Johnson & Johnson Vision Care, Inc.
Research & Development
Clinical Sciences

Statistical Analysis Plan

Evaluating the impact of JJVC senofilcon A-based contact lens with new UV-blocker on day and night driving performance

Protocol CR-5830

JJVCI Investigational Contact Lens senofilcon A-based with new UV-blocker

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Prepared by:	Jessica Cannon

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).

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AMENDMENT HISTORY

DOCUMENT CHANGE HISTORY			
Version	**Originator**	**Description of Change(s)**	**Date**
1.0	Jessica Cannon	Original SAP- Analysis Changes from Protocol for low luminance contrast threshold	November 7, 2017

ABBREVIATIONS

AE	Adverse event
BCVA	Best-Corrected Visual Acuity
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
JJVC	Johnson & Johnson Vision Care
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 study protocol CR-5830 titled "Evaluating the impact of JJVC senofilcon A-based contact lens with new UV-blocker on day and night driving performance" Version 3.0 Amendment 2.0 dated on September 14th, 2017. The test article is the JJVCI Investigational Contact Lens senofilcon A-based with new UV-blocker while the two controls are ACUVUE® OASYS® brand contact lens with HYDRACLEAR® Plus worn with spectacle frame without lenses (Control 1) and ACUVUE® OASYS® brand contact lenses with HYDRACLEAR® Plus worn with Transitions® XTRActive™- gray spectacles (Control 2)

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

The study aims to investigate the effect of senofilcon A contact lenses with new UV-blocker on vision and driving performance in both daytime and nighttime lighting under real world driving conditions. This will be achieved through field-based driving studies on a closed-road driving circuit at night and during the day. Quantitative methods will be used to assess vision and driving performance under a range of challenging conditions and appropriate masking,
order of testing randomization and control conditions will be used.

1.2. Study Objectives

The objective of this study is to evaluate the effect of JJVC senofilcon A-based contact lens with new UV-blocker on vison and day and night driving performance under real world driving conditions. This study is intended to support the Pre-Market Notification, 510(k), submission of ACUVUE® (senofilcon A) Soft Contact Lens with New UV Blocker.

1.3. Study Design

This is a randomized, single-masked, crossover, dispensing study, with 4 visits. Comparisons between the JJVC investigational lens and the two controls will occur at visit 2 (vision testing) and visit 3 and 4 (driving performance). Approximately 28 subjects will be screened and enrolled to ensure that at least 24 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, he/she will be randomized to the Test lens and one of the Control lenses for an initial lens fitting evaluation using a 2x2 crossover design (Test/Control1, Test/Control2, Control1/Test, Control2/Test); otherwise, the subject will be deemed ineligible for this study.

After the fitting evaluation at Visit 1, non-discontinued subjects will be scheduled for three additional visits. Visit 2 will occur approximately 24 hours after the initial visit, visit 3 will occur approximately 24 hours after visit 2 and visit 4 will occur approximately 1 week after visit 3. At Visit 2, eligible subjects will be randomized and laboratory testing will be conducted on all test articles in a random order based on the randomization scheme. Subjective assessment of driving performance in both daytime and nighttime will be performed in a random order, based on the

randomization scheme, in two different visits at Visit 3 and Visit 4. Unscheduled follow-up visits may occur during the study. The planned duration of lens wear is for the experimental procedures only (between 1-3 hours during visits 2-4). Participants will not have access to test articles at study closure.

1.4. Statistical Hypotheses for Study Objectives

1.4.1. Primary Hypotheses

1. The Test lens will be non-inferior to the Control 1 lens with respect to overall night driving performance. A non-inferiority margin of -0.25 will be used.

1.4.2. Secondary Hypotheses

1. The Test lens will be non-inferior to the Control 1 lens with respect to binocular low luminance high contrast visual acuity. A non-inferiority margin of 0.1 LogMAR will be used.

2. The Test lens will be no different than the Control 1 lens with respect to low luminance low contrast threshold without glare.

3. The Test lens will be no different than the Control 1 lens with respect to the percentage of road signs correctly identified at night driving.

4. The Test lens will be no different than the Control 1 lens with respect to average distance to correctly identify a pre-determined road sign at night driving.

5. The Test lens will be no different than the Control 1 lens with respect to the percentage of hazards avoided at night driving.
6. The Test lens will be no different than the Control 1 with respect to average pedestrian recognition distance at night driving.

1.5. Sample Size Justification

The study is designed and powered to demonstrate non-inferiority of the Test lens relative to the Control 1 lens with respect to night driving performance score. Assuming no difference between the Test and Control 1 lens, the sample size was calculated using a non-inferiority margin of -0.25. The sample size of 24 subjects is consider sufficiently large to test for non-inferiority with a minimum power of 80% and a two-sided type I error of 0.05. The plan is to enroll 28 eligible subjects with a target completion of 24 subjects. During the enrollment period, the subject dropout rate will be closely monitored, if an unexpectedly high dropout rate is observed, the target enrollment will be increased accordingly to ensure a minimum of 24 subjects per group complete the study.

