristics will be collected at Visit 1 and will be summarized by treatment arm. These are: Age, gender, race and ethnicity.

Age at informed consent will be used only to check the inclusion criteria no.3, i.e. subject must be between 18 and 39 (inclusive) years.

In the demographic characteristics summary, age will be derived as integer part of (first study visit date – date of birth + 1) / 365.25.

6.2. Baseline Disease Characteristics

The following baseline clinical characteristics will be summarized at subject level by treatment arm:

- CLUE™ Baseline Handling Questionnaire;

- Entrance distance Snellen Visual Acuity with their habitual contact lens correction in place.

6.3. Medical History

Past and concomitant medical history will be summarized by treatment separately, but they will be listed together.

6.4. Other Background Information

Habitual Contact Lens Information will be collected at Visit 1 and will be summarized by treatment.

The following Habitual Contact Lens Information will be reported at eye level:

- Lens type
- Sphere
- Monovision Distance Lens (yes/no/not-applicable)

While the remaining information will be reported at subject level:

- Lens Care Regimen
- Modality
- Cleaning
- Duration of the prescription (days) = Visit 1 Date - Approximate Prescription Date + 1.

In case of partial prescription date (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume 01-MMM-YYYY;
- UK-UKN-YYYY: Assume 01-JAN-YYYY.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Concomitant medications will be documented during screening and updated during the study.
Disallowed medications or any concomitant therapies that are disallowed for this study include: Any ocular medications or any systemic medications that (e.g., chronic steroid use) that are known to interfere with contact lens wear.

Prior and concomitant medications, will be coded using the WHO Drug Dictionary Enhanced Version WHODDRUG SEP 2017.

A prior medication is defined as a medication where both the start and end dates are before the date of first test lens insertion following randomization.

A concomitant medication is defined as one where the end date is either on or after the date of first test lens insertion following randomization or is missing. The start date of a concomitant medication can be before or after the date of the first test lens insertion following randomization. For a medication with partial or completely missing onset date, unless it can be determined to be "prior to the first test lens insertion following randomization" from the incomplete start date or end date (e.g., month, year is before the first test lens insertion date, or end date is before the first test lens insertion date), the medication will always be assumed to be concomitant. Medications initiated prior to the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, then assume the date of first dose of study drug;
- UK-UKN-YYYY: If the year is prior to the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, then assume the date of first dose of study drug;
- UK-UKN- UNKN: Assume date of first dose of study drug.

Missing stop dates for concomitant medications data will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- UK-UKN-YYYY: Assume 31-DEC-YYYY;
- UK-UKN- UNKN: Assume ongoing and leave it missing.

The total number of concomitant medications and the number and percentages of subjects with at least one concomitant medication will be summarized for both Randomized and PP analysis sets including also the number and percentages of subjects by preferred name, in descending order of frequency in the total column.

A listing for both prior and concomitant medications will be created for all the enrolled subjects.

7.2. Study Treatments

Study treatment will be dispensed to subjects meeting all eligibility requirements, including any dispensing requirements set forth in this clinical protocol. Subjects will be dispensed an adequate supply of test articles to complete the study.

The treatment (K-Lens or Placebo) will be daily self-administered by subjects for the whole duration of the study (6-9 days). Subjects must wear the lenses for at least 8 hours per day.

7.2.1. Treatment Compliance and Extent of Exposure

The treatment compliance will be assessed at follow-up visit (Visit 2) at eye level. The following information will be summarized by treatment at subject level for both subjects in PP and safety population:

- Number of days wearing the lens
- Wearing time on Visit 2 (hours)

The number of subjects not wearing the lens at Visit 2 will be tabulated at subject level by treatment for subjects in safety population.

No modification to the daily treatment regimen is planned.

8. Efficacy Analysis

All the efficacy analyses will be conducted on PP population comparing K-Lens against Placebo.

As supportive analysis, the efficacy analysis will be repeated on the mITT population regardless of missing data.

