Johnson & Johnson Vision Care Inc
Research & Development
Clinical Affairs

Statistical Analysis Plan

Long-term Evaluation of [redacted] UV Blocker

Protocol CR-5638

JJVCI Investigational Contact Lens [redacted]

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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	Jessica Cannon	Original SAP	December 15, 2016

ABBREVIATIONS

AE	Adverse event
CI	Confidence interval
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
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	Interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal investigator
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-5638 titled "Long-term Evaluation of [redacted] UV Blocker". The test article is the JJVCI Investigational Contact Lens [redacted] while the control is ACUVUE® OASYS®. This study is 2- Phase randomized, 8-visit, partially subject-masked (Control arm only), 14-week dispensing trial. The study lenses will be worn as daily wear (DW) for a period of 12 weeks, with follow-up visits occurring after 1-, 2-, 4-, 8- and 12-weeks. All visits up to visit 6 are considered to be Phase I of the study while visits 7 and 8 are considered to be Phase II of the study. After the 12-week follow-up has occurred (Phase I has completed); the habitual lenses will be worn for a period of two weeks with weekly visits (Phase II).

The document is intended to describe the guidance for statistical analysis up to the 12-week follow up (Phase 1) and will supersede section 9 in the protocol if there are any discrepancies (i.e. See Amendment History section)

1.2. Study Objectives

The primary objective of this long-term study is to evaluate the safety and efficacy the investigational contact lens [redacted] by comparison with ACUVUE® OASYS® both worn as daily wear modality for a period of 2 weeks.

1.3. Study Design

This is a randomized partially-masked, controlled, two arm parallel group, multi-site, 3-month dispensing study, with follow-up visits at 1-, 2-, 4-, 8- and 12-weeks of a JJVCI Investigational Contact Lens compared to Marketed Acuvue Oasys® Contact Lens. After the completion of the 12-week follow-up evaluation subjects will wear their habitual lenses for another 2 weeks, with weekly visits. Approximately 120 subjects will be screened and enrolled to ensure that at least 100 subjects complete the study.

The study begins with an initial visit (Visit 1 - Day 0). If a subject is found to meet all eligibility criteria, they will be randomized and fit with either Test or Control lens in both eyes; otherwise, the subject will be deemed ineligible for this study.

If the subject is dispensed study lenses at the initial visit, seven follow-up visits will be conducted. The follow-up visits will occur after the initial visit approximately at 1-, 2-, 4-, 8- and 12-weeks for the study lenses and 13- and 14-weeks for the habitual lenses. Unscheduled follow-up visits may occur during the study. Subjects will be advised to wear the study lenses at least 6 hours a day, for minimum of 5 days per week. On the day of the scheduled follow-up visit subjects are advised to wear the study lenses to the follow-up visits. Both the Test and Control lenses will be worn as a daily wear with lens replacement every two weeks including at the 2-, 4-, 8-week follow-up visits. Damaged or lost lenses may be replaced throughout the study.

Subjects enrolled must be at least 18 years of age at the time of consent, and habitual wearers of frequent replacement silicone hydrogel soft contact lenses in both eyes worn as daily wear.

1.4. Statistical Hypotheses for Study Objectives

This is a feasibility study and all the following hypotheses are exploratory in nature. Further analysis may be considered at the discretion of the Study Responsible Clinician.

1.4.1. Primary Hypotheses:

Efficacy

- The Test lens ([redacted] will be significantly lower than the Control lens (ACUVUE® OASYS®), with respect to Eyestrain caused by glare score. The assessments will be made at the 2-, 4-, 8- and 12-week follow-up visits.

- The Test lens ([redacted] will be statistically no different than the Control lens (ACUVUE® OASYS®) with respect to distance monocular LogMAR visual acuity. The assessments will be made at the 2-, 4-, 8- and 12-week follow-up visits.

Safety

- The Test lens ([redacted] will be statistically no different than the Control lens (ACUVUE® OASYS®) with respect to percentage of eyes with grade 3 or higher slit lamp findings (Biomicroscopy). The assessments will be made at each follow-up visit.

1.4.2. Secondary Hypotheses:

Efficacy

- The Test lens ([redacted] will be statistically no different than the Control lens (ACUVUE® OASYS®) with respect to average wearing time. The assessments will be made at the 2-, 4-, 8- and 12-week follow-up visits.