The non-inferiority margin and sample size calculations were based on available historical data from 6 published papers between 2009 and 2015 and from an investigator initiated study (IIS) sponsored by JJVC in 2016 that examined the effect of vision condition on driving performance. The Table below summarizes the studies considered in the meta-analysis.

Table 1: Summary of published papers considered in the meta-analysis

Year	Author	Paper Title	Sample Size	Age (Mean)	Driving Time	Study Group	Vision Condition
2002	Wood, JM	Age and Visual Impairment Decrease Driving Performance as Measured on a Closed-Circuit Road	139	57.4	Day & Night	Young	Corrected
						Middle-Age	Corrected
						Older	Uncorrected
						Older with ocular disease	Uncorrected
						older with moderate / severe ocular disease	Uncorrected
2005	Chaparro, A. et al.	Effects of Age Auditory and Visual Dual Tasks on Closed-Road Driving Performance	28	48.3	Day	Young	Corrected
						Older	Uncorrected
2006	Wood, JM. et al.	Bilateral cataract surgery and driving performance	47	71.1	Day	Normal vision	Corrected
						Cataract	Uncorrected
2009	Wood, JM. et al.	Interaction between visual status, driver age and distracters on daytime driving performance	39	47.9	Day	Normal vision	Corrected
						Blur	Uncorrected
						Cataract	Uncorrected
2010	Wood, JM. et al.	Effects of Simulated Visual Impairment on Nighttime Driving Performance	20	27.5	Night	Normal vision	Corrected
						Refractive blur	Uncorrected
						Simulated cataract	Uncorrected
2012	Wood, JM. et al.	Useful Field of View Predicts Driving in the Presence of Distracters	92	73.6	Day	Driving without visual distraction	Corrected
						Driving with visual distraction	Uncorrected
2014	Wood, JM. et al.	Differential Effects of Refractive Blur on Day and Nighttime Driving Performance	12	25.8	Day Night	Spectacles w/ Blur 0.00D	Corrected
						Spectacles w/ Blur +0.50D	Uncorrected
						Spectacles w/ Blur +1.00D	Uncorrected
						Spectacles w/ Blur +2.00D	Uncorrected
2016	Wood, JM. et al.	Investigation of the impact of uncorrected astigmatism on night driving performance*	10	24.4	Night	ACUVUE OASYS	Uncorrected
						ACUVUE OASYS for Astigmatism	Corrected

*JJVC sponsored IIS study (not published)

After categorizing the vision condition of the study groups into a binary variable as corrected and uncorrected, a Bayesian random effect mate-regression model was conducted on the pooled data

to evaluate the overall effect of uncorrected vision on driving performance. The model can be written as

$$y_{ij}|\mu_{ij} = \mu_{ij} + e_{ij}; \text{ with } e_{ij} \sim N(0, S_{ij}^2)$$

$$\mu_{ij} = \boldsymbol{X_{ij}\beta} + \delta_{ij}; \text{ with } e_{ij} \sim N(0, \sigma^2)$$

Here y_{ij} is the driving performance in vision condition group *i* in study *j*, $\boldsymbol{X_{ij}}$ is a vector of covariates from the i^{th} vision condition group and j^{th} study and $\boldsymbol{\beta}$ is the vector of regression coefficients. The term δ_{ij} is the random effect due to the between study variation while s_{ij}^2 represents the within study variation (known). The regression model included vision condition (corrected vs. uncorrected) and the covariates: driving time (day, night, day & night), average age and indicator variables of whether or not cone gap perception (not used in this study), course time and hazard avoidance were included in the calculation of the driving performance composite score.

We used independent vague normal N(0,1000) priors for the regression coefficients $\boldsymbol{\beta}$, vague inverse-gamma with shape and scale parameters of 0.001 for the variance parameter σ^2. The Metropolis sampler algorithm as implemented in the SAS MCMC Procedure (SAS/STAT 14.1, SAS Institute, 2015) was used to carry out parameter estimation. After a burn-in of 80,000 iterations, we run the algorithm for additional 500,000 iterations with a thinning factor of 100 to allow posterior chains of estimated parameters to converge. Convergence of the simulated chains was assessed using autocorrelation and sample trace plots.

The posterior mean difference in driving performance between corrected and uncorrected vision was estimated to be 0.579 with 95% credible interval (95% CrI) of (0.249, 0.917). The estimated variance was 0.0483 with 95% CrI of (0.0051, 0.1692).

With a sample size of 24 subjects, the estimated power for different scenarios of intra-class correlation (ICC) is shown in the table below:

Table 2: Statistical Power by ICC

Intra-class correlation (ICC)	Between subject variance σ^2	Effect size	Power (%)
.40	0.05	0.25	71
.50	0.05	0.25	85
.60	0.05	0.25	95

The sample size calculation was conducted using the PROC POWER Procedure (SAS/STAT 14.1, SAS Institute, 2015). The non-inferiority hypothesis testing problem of a 3x3 crossover design was formulated as a two-sample non-inferiority hypothesis testing (Peng Sun, 2010).