In addition, a sensitivity analysis will be conducted on the primary endpoint using the mITT population to assess the impact of missing data using a multiple imputation (MI) process. Missing values for visual acuity logMAR score will be imputed from a regression model with treatment group, analysis site and logMAR score at Visit 1 and Visit 2 as covariates. Twenty imputations[28] will be performed using SAS PROC MI with the Fully Conditional Specification (FCS) option to take into account non-monotone missing data pattern (see Appendix 12.2: Missing data pattern). In case the pattern of missing data will be monotone, the procedure will use an imputation method for data sets with monotone missingness. The adjusted means difference between treatments and its standard error will be displayed with corresponding two-sided 95% CI and non-inferiority flag calculated using the SAS MIANALYZE procedure to combine the results of the analyses performed by imputation. See Appendix 12.3 for the SAS PROC MI, PROC MIXED and PROC MIANALYSE specifications.

8.1. Primary Efficacy Endpoint

Primary analysis will be run on monocular contact lens-corrected distance visual acuity using a logMAR visual acuity scale measured at follow-up visit (Visit 2) for each eye.
This will be analyzed using a linear mixed effects model to test for non-inferiority of K-Lens relative to Placebo. LogMar score is assumed to be normally distributed and this will be verified visually with a QQ-plot of residuals, using the stored SAS output obtained from fitting the linear mixed model, and tested with a normality test. Lens group will be included as fixed effects in the model and investigator site as random effect.
Let y_{ijkl} be the visual acuity measured on the ith eye, i = [Left, Right], of the jth subject, $j = 1, 2, \ldots n_l$, assigned to the kth treatment, $k = 1, 2$, in the lth investigational site, $l = 1,2 \ldots, 5$. The proposed statistical model for the primary analysis is

$y_{ijkl} = \mu + Treatment_k + Site_l + \varepsilon_{i(jkl)}$, where

- μ: overall mean;
- $Treatment_k$: effect of the k^{th} treatment, a fixed effect;
- $Site_l$: effect of the l^{th} investigational site, a random effect;
- $\varepsilon_{i(jkl)}$: random error associated with the i^{th} eye of the j^{th} subject assigned to the k^{th} treatment in the l^{th} investigational site.

Here we assume $site_l$ and $\varepsilon_{ij(kl)}$ are independent and

- $site_l \sim N(0, \sigma^2_{site})$;
- $\begin{bmatrix} \varepsilon_{Left(jkl)} \\ \varepsilon_{Right(jkl)} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_{11} & \sigma_{12} \\ \sigma_{21} & \sigma^2_{22} \end{bmatrix} \right)$.

While the site effect and the error term will have a diagonal covariance matrix, there will be a correlation between the visual acuity of eyes belonging to the same subject. The model will take this into account using an unstructured covariance matrix (UN) between left and right eye. Should the estimation algorithm not converge, then a Compound Symmetry matrix (CS) will be used. In this case, the assumption is that observations coming from different eyes will have the same variance.

$$\begin{bmatrix} \varepsilon_{Left(jkl)} \\ \varepsilon_{Right(jkl)} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2 & \sigma_{12} \\ \sigma_{21} & \sigma^2 \end{bmatrix} \right)$$

The log-likelihood ratio test will be used to test for the homogeneity between the residual covariance structures across treatment groups. The Kenward and Roger method will be used to calculate the denominator degree of freedom.[25]

The null and alternative hypotheses for non-inferiority of K-Lens relative to Placebo are as follows:

$$H_0: \Delta \geq 0.1$$
$$H_A: \Delta < 0.1$$

where Δ is the mean difference in visual acuity between K-Lens and Placebo (K-Lens minus Placebo). The non-inferiority test will be based on the least-square mean difference (K-Lens minus Placebo) and corresponding 95% confidence interval calculated using the final selected model. The upper bound of the 95% confidence interval will be compared to the non-inferiority margin of 0.1 LogMAR. If the upper bound is less than 0.1, K-Lens will be considered non-inferior to Placebo with respect to visual acuity.

The following code will be used to run the mixed model.

```
proc glimmix data = dataset plots=ResidualPanel;
class treatment siteid subjid eye;
model logmar = treatment/ DDFM=KenwardRoger S;
random intercept /subject = siteid;
random eye / type=matrix_cov subject=subjid(siteid) group = treatment
residual;
lsmeans treatment / diff=control('Placebo') cl;
covtest 'Common Variance' Homogeneity;
ods output ParameterEstimates=mixparms Covtests=mixcovtest
CovParms=mixcovp diffs=diffs lsmeans=lsmeans;run;
```

Where:

- "Treatment" is the treatment group variable (K-Lens/Placebo);
- "Siteid" is the investigator site identifier;
- "Eye" is the variable to identify which eye the observation belongs to (left/right);
- "Subjid" is the subject identifier;
- "Matrix_cov" is the covariance structure (UN/CS) between the left eye visual acuity and right eye visual acuity.

