Johnson & Johnson Vision Care Inc
Medical Affairs

Statistical Analysis Plan

Investigation of ocular symptoms and signs in existing contact lens wearers following extensive digital device use: ACUVUE OASYS®, vs B+L Ultra™ (BASIL)

Protocol CR-5816

Status: Version 1.0
Date: 06 December 2016
Prepared by: Kingsley Ebare

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP) and ICH-E9 guideline (Statistical Principals for Clinical Trials).

Approval Signatures

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AMENDMENT HISTORY

Document Change History			
Revision	**Originator**	**Description of Change(s)**	**Date**
1.0	Kingsley Ebare	New SAP	06 December 2016

ABBREVIATIONS

AE	Adverse event
AICC	Akaike information criteria corrected
BCVA	Best-corrected visual acuity
CI	Confidence interval
CLUE	Contact Lens User Experience™
CRF	Case report form
CSR	Clinical study report
DMC	Data monitoring committee
eCRF	Electronic case report form
ETDRS	Early treatment diabetic retinopathy study
FDA	Food and Drug Administration
GEE	Generalized estimating equation
GSI	Global strategic insights
ICH	International Conference on Harmonization
IRT	Item response theory
ITT	Intent-to-treat
IVRS	Interactive voice response system
LSM	Least-square means
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal investigator
PP	Per protocol
PRO	Patient-reported outcomes
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SLF	Slit lamp findings
VA	Visual acuity

1. INTRODUCTION

1.1. Background

This document describes the data analysis specifications for protocol CR-5816 titled "Investigation of ocular symptoms and signs in existing contact lens wearers following extensive digital device use: ACUVUE OASYS®, vs B+L Ultra™ (BASIL)". The test article is the marketed Contact Lens ACUVUE OASYS® while the control is Ultra™. This study is a single-site, double-masked, randomized controlled crossover trial.

This document will serve as the final guidance for all the statistical analysis and sample size requirement for this study and will supersede section 9 in the protocol if there are any discrepancies (i.e. See Amendment History section).

1.2. Primary Objectives

- To assess subjective overall comfort in a group of existing contact lens wearers who are heavy digital device users (>8hrs in a typical day).

- To compare the subjective overall comfort ratings when these subjects are wearing ACUVUE OASYS® and ULTRA™ silicone hydrogel lenses, using a cross-over group design.

1.3. Secondary Objectives

- To compare the time to haze (TTH) when these subjects are wearing ACUVUE OASYS® and ULTRA™ silicone hydrogel lenses.

- To compare the comfortable wear time (CWT) and overall wear time (WT) when these subjects are wearing ACUVUE OASYS® and ULTRA™ silicone hydrogel lenses.

- To compare the subjective assessments of lens handling, as assessed using the Contact Lens User Experience (CLUE™) questionnaire, when these subjects are wearing ACUVUE OASYS® and ULTRA™ silicone hydrogel lenses.

- To compare the subjective assessments of Comfort at the end of the day, as assessed using the Contact Lens User Experience (CLUE™) questionnaire, when these subjects are wearing ACUVUE OASYS® and ULTRA™ silicone hydrogel lenses.

1.4. Study Design

This is a group sequential, adaptive, prospective, double-masked, randomized 2 x 2 crossover dispensing design. After eligibility for the study has been confirmed during the screening visit, eligible subjects will wear each of the study lenses (ACUVUE OASYS® with HYDRACLEAR® PLUS, ULTRA™ with MoistureSeal™ Technology) for four weeks, in accordance with manufacturers' guidelines, with the order of lens wear being randomized to subjects who wear the test lens in the first period followed by the control lens in the second period and subjects who wear the control lens in the first period followed by the test lens in the second period.

The study will be conducted in up to two phases using a Bayesian adaptive design: phase 1 will enroll up to 135 subjects (targeting 80 to complete), phase 2 will enroll additional subjects, if needed, with a target

completion of additional 50 subjects (130 subjects in total). An interim analysis at the completion of phase 1 will determine the requirement for phase 2.