As discussed above, the estimated posterior mean difference in driving performance between corrected vision (treated) and uncorrected vision (untreated) was estimated to be 0.579 with 95% credible interval (95% CrI) of (0.249, 0.917). We therefore used the lower bound of the 95% credible interval as the non-inferiority margin (~-0.25). This represents a discount of 43% from the estimated difference between corrected vision and uncorrected vision.

1.6. Randomization and Masking

Participants will wear all study lenses in a bilateral fashion. There will be three levels of randomization in this study: (1) Sequence of driving time (Day and Night), (2) Sequence of Lens wear (Test, Control 1 and Control 2) and (3) Driving route (A, B and C). Hazard and pedestrian locations will be randomized for each driving route.

Subjects will be first randomly assigned to one of two possible driving time sequences (Day/Night or Night/Day) using a 2x2 crossover design. Within each diving time (Day and Night) subjects will be randomly assigned to one of six possible lens wear sequences using a 3x3 Williams crossover design:

Table 3: 3X3 Williams Design

Sequence	Period 1	Period 2	Period 3
1	Test	Control 1	Control 2
2	Test	Control 2	Control 1
3	Control 1	Test	Control 2
4	Control 1	Control 2	Test
5	Control 2	Test	Control 1
6	Control 2	Control 1	Test

The design is balanced with respect to first order carry-over effect as every treatment follows every other treatment the same number of times.

Within each time and lens type combination subjects will be randomized to a driving route (Route 1, Route 2 and Route 3) to further reduce any potential selection bias. The randomization scheme will be generated using the PROC PLAN procedure from SAS Software Version 9.4 (SAS Institute, Cary, NC). The study site must follow the randomization scheme provided and complete enrollment per the randomization list and not preselect or assign subjects.

Every effort will be made to mask both the subject and the investigator, to reduce potential bias where ever possible. Subjects will be masked to the identity of the investigational product when only a contact lens correction is worn. However, if subjects perceive a change in light level during Test contact lens wear, they may become aware of the product being tested.

Subjects will also be aware of the test condition when the ACUVUE® OASYS® brand contact lenses with HYDRACLEAR® Plus is worn with Transitions® XTRActive™- Gray spectacle

frames (Control 2) as the other test conditions will involve contact lens wear with a spectacle frame without spectacle lenses.

Investigators will be involved in the on-road driving data collection (clinical personal within the vehicle) will be partially-masked as to the identity of the investigational product. (i.e. another investigator will fit the contact lens prior to the driving assessment).

Under normal circumstances, the mask should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the mask should be broken only if specific emergency treatment/course of action would be dictated be knowing the treatment status of the subject. In such cases, the investigator may, in an emergency contact the medical monitor. In the event the mask is broken; the sponsor must be informed as soon as possible. The date, time and reason for the unmasking must be documented in the subject record. The investigator is also advised not to reveal the study treatment assignment to the clinical site or sponsor personnel.

2. GENERAL STATISTICAL CONSIDERATIONS

All data summaries and statistical analyses will be performed using the SAS software version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics will be reported for all key variables as appropriate. Continuous data will be summarized descriptively by n, mean, standard deviation (SD), median, minimum (Min) and maximum (Max). Categorical data will be summarized descriptively by frequency count (n) and percentage (%) of subjects or eyes within each category level.

Summaries will be presented by visit and study lens type (Test, Control1, Control2), as applicable, for the analysis population set of interest. The denominator for all percentages will be the number of subjects (or eyes as applicable) with available data in the group/lens under consideration. Unscheduled visits will be summarized separately and will be excluded from the primary and secondary analysis.

The primary analysis will be conducted using the GLIMMIX Procedure (SAS/STAT 14.2, SAS Institute, Cary, NC). See **Error! Reference source not found.** for more details.

2.1. Level of Statistical Significance

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.

2.2. Analysis Sets

The study participants will consist of Open licensed drivers (aged 20-49 years) with more than one year of driving experience. Participants must be regular drivers with best-corrected monocular visual acuity of 20/20 (logMAR 0.00) or better in each eye. Participants must be regular soft contact lens wearers with refractive errors within the range of available study contact lenses supplied by JJVC with uncorrected astigmatism of no more than 1.00 DC.

The following three populations will be defined and used in the analysis and presentation of the data.

2.2.1. All Enrolled

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

2.2.2. Per-Protocol Population

The Per-protocol population will consist of 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.

2.2.3. Safety Analysis Set

Safety population be comprised of all subjects who were administered any test article excluding who drop out prior to administering any test article. At least one observation for safety endpoints should be recorded (e.g. slit-lamp finding, adverse events … etc.) or on after lens insertion start date.

Subjects will be analyzed as per treatment received.

2.3. Data Handling Rules

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. Dropout is expected to be one of the main reasons of missing data in the trial. Past soft contact lens trials don't provide any evidence that subject dropout is systematic or not at random.

2.4. Definition of Subgroups

No subgroup analysis is planned in this study.

2.5. Covariate Adjustment

All models will be adjusted for age and gender as fixed covariates. If these factors are not significant at the 15% significance level they will be removed from the final model.

3. INTERIM ANALYSIS AND DATA MONITORING

There will be no 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 on safety, per-protocol and all enrolled population using descriptive statistics for continuous variables, and numbers and percentages of subjects for categorical variables. Demographic information will include age, sex, race, ethnicity and iris color.

