Johnson & Johnson Vision

STATISTICAL ANALYSIS PLAN

Protocol CR-6305

Design Validation of senofilcon A with New UV-blocking Additive

ACUVUE® OASYS with Transitions™
senofilcon A with new UV-blocker

Version: 1.0

Date: 18 November 2018

Prepared by: Jessica Cannon, Johnson & Johnson Vision Care, Inc.

Compliance: The study described in this document was performed according to the principles of Good Clinical Practice (GCP).

AUTHORIZED SIGNATURES

The signature below constitutes the approval of this document and the attachments.

Author

[redacted] DATE

Title: Biostatistician II

Reviewers

[redacted] DATE

Title: Senior Manager of Biostatistics

Approvers

[redacted] DATE

Title: Principal Research Optometrist

Table of Contents

AMENDMENT HISTORY

Version Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
1.0	18 November 2018	Original Draft

ABBREVIATIONS

AE	adverse event
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	electronic case report form
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	interactive voice response system
LOCF	last observation carried forward
PI	principal investigator
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation

1. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for protocol CR-6305 Version 4.0 Amendment 3.0.

This document will serve as the final guidance for all the statistical analysis for this study and will supersede the Statistical Method section in the protocol if there are any discrepancies. Any deviation from the analysis plan will be documented as such in the clinical study report.

1.1. Study Objectives

Primary Objectives:
The primary purpose of this randomized study is to demonstrate that the 4GT Test lens senofilcon A with new UV-blocker, in its final lens design ECL600, meets the design validation requirements related to overall CLUE comfort, logMAR visual acuity, quality of vision in bright light, eye health, and fit acceptance.

Secondary Objective:
The secondary objective of this study is to demonstrate that the Test lens is equal or better than marketed product senofilcon A (ACUVUE® OASYS, Johnson & Johnson Vision Care, Inc.) with regards to overall CLUE vision and handling.

Other observations of interest include adverse events, keratometry, surface characteristics (deposits and wettability), daily wear time, reasons for discontinuation, and lens damage.

2. STUDY DESIGN

2.1. Overview

This study is a randomized, 2-visit, partially subject-masked, 2-arm parallel, dispensing trial. Approximately 236 subjects (118 subjects /arm) will be screened and enrolled to ensure that at least 224 subjects (112 subjects/arm) complete the study.

The study begins with an initial visit (Visit 1). If a subject is found to meet all eligibility criteria, they will be randomized to one of two study lenses (Test or Control) in a bilateral fashion.

If the subject is dispensed study lenses at the initial visit, one follow-up visit will be conducted. The follow-up visit will occur approximately two weeks after the initial visit. Unscheduled follow-up visits may occur during the study. Subjects will be advised to wear the study lenses at least five (5) days per week for at least six (6) hours per day for a period of two weeks. There is no planned lens replacement scheduled during this study.

2.2. Test Articles

Table 1: Test Article Labels

Test Article	Label	Report Labels
senofilcon A based contact lens with new UV-blocker	Test	Acuvue® Oasys with Transitions™
ACUVUE® OASYS Brand Contact Lenses with HYDRACLEAR® PLUS	Control	Acuvue® Oasys
All Test Articles	Total	Total

2.3. Targeted Study Population and Sample Size

Approximately 236 subjects will be enrolled to ensure that at least 224 subjects will complete the study (~112 per/arm). Enrolled subjects will be habitual wearers of spherical contact lenses. All subjects will be the age of 18 and ≤49 years old. Eligible presbyopes will be those that wear full distance contact lenses in both eyes, then wear reading glasses over them. Subjects will wear the Test or Control contact lenses approximately 2 weeks each in a bilateral fashion as DW.

Table 2: Planned Enrollment Strategy by Lens type and Site

	Test	Control	Total
Enrolled	118	118	236
Randomized	116	116	232
Completed	112	112	224
Number of enrolled per site	10-12	10-12	20-24

2.4. Test Article Allocation and Masking

Using a computer-generated randomization scheme will be used to randomly assign subjects, in blocks of 2, to one of the two possible study lenses (TEST or CONTROL). The random scheme will be generated using the PROC PLAN procedure from SAS Software Version 9.4 or higher (SAS Institute, Cary, NC).