Table 1 : 2- Treatment, 2-Period (2 x 2) Crossover Design

	Period 1	Period 2	
Habitual	Test →	Control →	Final Visit→
	Control →	Test →	Final Visit→

1.5. Statistical Hypotheses for Study Objectives

1.5.1. Primary Hypotheses:

- The overall CLUE comfort of ACUVUE OASYS® test lens will be non-inferior to the ULTRA™ control lens over the 4 weeks wear period.

1.5.2. Secondary Hypotheses:

- ACUVUE OASYS® test lens will be non-inferior to the control lens ULTRA™ with regards to time to haze (TTH) over the 4 weeks wear period using a non-inferiority margin of 2 seconds.
- ACUVUE OASYS® test lens will be non-inferior to the ULTRA™ control lens with regards to comfortable wear time and Average wear time over the 4 weeks lens period using a non-inferiority margin of 2 hours;
- In terms of Difference between total time of device use and comfortable wear time on a typical day, the test lens ACUVUE OASYS® will be non-inferior to the control lens ULTRA™ over the 4 weeks lens wear period using a non-inferiority margin of -2 hours.
- ACUVUE OASYS® test lens will be non-inferior to the ULTRA™ control lens with regards to lens handling over the 4 weeks lens wear period.
- ACUVUE OASYS® test lens will be non-inferior to the ULTRA™ control lens with regards to Comfort at the end of the day over the 4 weeks lens period using a non-inferiority margin of 0.67 odds ratio.

1.5.3. Tertiary Hypotheses:

- The overall comfort of the test lens will be non-inferior to the control lens for CLUE comfort in at least one of the study time points (2-week and 4-week).

1.6. Sample Size Justification

The sample size calculation was based on the primary endpoint overall CLUE comfort. An adaptive sample size approach is used to allow for modifications based on interim results, with a maximum of 130 evaluable subjects and a minimum of 80 evaluable subjects. Up to 130 subjects are targeted to complete the study. The enrollment of subjects will be conducted in two phases. In the first phase, up to 135

subjects will be initially enrolled and a minimum of 80 subjects are targeted to complete the first phase. An interim analysis will take place after the initially enrolled subjects have completed the study. The interim analysis will be used for the purpose of an early claim of success. If needed, additional subjects will be enrolled in phase 2 with 130 subjects targeted to complete the study.

Operating characteristics:

This section presents the operating characteristics of the design. The simulation details are presented in the next section. In Table 2, the Δ represents the difference in CLUE comfort between the test and control lenses (test – control). The Δ = -5 row corresponds to the null hypothesis for non-inferiority. The P(130) column shows the probability that the study results in a successful claim of non-inferiority with 130 subjects (i.e., power). The P (80) column shows the probability that the study results in an early successful claim of non-inferiority with 80 subjects.

Table 2. Probability of successful claim of non-inferiority using 2 sided 95% confidence intervals

	CLUE Comfort	
Δ	**P(80)**	**P(130)**
-5	.026	0.024
-2.5	.156	0.200
0	.539	0.624
2	.823	0.889

From the table above, under the null hypothesis, Δ = -5, there is a 0.024 probability of the trial resulting in non-inferiority. In the case of Δ = 2, there is a 0.889 probability of a successful claim of non-inferiority with a 0.823 probability of early claim of success.

Simulation details:

Using data generated from parameters of historical studies, we run 1000 2x2 crossover trials of 130 subjects for each scenario Δ : (a) -5, (b) -2.5, (c) 0 and (d) 2.

The simulation details are presented below:

Let the random variable $y_i = (y_{i1}, y_{i2}, y_{i3})$ denote the CLUE comfort score for the i^{th} subject at 1-day, 2 weeks and 4 weeks Follow-Up respectively. The likelihood of y_i is constructed as follows:

$$y_i \sim N(\mu, \Sigma)$$

where $\mu = (\mu_1, \mu_2, \mu_3)^T$ represents mean CLUE comfort at 1-day, 2 weeks and 4 weeks respectively, and Σ is a 3x3 variance-covariance matrix. The average means μ_1, μ_2 and μ_3 are given by:

$$\mu_1 = \mu_0 + \beta_1 \text{Lens} + \delta$$
$$\mu_2 = \mu_0 + \beta_1 \text{Lens} + \delta$$
$$\mu_3 = \mu_0 + \beta_1 \text{Lens} + \delta$$

The parameter $\beta 1 = \Delta$ is the mean difference between the test and control lenses while μ_0 represents the time effect which was assumed to be the same. The parameter δ represents the random subject effect.