Safety

- The Test lens ([redacted] will be statistically no different than the Control lens (ACUVUE® OASYS®) with respect to the percentage of reported symptoms, problems or complaints (yes/no). The assessments will be made at each follow-up visit.

1.5. Sample Size Justification

The plan is to enroll 60 eligible subjects per arm with a target completion of 50 subjects per arm. This is a feasibility study and the sample size was not based on any empirical calculation. A statistical power analysis is provided below for different scenarios of size effects.

The power analysis was based on historical data from 3 double masked randomized 2x2 Crossover bilateral multi-site studies ([redacted] and [redacted] Since this study is a 2-arm parallel study only data from the first period was used each of the historical studies in the summary below. There is not a historical study available with the same design and lenses, therefore [redacted] and [redacted] where chosen since both studies contain the Test lens [redacted] The study [redacted] was chosen since it contains the Control lens ACUVUE® OASYS®. In all three studies lenses were worn as a daily wear for approximately 2-weeks each. The follow-up visits occurred approximately at 1- and 2-weeks after the

initial visit. Out of 89 subjects enrolled in [redacted] 84 (94.4%) completed the study, 4 (4.5%) discontinued and 1 (1.1%) was enrolled but not dispensed (screen failure). Similarly, out of 71 subjects enrolled in [redacted] 67 (94.4%) subjects completed the study, and 2 (2.8%) discontinued and 2(2.8%) was enrolled but not dispensed. Lastly, out of 109 subjects enrolled in [redacted] 100 (91.7%) completed the study, 6 (5.5%) subjects were discontinued and 3 (2.8%) subjects were enrolled not dispensed. Of all 263 subjects who were dispensed in the studies, 185 (70.3%) were female and 78 (29.7%) were male. The ages of subjects ranged from 18 to 40 years with an average age of 29 years. Table 1 summarizes the primary endpoints data pooled from the three studies for the first period only.

Table 1: Summary of the primary endpoints data pooled from [redacted] [redacted] and [redacted] Period 1 Only

SLF Grade 2	Visits			
	1-Week		2-Week	
	Test	Control	Test	Control
Corneal Edema	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Conjunctival Injection	1(0.6)	0(0.0)	1(0.6)	0(0.0)
Tarsal Abnormalities	2(1.2)	11(10.7)	4(2.6)	9(9.0)
Corneal Neovascularization	0(0.0)	18(17.6)	0(0.0)	14(14.0)
Corneal Staining	0(0.0)	1(0.5)	0(0.0)	0(0.0)
Other Findings	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total Eyes (N)	154	102	150	100
Any SL Grade 2[b]	3(1.9)	30(29.4)	5(3.3)	23(23.0)
Any SLF Grade 3+	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Total Unique Eyes	154	102	150	100
Total Unique Subjects	77	51	75	50

% = nx100/N; SD = Standard Deviation
a SLF reported during an unscheduled visit were included in the following scheduled visit.
b The percent (%) of Any SLF Grade 2 is calculated using Total Unique Eyes as a denominator.

Primary Safety Endpoint (Slit Lamp Findings):

The power was estimated from the formula given by Diggle et al. (2002)[2] for clustered binary data for a pre-specified sample size of N=50 per arm:

$$Z_\beta = \frac{\left[\sqrt{\frac{N*\{n(p_1-p_2)^2\}}{1+(n-1)*\rho}} - Z_\alpha\sqrt{2\bar{p}\bar{q}}\right]}{\sqrt{(p_1q_1+p_2q_2)}}$$

where p_1: Response proportion in group 1 (Test), $q_1 = 1 - p_1$, p_2: Response proportion in group 2 (Control), $q_2 = 1 - p_2$, $\bar{p} = (p_1 + p_2)/2$, $\bar{q} = 1 - \bar{p}$, n: number of observations per cluster(n was set to 10; 2 eyes x 5 time points), N is the number of subjects per arm and ρ is the common correlation across the n observations. The term z_α is the z score that correspond to the pre-specified type I error error α. The term z_β is the z score that corresponds to the estimated power 1- β for pre-specified size effects.