If the hypothesis of homogeneity is accepted (chi-square test p-value > 0.05) the syntax "group = treatment" and the 'covtest' statement will be omitted from the final model.

8.2. Other Efficacy Endpoints

8.2.1. Subjective Assessment of Lens Handling

Individual CLUE handling items will be summarized using frequency tables of rating categories by treatment. The derived lens handling score at Visit 2 will be summarized using descriptive statistics by treatment arm.

8.2.2. Average Daily Wear Time (in Hours)

The average daily wear time and the comfortable wear time recorded at Visit 2 will be summarized at subject level by treatment arm.

8.2.3. Clinically Significant Slit-lamp Findings

Proportion of eyes with clinically significant (Grade 3 or 4) slit lamp findings overfitting and post-fit evaluations including unscheduled visits is a secondary endpoint and will be summarized by treatment arm.

8.2.4. Unacceptable Lens Fitting

Proportion of eyes with unacceptable fitting recorded at any evaluation performed on or after the first fitting is a secondary endpoint and will be summarized by treatment arm.

8.2.5. Reported Ocular Symptoms

Proportion of eyes with reported ocular symptoms at Visit 1, Visit 2 and any other unscheduled visit is a secondary endpoint and will be summarized by treatment arm.

9. Safety Analysis

Safety analysis will be conducted on safety population by treatment actually received by subjects.

9.1. Adverse Events

All adverse events will be coded using the MedDRA®. The version of the MedDRA will be indicated in the footnote of relevant AE tables based on the current version used in the clinical data. Number of subjects or eyes with adverse events and number of events will be tabulated by SOC and PT levels. Ocular and non-ocular adverse events will be summarized separately.

Ocular adverse events will be summarized at the eye level and at the subject level.

For eye level summaries, the individual eye will be considered as the unit of analysis. If multiple events occur in the same eye of the same subject, they will be counted only once for that eye.

For subject-level ocular adverse event summaries, the subject will be considered the unit of analysis. Therefore, if both of a subject's eyes report the same adverse event, the subject will be counted once in the numerator and denominator when calculating the percentage of subjects with that adverse event.

For non-ocular adverse events, the subject will be considered as the unit of analysis.

Treatment emergent adverse events (TEAE) are defined as those events that began on or after test lens insertion after randomization.

Significant non-ocular adverse events are non-serious TEAEs that led to temporary or permanent discontinuation of the test article.

Significant ocular adverse events are ocular adverse events with a significant diagnosis of any of the following:

- Contact Lens induced Peripheral Ulcer (CLPU)
- Significant Infiltrate Event (SIE)
- Superior Epithelial Arcuate Lesions (SEALS)
- Significant Elevation in IOP (Intraocular pressure)
- Argyrosis
- Pyogenic Granuloma
- Dacryocystitis
- Canaliculitis
- Other ocular AE reported as significant by the investigator

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

For both ocular and non-ocular events, the following summaries will be produced:

- Overall summary of TEAEs
- TEAEs by SOC and PT
- Serious TEAEs
- Significant TEAEs by SOC and PT
- TEAEs Relationship by SOC and PT
- TEAEs Severity by SOC and PT
- TEAEs Leading to Treatment Discontinuation

If an eye (for eye level ocular summaries) or a subject (for non-ocular summaries and subject-level ocular summaries) reports the same preferred term multiple times, the eye or the subject will only be counted once for that preferred term. As with the preferred term, if an eye or a subject reports multiple adverse events within the same SOC, then the eye or the subject will only be counted once for that SOC.

The relationship of adverse events to study medication will be classified as not related and related. Any adverse event with a relationship of related or possibly related will be considered related. Any event with a relationship of not related or unlikely related will be considered not related. If a subject reports multiple occurrences of the same adverse event, only the most closely related (conservative) occurrence will be presented. Adverse events that have missing/unknown relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing/unknown relationship. Severity will be classified as mild, moderate and severe. If a subject reported multiple occurrences of the same adverse event, only the most severe will be presented. Adverse events that have missing/unknown severity will be presented on tables as "Severe" but will be presented in the data listing with a missing severity.