The simulation was carried out with assumed standard deviation of 23 at 1-day, 2 weeks and 4 weeks respectively. All estimates were from the historical study CR-5751. Assumed correlation for consecutive measures of CLUE comfort at the respective time points within lens wear period was 0.5 and between lens wear periods was 0.25. CR-5751 was a dispensing, 2-site, double-masked, parallel trial with the same lenses as this study.

Posterior summaries generated from this simulated data were then summarized to estimate the probability of completing the study (P130) and early successful claim (P80) respectively. From the table above, assuming a $\Delta = 2$, there is a 0.823 probability of the trial resulting in early claim of non-inferiority based on CLUE comfort data.

The CLUE comfort cross-over model was fit for each simulated trial and each scenario of Δ to estimate the power and type I error of this adaptive design. Independent vague normal N(0, 10000) priors was used for all fixed effect regression parameters. Inverse Wishart IW(R, 3) prior was used for the variance-covariance matrix Σ. For the random subject effect δ, a non-informative flat prior was considered. The Metropolis sampler algorithm as implemented by the SAS/STAT 14.1 MCMC procedure was used to estimate posterior distributions of all unknown parameters. Inferences were made based on 2-sided 95% posterior credible intervals for relevant parameters.

1.7. Randomization and Masking

The study lenses will be worn in a bilateral and random fashion using a 2x2 crossover design. Permuted block randomization will be used to minimize the potential for treatment imbalance. A block size of two (2) sequences will be utilized. A computer-generated randomization scheme will be used to randomly assign subjects to one of the two possible lens wear sequences (TEST/CONTROL or CONTROL/TEST). The random scheme will be generated using the PROC PLAN procedure from SAS Software Version 9.4 (SAS Institute, Cary, NC)[3].

The investigational site will fit and dispense both study lens types. The study site must follow the randomization scheme provided and complete enrollment according to the randomization list and not pre-select or assign subjects. The randomized assignment of subjects will be performed at the first visit prior to the first fitting. The following must have occurred prior to randomization:

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

When the trial fitting assessment is ready to be conducted, the following steps should be followed:

1. Investigator or designee (documented on the Delegation Log) will consult the randomization scheme to obtain the study test article assignment for that subject prior to dispensing.

2. Investigator or designee will record the subject's number on the appropriate line of the randomization scheme.

3. Investigator or designee will pull the appropriate test articles from the study supply. All test articles that were opened, whether dispensed or not, must be recorded on the Test Article Accountability Log in the "Lenses Dispensed" section.

This is a double-masked study where subjects, investigators are masked to the identity of the study lenses during the study period.

The identity of the study lenses will be masked to subjects and study investigators. The study site will follow the randomization scheme provided and will complete enrollment according to the randomization list and will not pre-select or assign subjects. Every effort will be made to maintain double masking throughout the study; however, due to the visibility of identifier markings on certain lens types, this may not always be possible. To maintain masking of subjects and investigators during lens dispense at V2 and V6, an unmasked research assistant will transfer the study lenses and the original blister pack solution into paper cups designated to right and left eyes. The research assistant will take the paper cups to the exam room, where they will dispense the study lenses from the paper cups to the subject using disinfected tweezers. The subject is required to wash their hands prior to receiving the lenses for insertion. To maintain masking of subjects and investigators at the two Day 14 visits (V4 and V8), an unmasked research assistant will consult the randomization schedule to determine if lenses need to be replaced (ACUVUE OASYS® with HYDRACLEAR® PLUS) or remain the same (ULTRA™ with MoistureSeal™). In case of ACUVUE OASYS® with HYDRACLEAR® PLUS, the research assistant will prepare two paper cups with a new pair of study lenses to be dispensed to the subject after the biomicroscopy exam (ocular health permitting), in the same way as described above for the initial lens dispense at V2 or V6. In case of ULTRA™ with MoistureSeal™ lenses, the subject will receive the same pair of lenses (ocular health permitting, dispensed from a paper cup with saline solution) prior to leaving the CCLR. The subject is required to wash their hands prior to receiving the lenses for insertion.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Scheduled Visit Number	Description	Visit Window	Target Time Point
1	Enrollment Visit, Screening	0	-1
2	Baseline and dispensing Period 1	≥ 1 day from Visit 1	0
3	Follow-Up 1(1-day Period 1)	1 day after visit 2	1
4	Follow-up 2 (Day 14 Period 1)	12 to 16 days from Visit 2	14
5	Follow-up 3 (Day 28 Period 1)	25 to 31 days from Visit 2	28
6	Baseline and dispensing Period 1	≥ 7 days from Visit 5	0
7	Follow-Up 1(1-day Period 2)	1 day after visit 6	1
8	Follow-up 2 (Day 14 Period 2)	12 to 16 days from Visit 6	14
9	Follow-up 3 (Day 28 Period 2)	25 to 31 days from Visit 6	28