There were no SLF of grade 3 or 4 reported in any of the three studies. Using previous research in the $literature^{4,5}$, the anticipated proportion of eyes with any SLF grade 3 and 4 is estimated to be less than or equal to 0.5% in both test and control arms.

Table 2: Power calculation for various effect sizes and correlations for SLF

Test Proportion	Control Proportion	Delta	Rho	Power
0.001	0.0510	.005	0.25	33%
0.001	0.0510	.005	0.50	58%
0.001	0.0510	.005	0.75	71%
0.0025	0.0525	.005	0.25	36%
0.0025	0.0525	.005	0.50	61%
0.0025	0.0525	.005	0.75	73%
0.005	0.0550	.005	0.25	40%
0.005	0.0550	.005	0.50	64%
0.005	0.0550	.005	0.75	75%
0.01	0.0600	.005	0.25	48%
0.01	0.0600	.005	0.50	69%
0.01	0.0600	.005	0.75	78%

Primary Efficacy Endpoint (Visual Acuity):

The power calculations were performed using Diggle's formula $(Diggle\ et\ al.;\ 2002)^2$ for clustered continuous data for a pre-specified sample size of N=50 per arm:

$$Z_\beta = \sqrt{0.5 * \left(\frac{N(n\left[\frac{\mu_1-\mu_2}{\sigma^2}\right]^2)}{1+(n-1)\rho}\right)} - Z_\alpha$$

Where $\sigma 2$ is the assumed common variance in the two groups, $\mu 1 - \mu 2$: the difference in means between the two groups (Test - Control), n: number of observations per cluster, N is the number of subjects per arm and ρ is the common correlation across the n observations.

The plan is to enroll 60 eligible subjects per arm with a target completion of 50 subjects per arm. During the enrollment period, the subject dropout rate will be closely monitored, if unexpectedly high dropout rate is observed in certain arm(s), the targeted total enrollment number will be increased accordingly in order to ensure a minimum of 50 subjects per group to complete the 3-month follow-up. Below is a table of power calculations for different effect sizes and correlations.

Table 3: Power calculation for various effect sizes and correlations for LogMAR Visual Acuity

Rho	Effect Size	Power
0.10	0.10	95.1%
0.25		95.4%
0.50		96.0%
0.75		96.3%
0.10	0.25	74.0%
0.25		77.2%
0.50		81.1%
0.75		84.0%
0.10	0.50	14.8%
0.25		20.1%
0.50		28.8%
0.75		36.5%

1.6. Randomization and Masking

Subjects will be randomly assigned to either JJVCI Investigational Contact Lens (Test) or ACUVUE® OASYS® (Control) groups based on a computer-generated randomization schedule prepared before the study by the study biostatistician. The randomization will be stratified by study site and randomly permuted blocks of 2 assignments will be used to achieve 1:1 test versus control lens type ratio within each study site. The assignment of subjects will be performed at the first visit prior to the first fitting. The following must have occurred prior to assignment:

- 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

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 will be a partially-masked study. The identity of the study lenses will be masked to the subject and as much as possible to the investigator.

The following procedures will be followed:

- Subjects will not be aware of the identity of the study contact lenses.
- Investigators involved in the data collection will be masked as to the identity of the study lenses.

This is a partially-masked study. The dynamic nature (variable shade) of the Test lens makes full masking impossible. However, the identity of the Control lenses will be masked to the subject by way of investigational foil. This will reduce the likelihood that habitual wearers of ACUVUE OASYS recognize the Control lens and increase the likelihood that questionnaires will be answered unbiasedly.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Pooling Algorithm for Analysis Centers

Data will be pooled from multiple study centers for this analysis. The justification for pooling comes from three critical factors: the study sites follow one common protocol, the sponsor provides close monitoring of study site compliance, and the study sites use common data collection procedures.

2.2. Analysis Sets

2.2.1. 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 analysis population 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 (i.e. all available data).

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

Iris color information will be collected (Hue, and Lightness of iris) in order to categorize subjects into two groups "Dark" and "Light" iris to allow for comparisons within iris categories.