9.2. Subjects Reported Ocular Symptoms

Ocular symptoms reported at Visit 1, Visit 2 and any other unscheduled visit will be tabulated by treatment, visit and severity at eye level.
Possible symptoms are:

- Burning/Stinging
- Itchiness/Scratchiness
- Dryness
- Lens Awareness
- Grittiness/Foreign Body Sensation
- Redness
- Irritation/Discomfort
- Cloudy/Blurry/Hazy
- Variable Vision

- Other

9.3. Slit-lamp Findings

Any result of the slit-lamp assessment recorded at Visit 1, Visit 2 and any other unscheduled visit will also be tabulated at eye level by treatment, visit and grade. If no slit lamp finding is noted in one eye, this will be considered as having a Grade 0 and will be included in the table as well. Possible findings will be reported in the following order:

- Corneal Edema Grade
- Corneal Neovascularization Grade
- Corneal Staining Grade
- Corneal Staining Location
- Conjunctival Injection Grade
- Tarsal Abnormalities Grade
- Other Complications Grade

Corneal Neovascularization Location will only be presented in the listing of slit-lamp findings.

9.4. Reasons for Discontinuation

Primary reason for discontinuation collected at Visit 2 will be presented in Subject Disposition (see section 5).

9.5. Lens Information

The number of unplanned replacements, folded lenses and damaged lenses will be tabulated by treatment at eye level and subject level.

Type of damage will be summarized by treatment at eye and subject level and will include:

- Chip
- Discoloration
- Fracture
- Non-uniform Haze
- Non-wetting
- Petal Circular defect
- Scratch
- Tear
- Other

In addition, damage location will be tabulated by treatment at eye level and subject level, and will include:

- Peripheral
- Central
- Peripheral and Central

The reason for lens replacement and lens damage will be listed.

9.6. Lens fitting characteristics

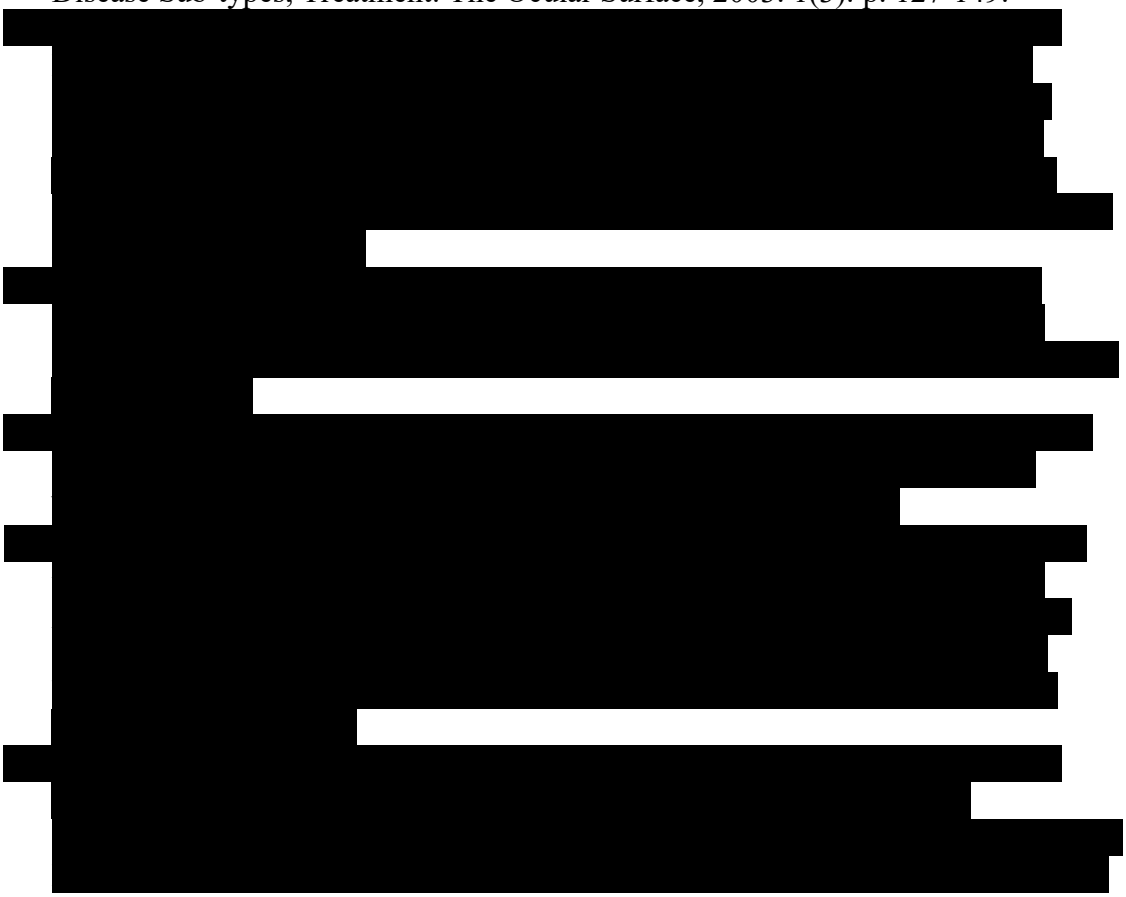
Frequencies of mechanical lens fitting characteristics including lens centration, lens movement and overall lens fitting acceptability at fitting and 1-Week Follow-up evaluations will also be tabulated at eye level by treatment.