2.2. Analysis Sets

2.2.1. Efficacy Analysis Set(s)

2.2.1.1. Primary Efficacy Analysis Set

Efficacy analyses will be performed on all randomized subjects who completed the study and did not substantially deviate from the protocol as determined by the trial cohort review committee prior to database hard lock (per-protocol population). Justification of excluding subjects with protocol deviations in the per-protocol population set will be documented in a memo to file. Additional post-hoc analyses may be conducted by including all randomized subjects who have been successfully dispensed and have at least one follow-up visit.

2.2.1.2. Secondary Efficacy Analysis Set

The secondary analyses will be performed on the per-protocol population as described above.

2.2.1.3. Tertiary Efficacy Analysis Set

The tertiary analyses will be performed on the per-protocol population as described above.

2.2.2. Safety Analysis Set

Safety analyses will be performed on the safety population, which will be comprised of all randomized subjects who have been successfully dispensed a study lens.

2.3. Definition of Subgroups

There will be no planned subgroup analysis in this study. Further exploratory analysis may be considered at the discretion of the Study Responsible Clinician

3. INTERIM ANALYSIS AND DATA MONITORING

This is a group sequential adaptive trial with one stopping rule for superiority. The study will be conducted in two phases. In Phase 1, up to 135 subjects will be successfully enrolled with a target completion of 80. The data from Phase 1 will then be analyzed to see if superiority can be concluded. If so, the enrollment will be stopped. If superiority cannot be concluded, the predictive probability (PP) of trial success will be calculated. If $PP < 0.20$, we stop the study for futility. If $PP \geq 0.80$, we continue the trial onto Phase 2 and recruit additional subjects with a target completion of 130 subjects. Otherwise the clinical team will make the decision whether or not the enrollment will continue in the second phase.

Adverse events, protocol deviations, and product complaints will be monitored throughout the study. For the purposes of this study the following definitions will apply:

- Adverse Event: any untoward medical occurrence in a patient or clinical investigation subject administered a test article whether or not caused by the test article or treatment.

- Protocol Deviation: any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

- Product Complaint: any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for clinical trial use.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Demographic characteristics will be summarized by randomization and overall for all subjects enrolled using descriptive statistics for continuous variables, and numbers and percentages of subjects for categorical variables. Demographic information will include age, sex, and race.

4.2. Disposition Information

The disposition (accountability) of all enrolled subjects will be presented by study lens and overall to show the number and percentage of subjects in each of the following status subgroups:

1. Completed: Subjects are considered to have completed the study if they have completed all required visits through Visit 9 (Day 28 Follow-up period 2).

2. Discontinued: Subjects are considered to have discontinued from the study if they are (i) randomized (ii) successfully dispensed and (iii) discontinued because of one of the following reasons: (a) unsatisfactory visual response due to study lens, (b) unsatisfactory lens fitting due to study lens, (c) lens discomfort, (d) lens handling difficulties, (e) withdrew consent, (f) lost to follow-up, (g) subject no longer meets eligibility criteria (e.g. pregnancy), (h) subject withdrawn by PI due to non-compliance to protocol, (i) discontinuation of study treatment as a result of the investigator's belief that for safety reasons it is in the best interest of the subject to stop treatment, (j) study lens no longer available, or (k) other, specify (additional details to be documented).