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 / not meets exclusion criteria
- Subject history and baseline information has been collected.

The dynamic nature of the Test lens makes it impossible to completely mask the study lens assignment. The subjects will be aware if they are wearing a photochromic lens or non-photochromic lens due to the function nature of the photochromic dye. Additionally, there is a slight difference in physical appearance between the Test and Control lenses when the Test lens

is activated by outdoor light that makes it difficult to mask investigative personnel. However, the control lens will be masked in the event that OASYS is the subject's habitual lens by chance, making this a partial-subject masked study.

2.5. Time and Event Schedule

Table 3: Time and Events Schedule

Visit Information	Visit 1 Screening, Baseline, Treatment 1	Visit 2 Follow-up, Final Evaluation
Time Point	Day 1	Day 14 ± 1
Estimated Visit Duration	2.5 hours	1.5 hours
Statement of Informed Consent	x	
Demographics	x	
Medical History/Concomitant Medications	x	x
Habitual Contact Lens Information	x	
Inclusion/Exclusion Criteria	x	
Baseline Questionnaires	x	
Entrance Visual Acuity	x	
Iris Color	x	
Keratometry	x	x
Subjective Sphero-Cylindrical Refraction	x	x
Slit Lamp Biomicroscopy	x	x
Lens Selection	x	
Lens Insertion & Settling	x	
Visual Acuity and Over Refraction	x	x
Lens Power Modification	x	
Subject Reported Ocular Symptoms	x	x
Visual acuity (distance Snellen)	x	x
Lens Fit Assessment	x	x
Lens Wettability	x	x
Dispense Patient Instruction Guide	x	
Dispense Test Article	x	x
Lens wear Compliance		x
Wearing Time and Compliance		x
Follow-up Questionnaire		x
Distance ETDRS logMAR Visual Acuity		x
Surface Deposits		x
Study Completion		x
Lens Removal and Storage		x
Final Evaluation		x

3. STUDY ENDPOINTS

3.1. Primary Endpoints

Primary Efficacy Endpoints:

CLUE Overall Comfort

Overall comfort scores will be assessed using the Contact Lens User Experience (CLUE™)[7] questionnaire at the two-week follow-up. CLUE is a validated patient-reported outcomes questionnaire to assess patient-experience attributes of soft, disposable contact lenses (comfort, vision, handling, and packaging) in a contact-lens wearing population in the US, ages 18-65. Derived CLUE™ scores using Item Response Theory (IRT) follow a normal distribution with a population average score of 60 (SD 20), where higher scores indicate a more favorable/positive response with a range of 0-120. A 5-point increase in an average CLUE™ score translates into 10% shift in the distribution of scores for population of soft contact lens wearers.[7] The comfort scores will be generated using the flexMIRT software Version 3 or higher (Chapel Hill, NC).

Distance Monocular Contact Lens Visual Acuity

Distance monocular contact lens visual performance (logMAR) is assessed for each subject eye at the two-week follow-up evaluation using EDTRS charts at a 4-meter distance under the lighting condition, Bright illumination high contrast.

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

The formula to compute logMAR score at a different distance other than the chart specified distance (i.e. 4 meters) is:

$$\text{LogMAR}_2 = \text{LogMAR}_1 + \log10(D_1/D_2)$$

where:

- LogMAR_1 is the logMAR score at the chart specified distance D_1;
- LogMAR_2 is the adjusted logMAR score at a different distance D_2.

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

Vision Satisfaction in Bright Lighting

Vision satisfaction in bright lighting will be assessed using the individual item (Item ID: V015_1) “I was satisfied with the quality of my vision in bright lighting” from the CLUE™

questionnaire. This item uses the response scale, 1: Strongly Disagree, 2: Disagree, 3: Neither Agree nor Disagree, 4: Agree and 5: Strongly Agree.

Primary Safety Endpoints:

Slit Lamp Findings (Grade 3 or Higher)
Slit Lamp Findings will be assessed for each subject eye at all study visits (schedule and unscheduled). SLF is a binary response where Y=1 for at least one Grade 3 or 4 slit lamp finding. The percentage of eyes with Grade 3 or higher slit lamp findings will be analyzed and will include corneal infiltrates. Eyes with multiple events will be counted only once.