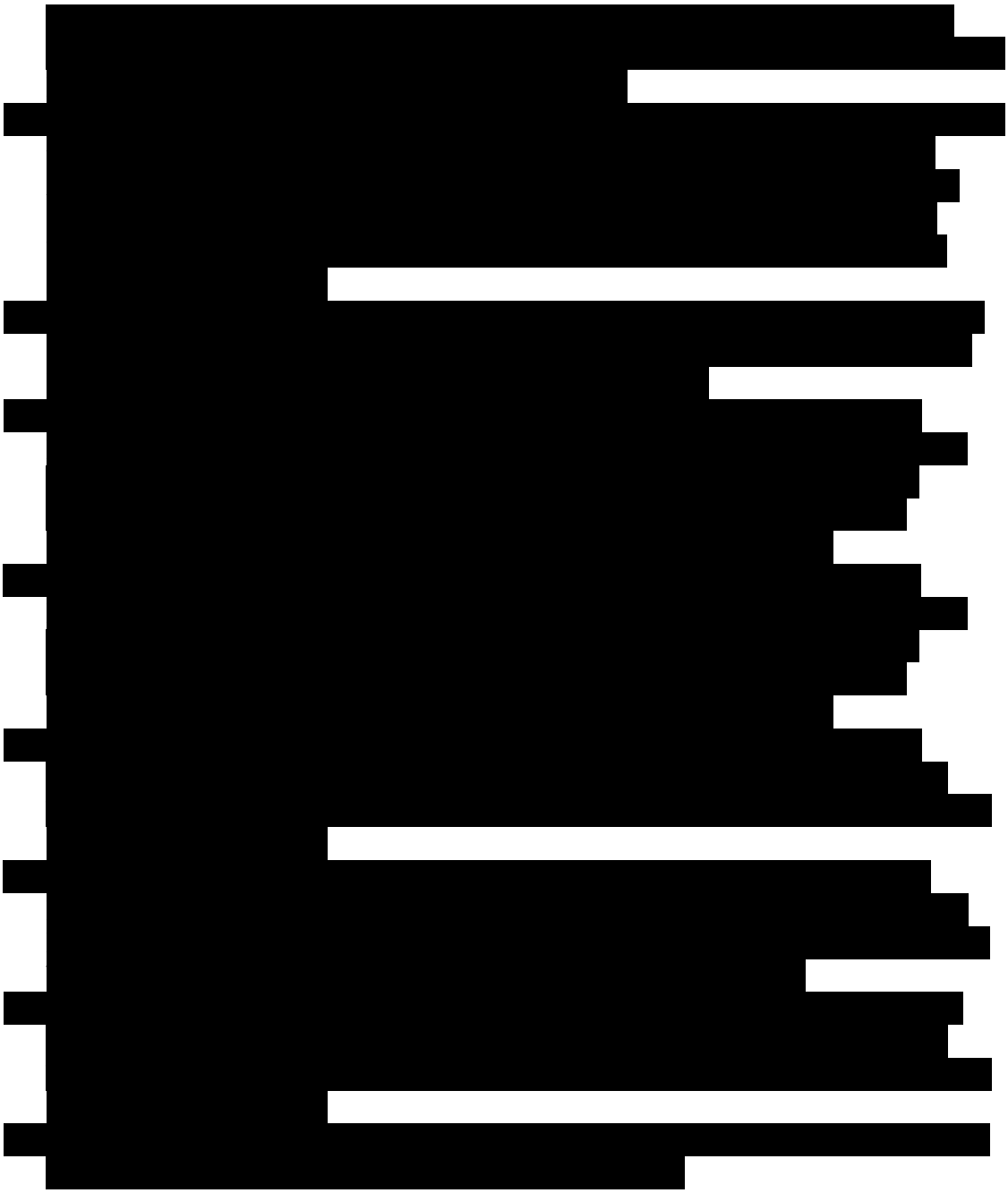
10. Changes in the Planned Analysis

The analysis will be conducted according to that specified in above sections. If for any reason a change is made, the change will be documented in the study report along with a justification for the change.

11. References

1. ISO 14155:2011: Clinical Investigation of Medical Devices for Human Subjects — Good Clinical Practice. Available at: https://www.iso.org/standard/45557.html
2. International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP). Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
3. Declaration of Helsinki - Ethical principles for Medical Research Involving Human Subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
4. United States (US) Code of Federal Regulations (CFR). Available at: https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR
5. Kumar, P., et al., Allergic rhinoconjunctivitis and contact lens intolerance. Clao j, 1991. 17(1): p. 31-4.
6. Pritchard, N., D. Fonn, and D. Brazeau, Discontinuation of contact lens wear: a survey. Int Contact Lens Clin, 1999. 26(6): p. 157-162.
7. Abelson, M.B., Conjunctival Allergen Challenge. Archives of Ophthalmology, 1990. 108(1): p. 84.
8. Abelson, M.B., L. Smith, and M. Chapin, Ocular Allergic Disease: Mechanisms, Disease Sub-types, Treatment. The Ocular Surface, 2003. 1(3): p. 127-149.





22. Wirth, R.J., et al., Development of the Contact Lens User Experience: CLUE Scales. Optom Vis Sci, 2016. 93(8): p. 801-8.
23. Lovie-Kitchin, J.E. and B. Brown, Repeatability and intercorrelations of standard vision tests as a function of age. Optom Vis Sci, 2000. 77(8): p. 412-20.