3. Total dispensed: Completed + Discontinued

4. Enrolled not Successfully Dispensed: Subjects are considered to be enrolled not successfully dispensed subjects if they were (i) enrolled to the study (provided informed consent) but failed to satisfy the eligibility criteria (inclusion/exclusion criteria), (ii) were not randomized to study lens for any reason, or (iii) if they are randomized but did not satisfactorily complete the dispensing process. This includes subjects who were dispensed a different type of study lens for each eye or who were dispensed same study lens for both eyes but did not return for any follow-up visits.

5. Total enrolled: Completed + Discontinued + Enrolled not Successfully Dispensed.

6. The percentage will be calculated using total enrolled as denominator.

Safety and efficacy analysis sets will be defined as subsets of dispensed subjects (Completed + Discontinued).

4.3. Treatment Compliance

Summaries of subjects' compliance information will be reported through tables for wear time and comfortable wear time.

4.4. Protocol Deviations

All reported protocol deviations will be listed.

4.5. Prior and Concomitant Medications

Listings of subjects' prior and concurrent medications will be reported.

4.6. Discontinuation

All reasons for discontinuation will be listed including lens type being used at time of discontinuation.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All planned analysis for this study will be conducted with a two-sided type I error rate of 5%.

The type I error rate may be inflated in a statistical design that incorporates interim analysis. From 1000 simulations we run under the null hypothesis of the primary endpoint (Δ = -5). The results showed that the one sided type I error rate for the primary endpoint was inflated from 2.5% to 3.05%. In order to maintain a 2.5% one-sided type I error, we set the posterior probability criterion for non-inferiority at the final analysis to 0.98.

The secondary hypotheses will be evaluated only in the event that the primary hypothesis passes. Therefore, we preserved the posterior probability criterion for superiority in the secondary analysis at 0.975.

5.1.2. Data Handling Rules

Missing or spurious values will not be imputed for the primary or secondary hypotheses. 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 of 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, sensitivity analysis will be conducted using multiple imputation methods if the proportion of subject dropout is greater than the 15%.

5.2. Analysis of CLUE Questionnaire

5.2.1. Definition

The contact lens user experience™ (CLUE) questionnaire 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. A 5 point increase in an average CLUE score translates into 10% shift in the distribution of scores for population of soft disposable contact lens wearers (Wirth et *al.*; 2016).

5.2.2. Analysis Methods for CLUE Aggregate Scores

Comfort CLUE scores will be analyzed using a Bayesian hierarchical model to compare between test and control lenses. The regression model will include baseline value, lens type, lens wearing sequence and lens wearing period as fixed effects. Subject will be included in the regression model as a random effect factor. Other subject characteristics such as age, gender, and CLDEQ-8 score will also be included as fixed effects when appropriate.

The Model:

Let $y_i = y_{1i}, y_{2i}, y_{3i}$ denote the CLUE comfort scores for the ith subject, at 1-day, 2-week and 4-week follow-up, respectively. The likelihood of yi is constructed as follows:

$$\mathbf{y_i \sim N(\mu, \Sigma),}$$

Where $\mu = (\mu_i, \mu_2, \mu_3)^T$ and Σ is a 3 x 3 variance-covariance matrix. Here μ_i, μ_2, μ_3 are given by:

$$\mu_1 = \mu_0 + \pi_1 + \beta_1 Base + \beta_{21} Lens + \beta_3 Sequence + \beta_4 Period + \delta_i$$

$$\mu_2 = \mu_0 + \pi_2 + \beta_1 Base + \beta_{22} Lens + \beta_3 Sequence + \beta_4 Period + \delta_i$$

$$\mu_3 = \mu_0 + \pi_3 + \beta_1 Base + \beta_{23} Lens + \beta_3 Sequence + \beta_4 Period + \delta_i$$