The FDA Biomicroscopy Scale measures the severity of the ocular clinical findings and goes from Grade 0 (none) to Grade 4 (severe). The procedure is explained in the [redacted] in section 12 Appendix D of the study protocol. The individual ocular finding results are considered as other endpoints.

Fit Acceptance Rate
Acceptable lens fit will be assessed at all study visits (scheduled and unscheduled) for each subject eye. Fit acceptance rate will be based on the lens fit acceptance of eyes wearing the Test lens only. Fit acceptance is a binary response where Y=1 if lens fit is acceptable and Y=0 otherwise. Unacceptable is defined as unacceptable if any one of the following criteria:

- limbal exposure at primary gaze or with extreme eye movement;
- edge lift;
- excessive movement in primary up gaze;
- insufficient movement in all three of the following conditions: primary gaze, up gaze, and push up test.

Eyes with multiple unacceptable fitting events will be counted only once. Fit rates of the Control lens will also be collected but are not a primary endpoint.

The procedure is explained in the [redacted] in section 12 Appendix D of the study protocol. The individual lens fitting characteristics are considered as other endpoints.

3.2. Secondary Endpoints

CLUE Overall Quality of Vision and Handling
Overall Quality of vision and handling scores will be assessed using the Contact Lens User Experience (CLUE)[1] questionnaire at the two-week follow-up.

3.3. Other Endpoints

- Average daily wear time (in Hours)
- Subject's Reported Ocular Symptoms
- Lens fitting characteristics

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

4. STATISTICAL HYPOTHESES FOR STUDY OBJECTIVES

4.1. Primary Hypotheses

All the primary hypotheses must be met in order to satisfy the primary objective of this study.

1. Subjects wearing the JJVCI Investigational contact lenses on a daily wear basis will have patient reported comfort at the 2-Week Follow Up visit that is non-inferior to that of subjects wearing predicate device on a daily wear basis. A non-inferiority margin of -5 CLUE points will be used.

2. Subjects wearing the JJVC Investigational contact lenses on a daily wear basis will report distance monocular visual acuity (logMAR: bright room luminance / high contrast charts) at the 2-Week Follow Up visit that is non-inferior to that of subjects wearing predicate device on a daily wear basis. A non-inferiority margin of 0.05 LogMAR will be used.

3. Subjects wearing the JJVCI Investigational contact lenses on a daily wear basis will have patient reported outcome (Agree and Strongly Agree) on the Quality of Vision in Bright Light at the 2-Week Follow Up visit that is non-inferior to that of subjects wearing predicate device on a daily wear basis. A non-inferiority margin of 10% will be used.

4. Subjects wearing the JJVC Investigational contact lenses on a daily wear basis will have a percentage of any grade 3 or higher slit lamp findings at all visits (scheduled and unscheduled) that is non-inferior to that of subjects wearing predicate device on a daily wear basis. A non-inferiority margin of 5% will be used.

5. At least 90% of eyes wearing the JJVC Investigational contact lenses on a daily wear basis will have acceptable fits across the fitting and follow-up visits.

4.2. Secondary Hypotheses

1. Subjects wearing the JJVCI Investigational contact lenses on a daily wear basis will have patient reported handling at the 2-Week Follow Up visit that is non-inferior to that of subjects wearing predicate device on a daily wear basis. A non-inferiority margin of -5 CLUE points will be used.

2. Subjects wearing the JJVCI Investigational contact lenses on a daily wear basis will have patient reported vision at the 2-Week Follow Up visit that is non-inferior to that of

subjects wearing predicate device on a daily wear basis. A non-inferiority margin of -5 CLUE points will be used.

4.3. Other Hypotheses

Not applicable.

5. ANALYSIS SETS

5.1. All Enrolled

The All Enrolled population will include all participants who sign an informed consent.

5.2. Intent-to-Treat (ITT)

All randomized subjects regardless of actual treatment and subsequent withdrawal from study or deviation from protocol. At least one observation should be recorded.

Safety variables will be summarized on both safety and PP populations whereas efficacy variables will be summarized on the per-protocol and Intent-to-Treat population.