24. Keselman, H., et al., A comparison of two approaches for selecting covariance structures in the analysis of repeated measurement. Communications in Statistics, 1998. Simulation & Computation(27): p. 591-604.

25. Kenward, M.G. and J.H. Roger, Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics 1997. 53(3): p. 983-997.
26. Health Information Portability and Accountability Act (HIPAA). https://www.hhs.gov/hipaa/for-professionals/privacy/index.html
27. Data Protection Act. http://www.legislation.gov.uk/ukpga/1998/29/contents
28. Graham, John W., Allison E. Olchowski and Tamika D. Gilreath (2007). "How many imputations are really needed? Some practical clarifications of multiple imputation theory." Prevention Science 8: 206–213.

12. Appendices

12.1. Schedule of Study Procedures

Visit Information	Visit 1 Screening, Baseline, Randomization, Lens Dispensing, Initial Clinical Assessments	Visit 2 1-Week Follow-up, Final Evaluation
Time Point	Day 1	Day 6-9
Estimated Visit Duration	2.0 hours	1.5 hours
Statement of Informed Consent	x	
Demographics	x	
Medical History/Concomitant Medications	x	x
Inclusion/Exclusion Criteria	x	
Habitual Contact Lens Information	x	
Compliance and Subject Reported Ocular Symptoms and Adverse Event Review	x	x
Entrance Snellen Distance Visual Acuity	x	x
Subjective Sphero-Cylindrical Refraction and visual acuities	x	x
Subjective Best Sphere Refraction and visual acuities	x	
Slit Lamp Classification Scale	x	x
Lens Assignment	x	
Lens Insertion & Settling	x	
Visual Acuity and Over Refraction	x	
Monocular logMAR Visual Performance (High Contrast, High Illumination)	x	x