Age is calculated in accomplished years at informed consent date.

The following baseline characteristics will be summarized at eye level:

- Monocular and binocular subjective spherocylindrical refractions on LogMAR scale
- Monocular and binocular Subjective best sphere refractions (logMAR)

4.2. Disposition Information

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.

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

1. Completed: Subjects are considered to have completed the study if they (i) provided informed consent, (ii) they are eligible and (iii) have completed all visits through Visit 4.

2. Discontinued: Subjects are considered to have discontinued from the study if (i) test article was administered and (ii) discontinued from the study. Reasons for discontinuation include: (a) Subject's death during the study (b) subject withdrawal of consent (c) Subject not compliant to protocol (d) subject lost to follow-up (e) subject no longer meets eligibility criteria (f) subject develops significant or serious adverse events causing discontinuation of study lens wear (e.g. an event during a measurement session at any visit) (g) subjects who have experienced a corneal infiltrative event (h) investigators clinical judgement regarding the subject safety reasons (that it is in the best interest of the subject to stop treatment) (i) lack of efficacy and safety including lens handling difficulties, poor vision, poor comfort, or unacceptable fit.

3. Total dispensed: Total number subjects for which test articles were administered (Completed + Discontinued)

4. Enrolled but Not Dispensed: Subjects are considered to be Enrolled Not Dispensed Subjects if they were (i) enrolled to the study (provided informed consent) but failed to satisfy the eligibility criteria (inclusion/exclusion criteria) or (ii) if they are randomized but did not receive a test article.

5. Total enrolled: Completed + Discontinued + Enrolled but Not Dispensed

The percentage will be calculated using total enrolled as denominator.

4.3. 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. All reported protocol deviations will be listed.

4.4. Medical History

A listing of medical and surgical history will be created for all enrolled subjects.

4.5. Prior and Concomitant Medications

Prior and concomitant medications will be documented during screening and updated during the study when applicable.

Disallowed medications or any concomitant therapies that are disallowed for this study include: Any ocular medications or any systemic medications that are known to interfere with contact lens wear.

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

4.6. Reasons for Discontinuation

Primary reasons for discontinuation, if any, will be tabulated using frequency count and percentage n (%) using the following categories:

- Adverse event (AE)
- 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 noncompliance to protocol
- Test Article No Longer Available
- Others

A listing of discontinued subjects will be created including lens type being used at time of discontinuation. Reasons for discontinuations categorized as Others will be specified in the listing.

5. PRIMARY ENDPOINTS

All the primary endpoints analyses will be conducted on PP population comparing the Test lens to Control lenses. Additional sensitivity analysis will be conducted on all subjects who were administered any test article excluding subjects who drop out prior to administering any test article. At least one observation should be recorded.

5.1. Definition

Overall driving performance score:

A closed road driving circuit environment will be used to evaluate the effects of the Test lens on night and day time driving performance. This approach involves driving a real vehicle on a closed road circuit (closed to all traffic except QUT vehicles), the driving environment can be modified to closely resemble real on-road conditions and safety can be assured. Quantitative methods will be used to assess vision and driving performance under a range of challenging conditions and appropriate masking, order of testing, randomization and control conditions will be used.

Overall driving performance score is a composite score calculated as the mean of the Z-scores of the following six driving measures: average sign recognition distance (in meters), percentage of correctly identified sign (~42 signs), percentage of hazard avoidance/detection (9 hazards), average pedestrian recognition distance (in meters), lane keeping (percentage of time inside the lane) and the inverse of driving lap time (in seconds). Equal weighting will be assigned to each measure. Where necessary the individual Z scores will be transformed (inverted) such that positive Z scores relate to better performance than the mean. This approach captures participants' performance relative to the group as a whole across conditions and takes into consideration the fact that some tasks may be prioritized over others during driving (Wood JM.; 2002).

Overall driving performance will be calculated for each participant by test article (Test, Control 1 and Control 2) and driving time (day and night).

5.2. Primary Analysis Methods

Overall driving performance score will be analyzed using a linear mixed model; sequence of lens wear, period, lens type, first order carry-over, driving time (day or night) and the 2-way interactions: lens*time, sequence*time, period*time and carry*time will be included in the model as fixed effects. Age will be included as fixed covariate when appropriate. An appropriate covariance structure will be selected to model the correlation between measurements across

periods within the same subject and driving time. Covariance structures that will be considered include:

- Compound Symmetry (CS)
- Heterogeneous Compound Symmetry (CSH)
- Unstructured (UN)
- Ante-dependence (ANTE(1))

For ANTE(1) structure, subject and driving time nested within subject will be included in the model as random effects. For the remaining structures only subject will be included as random effect. The covariance structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fit the data[12]. Heterogeneous residuals covariance structures (R-side) across driving time 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. Non-significant interactions at the 15% significance level will be excluded from the model. The interaction between lens type and driving time will be forced into the final model.

Comparisons between Test and Control 1 will be conducted overall across driving time and within each level of driving time. Results from the final selected model will be reported as least-square mean (LSM) differences with 95% confidence intervals.