3. INTERIM ANALYSIS AND DATA MONITORING

There will be one planned interim analysis 6 weeks after first subject first visit. The interim analysis will include an analysis of Eyestrain score caused by glare. This study is the first time that data pertaining to Eyestrain will be collected. The analysis will be conducted when all dispensed subjects have completed

the 4-week follow-up evaluation. There are no pre-specified stopping rules planned in this interim analysis.

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 (Phase I): Subjects are considered to have completed Phase I of the study if they have completed all scheduled visits through Visit 6 (12-week Follow-up Visit).

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: Unsatisfactory Lens Fitting due to study lens (a) Withdrew Consent (b) Lost to Follow Up (c) Subject no longer meets eligibility criteria (e.g. pregnancy) (d) Subject withdrawn by PI due to non-compliance to protocol (e) Discontinuation of study treatment as a result of the investigator's belief that for safety (f) Reasons it is in the best interest of the subject to stop treatment (g) Study lens no longer available (h) A scheduled visit was missed.

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

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% for primary and secondary hypotheses. Adjustment for multiple comparisons across time will be performed using Bonferroni's method. Both adjusted and unadjusted results will be reported.

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. Efficacy Endpoint(s)

5.2.1. Definition

The primary efficacy endpoints are contact lens monocular distance Visual Acuity (VA) on LogMAR scale using ETDRS charts and Eyestrain caused by glare score. VA will be evaluated under high luminance and high contrast conditions at 4 meters from ETDRS charts. Eyestrain caused by glare will be assessed using eyestrain items and will be scored using Item Response Theory.

The primary efficacy endpoints will be evaluated at 2-, 4-, 8- and 12-week follow-up visits.

The secondary endpoint is daily Average Wearing Time in hours.

The secondary efficacy endpoint will be evaluated at 2-, 4-, 8- and 12-week follow-up evaluations.

5.2.2. Analysis Methods

Efficacy Analysis:

Visual Acuity

Contact lens monocular distance best-corrected visual acuity (BCVA) on LogMAR scale will be analyzed using a linear mixed model to test for the differences between the Test and Control group at each follow-up visit. Lens group, time (1-, 2-, 4-, 8- and 12-weeks) and the interaction between lens and time will be included as fixed effects in the model; and investigator site, subject and eye nested within subject as random effects when appropriate. The covariance between residuals from the same eye and subject at different time points will be selected based on the finite-sample Corrected Akaike's Information Criterion. Covariance structures considered include Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Spatial Power (SP(POW)), *Ante*-dependence (ANTE(1)) and unstructured (UN). For ANTE (1) and SP (POW) structures, site, subject and eye nested within subject will be included as random effects. For the remaining structures only site and subjects will be included as random effects. The covariance structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fit the data. Heterogeneous residuals covariance structures (R-side) across lens groups will be considered when appropriate. The log-likelihood ratio test will be used to test for the homogeneity between the residual covariance structures. The Kenward and Roger method will be used for the denominator degree of freedom.

Comparisons between the Test and the Control groups will be conducted at each time point using a t-test on least-square means from the repeated measure analysis. Adjustment for multiple comparisons across time will be performed using Bonferroni's method with alpha equal to 0.01(0.05/5). The corresponding simultaneous confidence intervals of least-square means differences will be calculated with 99% confidence. Unadjusted multiple comparisons will be calculated with 95% confidence for each comparison.

Average Wear Time (AWT)

AWT (in hours) will be analyzed using a linear mixed model to test for difference between the Test and the Control groups. Lens Group, Time (2-, 4-, 8- and 12-week), and the interaction between lens and time will be included as fixed effects in the model; and site as random effect. The covariance between residuals from the same subject at different time points will be selected based on the finite-sample corrected Akaike's Information Criterion. Covariance structures considered include homogenous compound symmetry (CS), heterogeneous Compound symmetry (CSH), Spatial Power (SP (POW)), Ante-dependence (ANTE (1)) and unstructured (UN). For ANTE (1) and SP (POW) structures, site and subject will be included as random effects. For the remaining structures only site will be included as random effect. The covariance structure that returns the lowest AICC will be selected as the structure that best fit the data. Heterogeneous residuals covariance structures (R-side) across lens groups will be considered when appropriate. The log-likelihood ratio test will be used to test for the homogeneity between the residual covariance structures. The Kenward and Roger method will be used for the denominator degree of freedom.