Where BASE is the centered baseline values, π_1, π_2, π_3, the time effects (1-day, 2-week and 4-week follow-up) with the constraints $\pi_1 + \pi_2 + \pi_3 = 0$ and δ_i the random subject effect. Here we define Lens = 0 for the control lenses and Lens=1 for the test lenses. Therefore β_2. $(\beta_{21} + \beta_{22} + \beta_{23})/3$ stands for the difference in comfort scores between the test and control; a positive β_2. means the test is better than the control. Furthermore, the sequence = 0 for the order Control/Test and sequence = 1 for the order Test/Control while period = 1 for the first period and 0 for the second period.

The independent vague normal N(0,1000) priors for the regression coefficients μ_0 and β_i i= 1,2,3..., 4. For the variances of random effects, we also use independent vague priors, namely inverse gamma IG(0.001, 0.001) for σs2 and inverse Wishart IW(R,3) for Σ. R is determined by S = E[Σ] = 3R where S is the sample variance-covariance matrix of y_i.

The Metropolis sampler algorithm as implemented in the MCMC Procedure (SAS/STAT 13.2, SAS Institute, Cary, NC)[4] will be used to estimate the posterior distributions of the unknown parameters. Inferences will be made based on a posterior credible interval for the relevant parameters.

Hypothesis Testing for CLUE Aggregate Scores:

The null and alternative hypotheses for non-inferiority are as follows:

$$\text{H0: } \beta_2. \leq -5, \text{ Ha: } \beta_2. > -5,$$

where $\beta_2. = (\beta_{21} + \beta_{22} + \beta_{23})/3$.

Non-inferiority will be declared if the lower bound of the 2-sided 95% credible interval of the difference between Test and Control is greater than -5: $P(\beta_2. > -5|y) \geq .98$.
Superiority will be declared if the lower bound of the 2-sided 95% credible interval of the mean difference between Test and Control is greater than 0: $P(\beta_2. > 0|\, y) \geq .98$.

The superiority test will be performed only if non-inferiority can be established.

The cut-off for non-inferiority/superiority, 0.98, is selected to maintain a 0.05 two-sided type I error. Refer to section 5.1.1 for more details.

5.3. Analysis of Secondary Endpoints

5.3.1. Analysis of Time to Haze

Time to haze measures the time until a row of letters in a computerized chart is no longer "readable" while the eyes are kept open. The subject stands at a distance of 1m from the chart while wearing the study contact lenses.

Time to haze will be analyzed using a Bayesian hierarchical model to compare the test and the control. The regression model will be similar to the regression model used for the analysis of the CLUE aggregate (See section 5.2.2).

Hypothesis Testing for Time to Haze:

The null and alternative hypotheses for non-inferiority are as follows:

$$H0: \beta_{2.} \leq -2 \text{ seconds}, \quad Ha: \beta_{2.} > -2 \text{ seconds}.$$

where $\beta_{2.} = (\beta_{21} + \beta_{22} + \beta_{23})/3$.

Non-inferiority will be declared if the lower bound of the 2-sided 95% credible interval of the difference between Test and Control is greater than -2 seconds: $P(\beta_{2.} > -2|y) \geq .975$.
Superiority will be declared if the lower bound of the 2-sided 95% credible interval of the mean difference between Test and Control is greater than 0: $P(\beta_{2.} > 0|\, y) \geq .975$.

The superiority test will be performed only if non-inferiority can be established.

5.3.2. Analysis of Average and Comfortable Wear Time

Average and Comfortable Wear Time will be analyzed using a Bayesian hierarchical model to compare the test and the control. The regression model will be similar to the regression model used for the analysis of the CLUE aggregate (See section 5.2.2).

Hypothesis Testing for Average and Comfortable Wear Time:

The null and alternative hypotheses for non-inferiority are as follows:

$$H0: \beta_{2.} \leq -2 \text{ hours}, \quad Ha: \beta_{2.} > -2 \text{ hours}.$$

where $\beta_{2.} = (\beta_{21} + \beta_{22} + \beta_{23})/3$.