The null and alternative hypotheses for non-inferiority of Test lens relative to Control 1 are as follows:

$$H_0: \mu_T - \mu_C \leq -0.25$$
$$H_A: \mu_T - \mu_C > -0.25,$$

where μ_T and μ_C are the means of night driving performance score for Test and Control 1, respectively. Non-inferiority of the Test relative to Control 1 will be concluded if the lower limit of the 95% confidence interval of the LSM difference between Test and Control 1, at night driving time, is greater than - 0.25.

6. SECONDARY ENDPOINTS

All the secondary analyses will be conducted on PP. Additional sensitivity analysis will be conducted on all subjects who were administered any test article excluding subjects who drop out prior to administering any test article. At least one observation should be recorded.

6.1. Definition

Binocular visual performance:

The following measurements will be used to assess the performance of the test and control products in a controlled laboratory setting which simulate a wide range of visual conditions encountered while driving.

1. High luminance (~500 lux) high contrast (90%) LogMAR distance visual acuity

2. High luminance (~500 lux) low contrast (10%) LogMAR distance visual acuity
3. Low luminance (~1 lux) high contrast (90%) LogMAR distance visual acuity
4. High luminance (~500 lux) contrast threshold (Pelli-Robson chart)
5. Low luminance (~1 lux) contrast threshold (Mesotest II instrument by Oculus, Germany)

The order of the vision tests will be randomized for each condition. The ETDRS logMAR chart will be used, which is scored on a letter by letter basis (-0.02 log units per letter correctly identified). A number of different EDTRS charts will be used to reduce potential learning effects. Letter contrast sensitivity will also be determined binocularly using the Pelli-Robson chart, scored on a letter by letter basis (0.05 log units per each letter correctly identified). The ETDRS logMAR chart and the Pelli-Robson contrast sensitivity chart are validated techniques routinely used in research to accurately quantify visual performance. Room illuminance will be controlled using dimmer switches and quantified using a lux meter.

There will be two secondary endpoints considered from binocular visual performance evaluation:

- Low luminance ~1 lux) high contrast (90%) distance visual acuity
- Low luminance (~1 lux) contrast threshold

During low luminance contrast threshold evaluation, five Landolt C targets in random orientation will be presented for each of the four contrast levels 95%, 80%, 63% and 50%. Participants will be asked to correctly identify the orientation of the Landolt C. The number of correct response will be recorded for each contrast level. This entire test will be done with and without the presence of a glare source.

Sign recognition (percentage)

Participants will be instructed to report the identity of a percentage of the standard road signs (typically about 42 signs dependent on the route travelled) containing about 65 items of information as they drive around the circuit. We will also measure the recognition distance using the in-vehicle measurement system for one specific road sign while the participant is driving.

Hazard avoidance:

Participants will be required to report and avoid hitting any of nine large, low contrast grey foam "hazards" (220 cm x 80 cm x 15 cm) positioned orthogonally in the driving lane along the roadway, the locations of which will be randomized between trials.

Pedestrian recognition distance:

The in-vehicle measurement system will be utilized to determine the distance at which the participant (as a driver) first recognizes the presence of two pedestrians positioned at the side of the road. An experimenter will act as the pedestrian and "walk in-place" at the end of a 400 m straight section of roadway which starts and finishes at approximately the same elevation, but features a dip halfway along its length. The pedestrian will not be surrounded by any visual clutter or lighting. To reduce expectancy effects, a series of four flashing LEDs and four retro-reflective bollards will be positioned around the circuit to increase the instances of flashing lights and retro-reflective material being presented to the driver. Figure 2 shows an example of a low contrast hazard (grey foam) in the driving lane in front of some retroreflective bollards and signage.

On each lap the pedestrian will walk in place as the test vehicle approaches, facing directly towards

the oncoming vehicle; this allows for the inclusion of naturalistic motion and ensures the safety of the pedestrian. The pedestrian will wear biomotion reflective strips on the moveable joints, which has been shown to be a configuration that allows good discrimination between different levels of spherical blur[2].

The main dependent variable is the driver's response distance to the pedestrian which is defined as the distance from the test vehicle to the pedestrian at that moment when the response button is pressed to indicate recognition of the presence of the pedestrian at the side of the road.

High luminance binocular visual performance:

This includes the following endpoints:

1. High luminance (~500 lux) high contrast (90%) logMAR distance visual acuity
2. High luminance (~500 lux) low contrast (10%) logMAR distance visual acuity
3. High luminance (~500 lux) contrast threshold (Pelli-Robson chart)

6.2. Secondary Analysis Methods

Binocular distance visual acuity (LogMAR)

Binocular low luminance high contrast distance visual acuity will be analyzed using a linear mixed model to test for the difference between Test and Control 1. Sequence of lens wear, period, lens type, first order carryover effect will be included in the model as fixed effects. An appropriate covariance structure will be chosen to model the residual errors between measurements within the same subject across periods. Covariance structures considered will be:

- Compound Symmetry (CS)
- Heterogeneous Compound Symmetry (CSH)
- Unstructured (UN)
- Ante-dependence (ANTE(1))

For ANTE(1) structure, subject will be included in the model as random effects. The covariance structure that returns the lowest AICC will be selected as the structure that best fit the data.