Visit Information	Visit 1 Screening, Baseline, Randomization, Lens Dispensing, Initial Clinical Assessments	Visit 2 1-Week Follow-up, Final Evaluation
Time Point	Day 1	Day 6-9
Estimated Visit Duration	2.0 hours	1.5 hours
Lens Fit Assessment	x	x
Reported Average Wearing Time		x
CLUE Handling	x	x
Exit Snellen Distance Visual Acuity	x	x
Dispense Patient Instruction Guide	x	
Dispense Test Article	x	
Study Completion		x

12.2. Missing Data Pattern

Having 2 visits only and assuming the probability of observing the score at Visit 2 does not depend on the presence of the score at Visit 1, these are the possible patterns:

Group	Score V1	Score V2
1	X	X
2	X	.
3	.	X
4	.	.

Where ‘X’ represent a non-missing data and “.” represents a missing data.

These patterns apply to both left and right eye.

12.3. SAS Code for Sensitivity Analysis

The following SAS code will be used to generate the sensitivity analysis for the difference in visual acuity logMAR score (K-Lens versus Placebo), using a MI process for imputation of missing data.

Multiple imputation phase

```
proc mi data= yyyyyyy nimpute=20 seed=51343672 out=outmi ;
      class SITEID TREATMENT;
      var SITEID TREATMENT LOGMARV1_OD LOGMARV1_OS LOGMARV2_OD LOGMARV2_OS;
      fcs discrim(SITEID TREATMENT /classeffects=include) reg (LOGMARV1_OD LOGMARV1_OS LOGMARV2_OD
LOGMARV2_OS /details);
run;
```

In case the analysis of the missing data will show a monotone pattern, the same procedure will be executed with the MONOTONE statement.

```
proc mi data= yyyyyyy nimpute=20 seed=51343672 out=outmi ;
      class SITEID TREATMENT;
      var SITEID TREATMENT LOGMARV1_OD LOGMARV1_OS LOGMARV2_OD LOGMARV2_OS;
      monotone discrim (SITEID TREATMENT /classeffects=include) reg (LOGMARV1_OD LOGMARV1_OS
LOGMARV2_OD LOGMARV2_OS /details);
run;
```

where LOGMARV1_OD is the logmar score at the last visit, excluding unscheduled, prior to visit 2 for the right eye;
LOGMARV1_OS is the logmar score at the last visit, excluding unscheduled, prior to visit 2 for the left eye;
LOGMARV2_OD is the logmar score at visit 2 for the right eye;
LOGMARV2_OS is the logmar score at visit 2 for the left eye;
SITEID is site identifier within each study;
TREATMENT is the treatment variable (K-Lens/Placebo);

Analysis by imputation at each visit

```
proc glimmix data = outmi;
by _imputation_;
class treatment siteid subjid eye;
model logmar = treatment/ DDFM=KenwardRoger S;
random intercept /subject = siteid;
random eye / type=UN subject=subjid(siteid) group = treatment residual;
lsmeans treatment / diff=control('Placebo') cl;
covtest 'Common Variance' Homogeneity;
ods output ParameterEstimates=mixparms Covtests=mixcovtest CovParms=mixcovp diffs=diffs
lsmeans=lsmeans;
run;
```

If the hypothesis of homogeneity is accepted (chi-square test p-value > 0.05) the syntax "group = treatment" and the 'covtest' statement will be omitted from the final model.

The model will take into account using UN covariance matrix for each imputation dataset. In case the algorithm will not converge with the UN for a particular dataset, then the CS matrix will be used for such imputation dataset. This will be reviewed on a case by case basis.

Results combined for the inference at each timepoint and visit

```
proc mianalyze data=diffs;
  modeleffects estimate;
  stderr stderr;
  ods output parameterestimates=parest;
run;

proc mianalyze data=lsmeans;
  by treatment;
  modeleffects estimate;
  stderr stderr;
  ods output parameterestimates=parest_lsmeans;
run;
```

where SITEID is site identifier within each study;
SUBJID is subject identifier;

TREATMENT is the treatment variable (K-Lens/Placebo);
LOGMAR is visual acuity logMAR score at Visit 2.