5.3. Safety Population

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.

5.4. Per-Protocol (PP)

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

6. DEFINITIONS AND DERIVED VARIABLES

6.1. Age

Age will be calculated using the Date of Birth (DOB) and the date of the consenting the subject and presented as age at last birthday as an integer.
Age = Integer part of [(Date of Baseline visit – Date of Birth) / 365.25]

6.2. Average daily wear time (in Hours)

Average daily wear time will be calculated as the number of hours between subjects reported time of insertion and time of removal of the study lenses, on an average day, at 2-Week Follow-up evaluation.

6.3. Iris Category

Iris color will be categorized into either dark or light based on the subjects' hue and lightness of their iris using Johnson & Johnson's Iris Color Scale. If hue is brown or lightness is dark then the subject will be classified as having a dark iris, if hue is light then the subject will be classified as having a light iris. If lightness is medium and hue is green, blue or grey then the subject will be classified as having a light iris; otherwise subjects will be classified as having a dark iris.

6.4. Visit Windows

Table 4: Visit Window information

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1	Baseline	1	1
1	Fitting	1	1
2	2-Week Follow-up	13 to 15	14

[a] The first treatment day is Day 1.

6.5. Definition of Subgroups

There is no planned subgroup analysis for this study.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1. Statistical Software

All data summaries and statistical analyses will be performed using the SAS software Version 9.4 or higher (SAS Institute, Cary, NC)[2].

7.2. Summary Statistics

Throughout the analysis of data, the results for each subject/eye will be used when available for summarization and statistical analysis. Unscheduled visits will be summarized separately and will be excluded from the efficacy statistical analysis but will be included in the analysis of safety endpoints (slit lamp findings and lens fitting).

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables and safety variables as appropriate. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum). Frequency count and percentage of subjects or eyes within each category will be provided for categorical data.

Safety variables will be summarized on both safety and PP populations whereas efficacy variables will be summarized on the PP and ITT populations.

7.3. Reporting Numerical Values

Means, medians and confidence/credible intervals 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. 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.

7.4. Sample Size Justification

This study was designed and powered to show non-inferiority of the Test lens compared to the Control lens with respect to logMAR Visual Acuity, Slit Lamp Findings (Grade 3 or higher) and CLUE comfort. It was assumed there was no difference between the Test and Control lens with respect to slit lamp findings and a 1 letter difference (0.02) between the Test and Control lenses with respect to visual acuity logMAR. Based on data from 3 historical studies, it was assumed there was a 2-point difference between the Test and Control lenses with respect to CLUE comfort based on the summary statistics from the first period of the historical studies.

In addition to the endpoints mentioned above this study was also powered to demonstrate non-inferiority of the Test lens relative to the Control lens with respect to vision satisfaction in bright lighting and the proportion of eyes with acceptable fitting while the Test lens is significantly superior to 90%.

Unless otherwise specified, the sample size was calculated to achieve a minimum statistical power of 80% and a type I error of 5%.

A total of 5 historical studies were utilized in the sample size calculation. Table 5 displays the studies, their corresponding study design and the number of subjects enrolled and completed per-protocol.

Table 5: Historical Studies Included in Sample Size Calculation

Study	Study Design	Endpoints Collected	No. Enrolled	No. Completed Per-Protocol
[redacted]	2X3 Crossover	CLUE, SLF Lens Fit	135	132
[redacted]	2X3 Crossover	CLUE, Visual Acuity (logMAR), SLF, Lens Fit	133	121
[redacted]	2X3 Crossover	CLUE, SLF Lens Fit	92	78
[redacted]	Single-Arm	SLF, Lens Fit	54	48
[redacted]	Single-Arm	SLF, Lens Fit	56	41

Table 6: Descriptive Summary of CLUE Scores by Domain Pooled Across Historical Studies ([redacted]) – 2-Week Follow-up Evaluation-Period 1 Only

CLUE Domain [Mean(SD)[1]]	Test	Control

Comfort	66.66 (21.066)	63.90 (24.197)
Handling	69.32 (18.454)	71.11 (20.429)
Overall Quality of Vision	64.49 (17.221)	64.44 (23.351)