Comparison between the Test and the Control groups will be conducted at each time point using a t-test on least square means from the repeated measure analysis. Adjustment for multiple comparisons across time (2-, 4-, 8- and 12-weeks) will be performed using Bonferroni's method with alpha equal to 0.0125(0.05/4). The corresponding simultaneous confidence intervals of least-square means differences will be calculated with 98.75% confidence. Unadjusted multiple comparisons will be calculated with 95% confidence for each comparison.

Eyestrain caused by glare score
Eyestrain items will be scored using item response theory. A lower score indicates less eyestrain, whereas higher score indicates more eyestrain. Eyestrain score will be analyzed using a linear mixed model to test for difference between the Test and the Control groups. Lens Group, time (2-, 4-, 8- and 12-week), iris category and all interactions between lens group, time and iris category will be included as fixed effects in the model; and site as random effect. The covariance between residuals from the same subject at different time points will be selected based on the finite-sample corrected Akaike's Information Criterion. Covariance structures considered include homogenous compound symmetry (CS), heterogeneous Compound symmetry (CSH), Spatial Power (SP (POW)), Ante-dependence (ANTE (1)) and unstructured (UN). For ANTE (1) and SP (POW) structures, site and subject will be included as random effects. For the remaining structures only site will be included as random effect. The covariance structure that returns the lowest AICC will be selected as the structure that best fit the data. Heterogeneous residuals covariance structures (R-side) across lens groups will be considered when appropriate. The log-likelihood ratio test will be used to test for the homogeneity between the residual covariance structures. The Kenward and Roger method will be used for the denominator degree of freedom.

If the interaction between lens and iris category is significant at the 15% significance level, then comparison between lenses within each iris category will be conducted. If the interaction between lens, iris category and time is significant at the 15% significance level, then comparison between lenses within each iris category at each timepoint will be conducted.

Comparison between the Test and the Control groups will be conducted at each time point using a t-test on least-square means from the repeated measure analysis. Adjustment for multiple comparisons across time will be performed using Bonferroni's method with alpha equal to 0.0125 (0.05/4). The corresponding simultaneous confidence intervals of least-square means differences will be calculated with 98.75% confidence. Unadjusted multiple comparisons will be calculated with 95% confidence for each comparison.

6. SAFETY

6.1. Analysis Specifications

6.1.1. Level of Significance

All planned analysis for this study will be conducted with a two-sided type I error rate of 5% for primary and secondary hypotheses. Adjustment for multiple comparisons across time will be performed using Bonferroni's method. Both adjusted and unadjusted results will be reported.

6.1.2. 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.

6.2. Safety Endpoint(s)

6.2.1. Definition

The primary safety endpoint is the frequency per eye of any corneal infiltrate or any grade 3 or higher SLF including conjunctival injection, corneal edema, corneal neovascularization, corneal staining, tarsal abnormalities, or any other complications. SLFs will be evaluated using the FDA grading scale ranging from 0 to 4, with grade 0 represents the absence of findings and 1 to 4 representing successively worse findings (i.e. Grade 1 = trace, Grade 2 = Mild, Grade 3 = moderate and Grade 4 = severe).

The safety endpoint will be evaluated at 1-, 2-, 4-, 8- and 12-week follow-up visits and during unscheduled visits. Events occurring during an unscheduled visit will be counted in the subsequent scheduled visit. For example, if a SLF grade 3 or higher occurs between Visit 1 and Visit 2, it will be counted in Visit 2. If there are multiple events at a given time point for one eye, it will be counted only once.

The secondary safety endpoint is the frequency per eye of any reported ocular symptoms, problems, or complaints.

The safety endpoints will be evaluated at 1-, 2-, 4-, 8- and 12-week follow-up visits and during unscheduled visits. Events occurring during an unscheduled visit will be counted in the subsequent visit. For example, if an ocular symptom, problem, or complaint is reported between Visit 1 and Visit 2, it will be counted in Visit 2. If there are multiple events at a given time point for one eye, it will be counted only once.