Non-inferiority will be declared if the lower bound of the 2-sided 95% credible interval of the difference between Test and Control is greater than -2 hours: $P(\beta_{2.} > -2|y) \geq .975$.
Superiority will be declared if the lower bound of the 2-sided 95% credible interval of the mean difference between Test and Control is greater than 0: $P(\beta_{2.} > 0|\, y) \geq .975$.

The superiority test will be performed only if non-inferiority can be established.

5.3.3. Analysis of comfortable digital device use while wearing study lenses.

For this endpoint, subjects are asked to state the average time (in hours) of digital device use in a day for the preceding week. Subjects are also asked to state the comfortable time spent on digital device. Of key interest is the difference between the average digital device use and the comfortable digital device use. All valid responses must include (1) Responses for average and comfortable digital device use and (2) comfortable digital device use while wearing study lenses should not be greater than the average digital device use while wearing study lenses.

This endpoint will be analyzed using a Bayesian hierarchical model to compare the test and the control lenses. The regression model will be similar to the regression model used for the analysis of the CLUE aggregate (See section 5.2.2).

Hypothesis testing for difference between Average and Comfortable digital device use while wearing study lenses:

The null and alternative hypotheses for non-inferiority are as follows:

H0: $\beta_{2.} \geq 2$ hours, Ha: $\beta_{2.} < 2$ hours.
where $\beta_{2.} = (\beta_{21} + \beta_{22} + \beta_{23})/3$.

Non-inferiority will be declared if the lower bound of the 2-sided 95% credible interval of the difference between Test and Control is less than 2 hours: $P(\beta_{2.} < 2|y) \geq .975$.
Superiority will be declared if the lower bound of the 2-sided 95% credible interval of the mean difference between Test and Control is lower than 0: $P(\beta_{2.} < 0|\, y) \geq .975$.

The superiority test will be performed only if non-inferiority can be established.

5.3.4. Analysis of Comfort at the end of the day

P3 questionnaires including the item "Comfort at the end of the day" (Item ID: P3_0006_p36) will be administered at each follow-up visit using five-point scales Excellent (1) to poor (5).

Analysis will be performed using Bayesian multinomial models for ordinal data. Each regression model will include lens type, lens wearing sequence, and lens wearing period. Other subject characteristics such as age and gender will also be included as fixed effects when appropriate.

The Model:

Let $y_{ijklm} = (y_{ijklm1}, y_{ijklm2}, y_{ijklm3}, y_{ijklm4}, y_{ijklm5})$ denote the rating for the item "Comfort at the end of the day" for the ith subject assigned to the lth study lens and the kth sequence in the jth period at the mth follow-up time point.
Possible values of y_{ijklm} are 1 if the subject rating is n and 0 otherwise (n= 1 for Excellent, …, 5 for poor).
The likelihood of y_{ijklm} is constructed as follows:

$$y_{ijklm} \sim \text{Multinomial}\,(p_{ijklm1}, p_{ijklm2}, p_{ijklm3}, p_{ijklm4}, p_{ijklm5},),$$
$$p_{ijklm1,} = \gamma_{ijklm1}$$
$$p_{ijklmn,} = \gamma_{ijklmn} - \gamma_{ijklm(n-1)} \quad 2 \leq n \leq 4$$
$$p_{ijklm5,} = 1 - \sum_{n=1,\ldots,4} p_{ijklmn}$$

$$\text{logit}\left(\gamma_{ijklmn}\right) = \theta_n + \beta_1\, Lens_l + \beta_2\, Period_j + \beta_3\, Seq_k + \beta_4\, time_m + \delta_1 + \delta_2$$

where θ_n is the intercept for levels n = 1, 2, 3, 4, $p_{ijklm1,} = Pr(\gamma_{ijklm1} = 1)$ for P3 item "Comfort at the end of day". Here we assume the random subject effects are independent and identically distributed (i.i.d) as $\delta_1 \sim N(0, \sigma_P^2)$ and random time effects are i.i.d as $\delta_2 \sim N(0, \sigma_m^2)$ for l = 1, 2 (lens), j = 1,2 (period), k = 1, 2 (sequence), i = 1 . …n (subject).
In this model, the treatment i will be determined by the period j and sequence k, so we denote i as a function of j and k. We define $Lens_1 = 0$ for the control lenses and $Lens_2 = 1$ for the test lenses. The odds ratio for having higher rating for this endpoint can be written as OR = e^{β_1}.