[1]SD = Standard Deviation

Table 7: Descriptive Summary of Visual Acuity (logMAR) - [redacted] – 2-Week Follow-up Evaluation-Period 1 Only

Visual Acuity High Illumination High Contrast	**Test**	**Control**
[Mean(SD)[1]]	-0.088 (0.0862)	-0.0622 (0.0740)

[1]SD = Standard Deviation

Table 8: Descriptive Summary of Mechanical Lens Fitting Pooled Across all Historical Studies

Any Unacceptable Lens Fit[1] [n(%)]	**Test n (%)**	**Control n (%)**
Fitting Evaluation	0(0.0)	0 (0.0)
2-Week Follow-up	0 (0.0)	0 (0.0)

[1]The percent of any unacceptable fit is calculated using Total Unique eyes as a denominator

Table 9: Descriptive Summary of Slit Lamp Findings Pooled Across all Historical Studies

SLF Grade 2	**Test n (%)**	**Control n (%)**
Corneal Edema	0 (0.0)	0 (0.0)
Conjunctival Injection	59 (6.86)	59 (21.85)
Tarsal Abnormalities	51 (5.93)	24 (8.89)
Corneal Neovascularization	3 (0.35)	0 (0.0)
Corneal Staining	3 (0.35)	0 (0.0)
Other Findings	0 (0.0)	0 (0.0)
Total Eyes (N)	860	270
Any SLF Grade 2[2]	116 (13.48)	83 (33.74)
Any SLF Grade 3+	0 (0.0)	0 (0.0)
Total Unique Eyes	860	270
Total Unique Subjects	430	135

%= nx100/N; SD=Standard Deviation

[1]All SLF reported for this study are combined for the purposes of summarizing

[2] The percent (%) of Any Grade 2 is calculated using the Total Unique Eyes as the denominator

Table 10: Descriptive Summary of Individual Item from [redacted] – 2-Week Follow-up

Questionnaire Item/ Response	Test	Control
Vision Satisfaction in Bright Light [n(%)]		
Strongly Agree	72 (29.75)	51 (21.07)
Agree	129 (53.31)	130 (53.72)
Neither Agree Nor Disagree	24 (9.92)	21 (8.68)
Disagree	17 (7.02)	33 (13.64)
Strongly Disagree	0 (0.0)	7 (2.89)

CLUE Comfort Scores

With respect to CLUE comfort, based on historical data from Period 1, a mean difference of 2 points was assumed and a standard deviation of 21, an additive equivalence test in PROC Power for two sample means was used to Test for non-inferiority. A non-inferiority margin of -5 points was used since this is considered to be no more than a 10% shift in the distribution of CLUE scores.

Mechanical Lens Fit (Test Lens)

The estimated sample size to test the primary hypothesis (H0 PT ≤ P0, H1: PT > P0) is 100. The sample size was calculated using PROC POWER for one sample proportion using an exact Test of a Binomial Proportion.

Visual Performance (logMAR)

Sample size calculation for visual performance (logMAR) was carried out using an approximation of the power of an F-test derived from the non-centrality parameter calculated form the observed F statistic of a linear model[8].

Model details:
visual performance was analyzed using a linear mixed model. Lens type was included as the only fixed effect. A compound symmetric (CS) covariance matrix was used to model the correlation between measurements within the same subject. Below is the variance-covariance matrix used in the visual performance model.

$$\sum_{Visual\ Acuity} \begin{pmatrix} 0.004047 & 0.002894 \\ 0.002894 & 0.004737 \end{pmatrix}$$

Slit Lamp Findings

There were no Grade 3 or higher SLFs observed in any of the historical studies. Assuming no difference between study lenses and a correlation 0.70 between left and right eyes within the same subject (intra-subject correlation), a reference rate of no more than 5% was assumed (worse-case scenario) with a non-inferiority odds ratio margin of 2. A total of 2000 replicating trials were simulated, each replicated sample was analyzed using a generalized estimating equation (GEE) model with a binary distribution and the logit as the link function. Each model included lens type as the only fixed, eye was included as a random effect. The Odds ratio and corresponding 95% confidence interval was used estimate differences between the Test and Control lenses. The upper limit of each 95% confidence interval was compared to 2; if the upper limit was below 2 then NI=1; otherwise NI=0. Statistical power was calculated at the average NI. A sample size of 224 (112 per arm) was chosen to achieve a minimum statistical power of 80%.