6.2.2. Analysis Methods

Slit Lamp Findings (SLF)

SLF responses will be categorized into a binary outcome as 0 if no Grade 3 or higher SLF or 1 if any Grade 3 or higher SLF. Events occurring during an unscheduled visit will be counted in the subsequent scheduled visit. For example, if a SLF grade 3 or higher occurs between Visit 1 and Visit 2, it will be counted in Visit 2. If there are multiple events at a given time point for one eye, it will be counted only once. The safety endpoint will be analyzed using a Generalized Estimating Equation (GEE) model (Zeger and Liang; 1986)2 with a binomial distribution and logit link function. The regression model will include terms for lens group, time (1-, 2-, 4-, 8- and 12-week) and the lens group by time interaction (group*time). Appropriate working correlation matrix will be selected to take on consideration the correlation between measurements within each subject using Quasilikelihood Information Criterion (QIC). Working correlation structures to be considered will include independence (IND), exchangeable (Exch), autoregressive AR(1) and unstructured (UN). The covariance structure that returns the lowest QIC will be selected as the structure that best fit the data. If all model fails to converge, a reduced model will be considered by removing group*time and time from the model.

For unadjusted estimates the odds ratio of outcome 1 between the Test and the Control groups will be calculated with a 95% confidence interval to test for the difference between the Test and Control groups. For adjusted estimates the odds ratio of outcome 1 between the Test and the Control groups will be calculated with a simultaneous 99% confidence interval to test for the difference between the Test and Control groups.

If there are no sufficient SLF findings of Grade 3 or higher, analysis will be performed on any SLF grade 2 or higher SLF. Further analyses by subject, visit and/or slit lamp findings category will also be considered if necessary.

Ocular Symptoms, problems or complaints

Reported ocular symptoms, problems or complaints (0 = No, 1 = Yes) at any visit will be analyzed using a GEE model for clustered binary outcome to assess the difference between the Test and Control groups. The regression model will include terms for lens group, time (1-, 2-, 4-, 8- and 12-week) and the lens group by time interaction. Appropriate working correlation matrix will be selected to take on consideration the correlation between measurements within each subject using Quasi-likelihood Information Criterion (QIC). Working correlation structures to be considered will include exchangeable, autoregressive AR(1) and unstructured (UN).

If the interaction lens by time is significant at the 15% significance level, the difference between the Test and Control will be assessed for each follow-up visit.

For unadjusted estimates the odds ratio of outcome 1 between the Test and the Control groups will be calculated with a 95% confidence interval to test for the difference between the Test and Control groups. For adjusted estimates the odds ratio of outcome 1 between the Test and the Control groups will be calculated with a simultaneous 99% confidence interval to test for the difference between the Test and Control groups.

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, corneal inflammatory events (CIEs) and contact lens papillary conjunctivitis (CLPC).

6.4. Contact Lens Corrected Visual Acuity

A shift from the initial corrected lens visual acuity to the final corrected lens visual acuity will be presented across both eyes using counts and percentages for Safety test eyes. The aforementioned summary will also be broken out by visit. The count of the number of eyes that had a corrected lens visual acuity of 20/30 or better at the initial and final visits will be presented by completed and discontinued eyes. In addition, the count of the number of eyes with a visual acuity with lens within 1 and worse than 1 Snellen line of best corrected at the final visit will be reported for both completed and discontinued eyes. A detailed listing of eyes that worsened by 2 or more lines at final visit compared to baseline will be presented.

6.5. Unscheduled Lens Replacement

The number of unscheduled lens replacements and corresponding reasons will be tabulated by visit and overall across eyes for both completed and discontinued eyes.

6.6. Other Safety Parameters

Lens deposit, lens debris, Keratometry, and lens centration and movement will also be descriptively summarized.

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.

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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1. SAS Institute Inc: SAS® 9.4 Statements: Reference, Third Edition. Cary, NC: SAS Institute Inc; 2014.
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4. Reindel W, Merchea MM, Rah MJ, Zhang L., Meta-analysis of the ocular biocompatibility of a new multipurpose lens care system. Clin Ophthalmol. 2013;7:2051-6. doi: 10.2147/OPTH.S48914.
5. SUMMARY OF SAFETY AND EFFECTIVENESS DATA. VISTAKON® (senofilcon A) Contact Lens, Clear and Visibility Tinted with UV Blocker - PMA Number: P040045, December 20, 2005.