The null and alternative hypotheses for non-inferiority of Test lens relative to Control 1 are as follows:

$$H_0: \mu_T - \mu_C \geq 0.1$$
$$H_A: \mu_T - \mu_C < 0.1,$$

where μ_T - μ_C is the mean difference between Test lens and Control 1 lens. Non-inferiority of the Test lens relative to the Control 1 lens will be concluded if the upper limit of the 95% confidence interval of the LSM difference between Test and Control 1 is less than 0.1.

Low luminance contrast threshold (%)

Low luminance contrast threshold will be analyzed using a generalized linear mixed model with a binomial distribution and the logit and the link function. Sequence, period, lens type, first order carry-over, contrast level and the interaction contrast level by lens type will be included as fixed effects and subject as random effect. An unstructured covariance matrix (UN) will be used to model the correlation between measurements from the same subject and period across contrast level. If convergence problems are encountered with the unstructured covariance matrix, a model with compound symmetry covariance matrix (CS) will be considered

The null and alternative hypotheses for no-difference between Test and Control 1 are as follows:

$$H_0: OR = 1$$
$$H_A: OR \neq 1,$$

where OR is the odds ratio of the number of correctly identified orientation of the Landolt C. No statistical difference between Test lens and Control 1 lens will be concluded if 1 falls within the 95% confidence interval of the LSM ratio, OR, of Test Over Control 1.

Sign Recognition and Hazard Avoidance (%)

Proportion of correctly identified sings and proportion of hazard avoidance will be analyzed separately using a generalized linear mixed model with beta distribution and logit link function. Each model will include sequence, period, lens type, first order carry-over, driving time (day or night), and the 2-way interactions: lens*time, sequence*time, period*time and carry*time as fixed effect factors. An unstructured covariance matrix (UN) will be used to model the correlation between measurements from the same subject across periods. If convergence problems are encountered with the unstructured covariance matrix, a model with compound symmetry covariance matrix (CS) will be considered. Non-significant interactions at the 15% significance level will be excluded from the model. The interaction between lens type and driving time will be forced into the final model.

The null and alternative hypotheses for no-difference between Test and Control 1 are as follows:

$$H_0: OR = 1$$
$$H_A: OR \neq 1,$$

where OR is the odds ratio of hazard avoidance at night driving time of Test over Control 1. No statistical difference between Test and Control 1 will be concluded if 1 falls within the 95% confidence interval of the odds ratio.

Pedestrian Distance Recognition and Road Sign Recognition

Pedestrian distance recognition and road sign recognition distance (or log-transformed distance) will be analyzed separately using a linear mixed model; sequence of lens wear, period, lens type, first order carry-over, driving time (day or night), and the 2-way interactions: lens*time, sequence*time, period*time and carry*time will be included in the model as fixed effects. Age will be included as fixed covariate when appropriate. An appropriate covariance structure will be

selected to model the correlation between measurements across periods within the same subject and driving time. Covariance structures that will be considered include:

- Compound Symmetry (CS)
- Heterogeneous Compound Symmetry (CSH)
- Unstructured (UN)
- Ante-dependence (ANTE(1))

For ANTE(1) structure, subject and driving time nested within subject will be included in the model as random effects. For the remaining structures only subject will be included as random effect. The covariance structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be selected as the structure that best fit the data[12]. Heterogeneous residuals covariance structures (R-side) across driving time 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. Non-significant interactions at the 15% significance level will be excluded from the model. The interaction between lens type and driving time will be forced into the final model.

Results from the final selected model will be reported as least-square mean (LSM) estimates with 95% confidence intervals.

The null and alternative hypotheses for non-inferiority of Test lens relative to Control 1 are as follows:

$$H_0: \mu_T - \mu_C = 0$$
$$H_A: \mu_T - \mu_C \neq 0,$$

where μ_T - μ_C is the mean difference of distance recognition at night driving between Test and Control 1. No statistical difference between Test and Control 1 will be concluded if 0 falls within the 95% confidence interval of the LSM difference between Test and Control 1.

7. OTHER ANALYSIS

Further comparisons between the test lens and the control lenses will be conducted using the same models described in the primary and secondary analysis sections 5.2 and 6.2. The following hypotheses will be tested:

1. The Test lens will be non-inferior to at least one of the Control lenses (Control 1 or Control 2) lens with respect to overall daytime driving performance. A non-inferiority margin of -0.25 will be used.

2. The Test lens will be non-inferior to the Control 2 lens with respect to overall night driving performance. A non-inferiority margin of -0.25 will be used.

3. The Test lens will be non-inferior to the Control 2 lens with respect to binocular low luminance high contrast visual acuity. A non-inferiority margin of 0.1 LogMAR will be used.

4. The Test lens will be no different than the Control 2 lens with respect to low luminance low contrast threshold without glare.

5. The Test lens will be no different than the Control 2 lens with respect to the percentage of road signs correctly identified at night driving.