Using a reference rate for the control that does not exceed 5% and no more than a 5% difference between the Test and Control lenses translates to an odds ratio margin of 2. A reference rate of 5% was used since this is the worst-case scenario.

Vision Satisfaction

Vision satisfaction in bright lighting sample size estimate was calculated using historical data [redacted]. One-thousand boot strap samples were simulated based on the historical data. For each replicated sample a generalized linear mixed model was used with a multinomial distribution and the cumulative logit as the link function. Lens wear was included in the model as the only fixed effects.

Using a reference rate of 0.50 for the Control lens and assuming no difference between the Test and Control a 10% difference translate to a cumulative odds ratio margin of 0.67. the reference rate of 0.50 was used since this is considered to be the worst-case scenario.

Table 11: Sample Size Estimates and Power Calculations for Primary Endpoints

Endpoint	Number per Subjects to Complete	Power
Distance Monocular Visual Acuity (logMAR)	30	86%
SLFs (Grade 3 or Higher)	224	80%
Acceptable lens Fit	100	82%
CLUE Comfort	224	87%
Vision Satisfaction in Bright Lighting	40	87%

Table12: Sample Size Estimates and Power Calculations for Secondary Endpoints

Endpoint	Number per Subjects to Complete	Power
CLUE Handling	224	63%
CLUE Overall Quality of Vision	224	71%

As indicated in Table 10 and 11 above, the sample size chosen for this study was primary driven by Slit Lamp Findings (Grade 3 or higher) and CLUE Comfort. The plan is to enroll 236 eligible subjects (118 subject per arm) with a target of 112 subjects to complete each arm in the study. During the enrollment period, the subject drop-out rate with be closely monitored, if an unexpectedly high dropout rate is observed, then the targeted total enrollment number maybe be increased accordingly to ensure that a minimum of 224 subjects complete the study.

7.5. Statistical Significance Level

All planned analysis will be conducted with an overall type I error rate of 5%. There will be neither adjustment for multiple tests nor adjustment for multiplicity of endpoints. Unless otherwise specified, all statistical tests will be 2-sided.

7.6. Handling of Missing Data and Drop-outs

Missing or spurious values will not be imputed. 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 may be considered by automatically sampling all missing values and incorporating them in the Markov chain for the parameters using the PROC MCMC procedure.

8. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

There will be no interim read performed on this study.

9. SUBJECT INFORMATION

9.1. Disposition Information

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

1. Completed: Subjects are considered to have completed the study if they (a) provided informed consent and/or assent; (b) they are eligible; (c) completed all three phases of testing; and (d) have not withdrawn/discontinued from the study.

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) Adverse Event (b) unsatisfactory visual response due to test article (c) satisfaction lens fitting due to test article (d) lens discomfort (e) lens handling difficulties (e) withdrew consent during study (f) lost to follow-up (g) subject no longer meets eligibility criteria (h) subject withdrawn by PI to non-compliance to protocol (i) test article no longer available

3. Assigned and Test Article Administered: 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 and/or assent) 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.

9.2. 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.

9.3. Demographics and Baseline Characteristics

Demographic characteristics will be summarized by Per-Protocol, safety, and all enrolled population using descriptive statistics for continuous variables, and numbers and percentages of subjects for categorical variables. Demographic information will include age, gender, race, ethnicity and iris category.

9.4. Treatment Compliance and Extent of Exposure

Average daily wear time and average daily comfort wear time will be provided in the summary table. Non-compliance will be reported in protocol deviation.

9.5. Prior and Concomitant Medications

Prior and concomitant medications will be documented during screening and updated during the study when applicable. A listing for both prior and concomitant medications will be created for all enrolled subjects.

Disallowed medications for this study include: Estrogens, Antihistamines, Anticholinergics, Beta-blockers and Psychotropics.

Concomitant therapies that are disallowed include: Not applicable.