We will use independent vague N (0, 1000) priors for the regression coefficients βs s = 1…5.
For θ_n, we are considering the following priors:

π0(θ) ~ N(0,1000)
π0(θ2| θ1) ~ N(0,1000)I(θ>θ1)
π0(θ3| θ2) ~ N(0,1000)I(θ>θ2)
π0(θ4| θ3) ~ N(0,1000)I(θ>θ3)

For the variance of the random effects, we also use vague independent priors, namely σs2 ~ inverse-gamma (0.001, 0.001). The Metropolis sampler algorithm as implemented in the SAS/STAT MCMC Procedure will be used to estimate the posterior distributions of the unknown parameters. Inferences will be made based on a posterior credible interval for the relevant parameters.

Hypotheses Testing:

Results will be reported as regression coefficient mean estimates and odds ratios with 95% credible intervals. For this item, the null and alternative hypotheses for non-inferiority are as follows: H0: OR ≤ 0.67 Ha: OR > 0.67; where OR represents the odds ratio of having higher rating of the Test lens compared to the Control lens. Non-inferiority will be declared if the lower bound of the 95% credible interval of OR is greater than 0.67.

Superiority will be declared if the lower bound of the 2-sided 95% credible interval of ORis greater than 1: Pr(OR= eβ1 > 1| y) = 0.975 .

6. SAFETY

6.1. Analysis Specifications

6.1.1. Level of Significance

No statistical analyses will be completed on safety data. Safety parameters will be summarized using descriptive statistics.

6.1.2. Data Handling Rules

Missing or spurious values will not be imputed. The count of missing values will be included in the summary tables and listings.

6.2. Primary Safety Parameters

The safety parameters for this study are:

- Adverse events
- Biomicroscopy
- Lens deposit
- Lens fitting characteristics
- Ocular symptoms
- Average wear time
- Snellen Visual Acuity
- Reasons for discontinuation

The safety parameters will be tabulated using frequency distribution tables and descriptive statistics. There will be no statistical analyses of these variables.

6.3. Adverse Events

Listings of all reported ocular and non-ocular AEs and SAEs will be reported. There will be separate summaries for adverse events and infiltrative adverse events.

6.4. Discontinuation Reasons

The number of discontinued eyes by the analysis time point will be displayed by visit. An aggregate number of discontinued eyes will also be tabulated at the analysis time point.

7. REPORTING CONVENTIONS

P-values greater or equal than 0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.0001". All percentages will be reported to one decimal place. The mean and median will be reported to one decimal place greater than the original data. The standard deviation will be reported to two decimal places greater than the original data. Minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

8. QUALITY ASSURANCE MEASURES

8.1. Data Quality

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites and review of protocol procedures with the principal investigator. The principle investigator, in turn, must ensure that all sub-investigators and study staff are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study article.

Guidelines for case report form completion will be provided and reviewed with study personnel before the start of the study. The case report forms will be reviewed for accuracy and completeness during monitoring visits and after transmission to data management. Any data discrepancies will be resolved with the investigator or designee, as appropriate.

Quality Assurance representatives from Johnson & Johnson Vision Care, Inc. may visit study sites to review data produced during the study and to access compliance with applicable regulations pertaining to the conduct of clinical trials. The study sites will provide direct access to study-related source data/documents and reports for the purpose of monitoring and auditing by Johnson & Johnson Vision Care, Inc. and for inspection by local and regulatory authorities.

8.2. Statistical Programming

The statistical programming will follow analysis dataset specification as well as table shell specification. To ensure the validity of the analysis datasets as well as table and listing results, an independent program reviewer will be designated.

8.3. Statistical Analysis

All statistical analyses will be reviewed by a second statistician to ensure proper execution and compliance to the analysis planned in the SAP. The executive summary will be reviewed by a second statistician to ensure the interpretations of the statistical analysis results are valid.

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