6. The Test lens will be no different than the Control 2 lens with respect to average distance to correctly identify a pre-determined road sign at night driving.

7. The Test lens will be no different than the Control 2 lens with respect to the percentage of hazards avoided at night driving.
8. The Test lens will be no different than the Control 2 with respect to average pedestrian recognition distance at night driving.

Multiple comparisons between the test lens and the control lenses with respect to driving performance (Hypotheses 1 and 2) will be adjusted to control for type I error using bonferroni's method. For the remaining hypotheses, the comparisons will be conducted with a two-sided type I error rate of 5%.

8. SAFETY ENDPOINTS

Safety analysis will be conducted on safety population and by study lens worn when appropriate.

8.1. Adverse Events

Listings of all reported ocular and non-ocular AEs will be created. There will be separate listings for serious and significant ocular adverse events.

8.2. Slit-Lamp Findings

Any result of the slit-lamp assessment recorded at the entrance and the exit of each visit including unscheduled visits will be tabulated at eye level. Possible findings will be reported in the following order:

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

Findings tabulated as Other Complications will be specified in the listing.

8.3. Entrance and Exit Visual Acuity (LogMAR)

Recorded visual acuity at the entrance and exit of each visit including unscheduled visits will be tabulated at eye level and subject level.

8.4. Unscheduled Lens Replacement and Lens Damage

The number of unscheduled lens replacements, folded lenses and damaged lenses will be tabulated separately by lens at eye level and subject level. For damaged lenses, the damage type and its location will be reported.

8.5. Product Quality Complaints

All reported product quality complaints will be tabulated by lens and lot number at subject level.

9. OTHER ENDPOINTS

9.1. Lens Fitting Characteristics

Mechanical lens fitting characteristics including lens centration, lens movement and overall lens fitting acceptability at fitting evaluation (Visit 1) will be summarized on the safety population by study lens using frequency tables.

9.2. Contact Lens Corrected Visual Acuity (LogMAR)

Monocular and binocular contact lens corrected distance visual acuity measured at Visit 1 will be summarized on the safety population by study lens using descriptive statistics.

9.3. Vision and Nighttime Driving Questionnaire

Individual items of vision and nighttime driving questionnaire will be summarized on the PP population by study lens using frequency tables of rating categories.

9.4. Pupil Diameter

All pupil diameter measures from visit 2, 3 and 3 will be summarized at the eye level by study lens and luminance level (high and low luminance).

9.5. Lighting Levels

10. MEASURES OF AMBIENT LIGHT LEVELS AT THE DRIVING TRACK WILL BE SUMMARIZED DESCRIPTIVELY BY STUDY LENS, DRIVING TIME AND LOCATION (I.E. INSIDE AND OUTSIDE THE VEHICLE) 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.

11. QUALITY ASSURANCE MEASURES

11.1. 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.

11.2. 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.

11.3. 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.

APPENDIX A SAS SYNTAX CODE

Primary Endpoint:

Overall driving performance scores

```
PROC GLIMMIX DATA = ads plots=studentpanel;
CLASS driveseq asper trta carry1a parcat5 subjid sexn ;
MODEL aval= age sexn driveseq|parcat5 asper|parcat5 trta|parcat5 carry1a|parcat5/ DDFM=KR2 S;
RANDOM INTERCEPT / SUBJECT=subjid;
RANDOM INTERCEPT / SUBJECT = parcat5(subjid); *only included if ANTE(1) is used;
RANDOM asper / RESIDUAL SUBJECT=parcat5(subjid) TYPE=covariance_matrix group=parcat5;
**Remove GROUP = time from the statement above if the test for homogeneity is rejected at 5%
significance level;
COVTEST "Common Varaince" Homogeneity; **test for homogeneity used along with GROUP = time;
LSMEANS trta*parcat5 /slicediff = parcat5 CL ;
**Primary analysis;
ESTIMATE "Night: Test vs Control1" trta -1 0 1  trta*parcat5 0 -1 0 0 0 1  / CL ;
**Other Analysis;
ESTIMATE "Day: Test vs Control1"    trta -1 0 1  trta*parcat5 -1 0 0 0 1 0,
                "Day: Test vs Control2"    trta 0 -1 1  trta*parcat5 0 0 -1 0 1 0,
                "Night: Test vs Control2"  trta 0 -1 1  trta*parcat5 0 0 0 -1 0 1 / ADJUST= bonferroni CL ;
RUN;
```

Where ads: Analysis data set
subjid: subject identification
aval: overall driving performance score
sexn: Gender
driveseq: Lens wear sequence (6 levels)
asper: Study Period (3 levels)
trta: Study lens type (Test, Control1, Control2)
parcat5: Driving time (day or night)
carry1a: First order carryover effect
covariance_matrix: CS, CSH, UN and ANTE(1). The covariance structure that returns the lowest AICC will be selected as the structure that best fit the data.

Secondary Endpoints:

Binocular distance visual acuity (LogMAR)

```
PROC GLIMMIX DATA = ads plots=studentpanel;
CLASS TSEQPG2 aperiod trta carry1a subjid sexn ;
MODEL aval= age sexn tseqpg2 aperiod trta carry1a / DDFM=KR2 ;
RANDOM INTERCEPT / SUBJECT=subjid; *only included if ANTE(1) is used;
RANDOM aperiod / RESIDUAL SUBJECT=subjid TYPE=covariance_matrix ;
LSMEANS trta / CL;
ESTIMATE "Test vs Control1" trta -1 0 1, *secondary analysis;
                "Test vs Control2" trta 0 -1 1 / CL; *other analysis;
RUN;
```

Where ads: Analysis dataset
subjid: subject identification
sexn: Gender
tseqpg2: Lens wear sequence (6 levels)
aperiod: Study Period (3 levels)
trta: Study lens type (Test, Control1, Control2)
carry1a: First order carryover effect
covariance_matrix: CS, CSH, UN and ANTE(1). The covariance structure that returns the lowest AICC will be selected as the structure that best fit the data.

Low Luminance contrast threshold

```
PROC GLIMMIX DATA= ads;
CLASS tseqpg2 aperiod trta carry1a subjid parcat6 sexn ;
MODEL aval/n= age sexn tseqpg2 aperiod trta|parcat6 carry1a / S DIST=BINOMIAL LINK=LOGIT;
RANDOM INTERCEPT / SUBJECT=subjid;
RANDOM parcat6 / RESIDUAL SUBJECT=aperiod(subjid) TYPE= covariance_matrix;
ESTIMATE "Test vs Control1" lens -1 0 1, *secondary analysis;
                "Test vs Control2" lens 0 -1 1 / CL ILINK EXP; *other analysis;
RUN;
```

Where ads: Analysis data set
n: number of targets
subjid: subject identification
sexn: Gender
tseqpg2: Lens wear sequence (6 levels)
aperiod: Study Period (3 levels)
trta: Study lens type (Test, Control1, Control2)
parcat6: Contrast level (4 levels)
carry1a: First order carryover effect
covariance_matrix: Compound Symmetry (CS) and Unstructured (UN)

Sign Recognition and Hazard Avoidance

```
PROC GLIMMIX DATA= ads;
CLASS driveseq asper trta carry1a parcat5 sexn;
MODEL aval= age sexn driveseq asper|parcat5 trta|parcat5 carry1a / DDFM=KR2 S DIST=BETA
LINK=LOGIT;
RANDOM INTERCEPT / SUBJECT=subjid;
RANDOM asper / RESIDUAL SUBJECT= parcat5 (subjid) TYPE=covariance_matrix;
**Secondary analysis;
ESTIMATE "Night: Test vs Control1" trta -1 0 1  trta*parcat5 0 -1 0 0 0 1  / CL ILINK EXP;
**Other Analysis;
ESTIMATE "Day: Test vs Control1"    trta -1 0 1  trta*parcat5 -1 0 0 0 1 0,
                "Day: Test vs Control2"    trta 0 -1 1  trta*parcat5 0 0 -1 0 1 0,
                "Night: Test vs Control2"  trta 0 -1 1  trta*parcat5 0 0 0 -1 0 1 / ADJUST=bonferroni CL
ILINK EXP ;
```

```
RUN;
```

Where ads: Analysis dataset
subjid: subject identification
sexn: Gender
driveseq: Lens wear sequence (6 levels)
asper: Study Period (3 levels)
trta: Study lens type (Test, Control1, Control2)
parcat5: Driving time (day or night)
carry1a: First order carryover effect
covariance_matrix: Compound Symmetry (CS) and Unstructured (UN)

Pedestrian Distance Recognition and Road Sign Recognition

```
PROC GLIMMIX DATA= ads;
CLASS driveseq asper trta carry1a parcat5 sexn;
MODEL aval= age sexn driveseq asper|parcat5 trta|parcat5 carry1a / DDFM=KR2 S;
RANDOM INTERCEPT / SUBJECT=subjid;
RANDOM INTERCEPT / SUBJECT = parcat5(subjid);  *only included if ANTE(1)is used;
RANDOM asper / RESIDUAL SUBJECT=time (subjid) TYPE=covariance_matrix;
LSMEANS trta*parcat5 /slicediff = parcat5 CL ;
**Secondary analysis;
ESTIMATE "Night: Test vs Control1" trta -1 0 1  trta*parcat5 0 -1 0 0 0 1  / CL ;
**Other Analysis;
ESTIMATE "Day: Test vs Control1"    trta -1 0 1   trta*parcat5 -1 0 0 0 1 0,
                "Day: Test vs Control2"    trta 0 -1 1  trta*parcat5 0 0 -1 0 1 0,
                "Night: Test vs Control2"  trta 0 -1 1  trta*parcat5 0 0 0 -1 0 1 / ADJUST= bonferroni CL ;
RUN;
```

Where ads: Analysis dataset
subjid: subject identification
driveseq: Lens wear sequence (6 levels)
asper: Study Period (3 levels)
trta: Study lens type (Test, Control1, Control2)
parcat5: Driving time (day or night)
carry1a: First order carryover effect
covariance_matrix: CS, CSH, UN and ANTE(1). The covariance structure that returns the lowest AICC will be selected as the structure that best fit the data.

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