9.6. Medical History

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

10. STATISTICAL ANALYSIS

10.1. Primary Analysis

Primary efficacy analysis:

All the efficacy analyses will be conducted on PP population. As sensitivity analysis, the efficacy analysis will be repeated on the ITT population

Visual Acuity

Distance monocular visual acuity (logMAR) will be tested under bright illumination bright contrast conditions at the 2-week follow-up evaluation and will be analyzed using a Bayesian normal random-effects model to compare the Test and Control lenses. The regression model will include lens type as the only fixed effect. Clinical site and subject will be included as random effects. Other subject characteristics such as gender and age will be included as fixed effects when appropriate.

The Model:

Let y_{ijkl} the visual acuity (logMAR) for the l^{th} subject at the k^{th} site, assigned to the i^{th} lens for the j^{th} eye. The likelihood for y_{ijkl} is constructed as follows:

$$y_{ijkl} \sim N(\mu_{ijkl}, {\sigma_{ijkl}}^2)$$

Where,

$$\mu_{ijkl} = \mu_0 + \beta_1 Lens_i + \gamma_{l(k)} + \alpha_k$$

In this model, lens we define $Lens_i$=0 for the Control lens and $Lens_i$=1 for the Test lens. So β_1 stands for the difference between the Test and Control lens with respect to logMAR visual performance. A negative β_1 indicates the Test performed better than the Control lens.

We assume random subject effects are independent and identically distributed (i.i.d) as $\gamma_j \sim$ N(0, $\sigma^2_{subject}$) as random subject and, the random site effect is i.i.d as $\alpha_k \sim$ N(0, σ^2_{site}) for i=1,2 (lens), j=1, 2 (eye), k=1, 2, 3, 4, 5, 6 (site).

For the β coefficients, independent non-informative priors N(0, 1000) will be used. For the variance of random effects $\sigma^2_{subject}$ and σ^2_{site} independent non-informative conjugate priors inverse-gamma(0.001, 0.001) will be used. For σ^2_{ijkl}, non-informative conjugate priors inverse-gamma(0.001, 0.001) will be used where σ^2_{ijkl}, is the variance of y_{ijkl}. The metropolis sampler algorithm as implemented in the SAS/STAT MCMC 14.2[14] procedure will be used to estimate the posterior distribution of the unknown parameters. Inferences will be made based on the 95% posterior credible intervals for relevant parameters.

Hypothesis Testing

The null and alternative hypothesis for visual acuity (logMAR) to test for non-inferiority of the Test lens relative to the Control lens is as follows:

$$H_0: \beta_1 \geq 0.05$$
$$H_A: \beta_1 < 0.05$$

Non-inferiority will be declared if the upper limit of the 95% credible interval of the difference between the Test and Control is below 0.05, i.e. P($\beta_1 < 0.05$) ≥ 0.975.

CLUE Overall Comfort

CLUE Comfort scores will be analyzed using a Bayesian normal random-effects model to compare the Test and Control lenses at the 2-week follow-up evaluation. The regression model will include baseline CLUE comfort scores and lens type as fixed effects. Clinical site will be included as random effects. Other subject characteristics such as age, gender, race and iris category will be included as fixed covariates when appropriate.

The Model:
Let y_{ijk} denote the CLUE Comfort score for the k^{th} subject at the j^{th} site, assigned to the i^{th} lens. The likelihood for y_{ijk} is constructed as follows:

$$y_{ijk} \sim N(\mu_{ijk}, {\sigma_{ijkl}}^2)$$

Where

$$\mu_{ijkl} = \mu_0 + \beta_1 Lens_i + \beta_2 \text{baseline} + \gamma_j$$

In this model, we define $Lens_i$=0 for the Control lens and $Lens_i = 1$ for the Test lens. So β_1 stands for the difference between the Test and Control lens with respect to CLUE comfort; A positive β_1 indicates the Test performed better than the Control.

We assume random site effects are independent and identically distributed (i.i.d) as $\gamma_j \sim N(0, \sigma^2_{site})$ for site for j=1, 2, 3, 4, 5, 6 (site) .

For the β coefficients, independent non-informative priors N(0, 1000) will be used. For the variance of random effect of σ^2_{site} an independent non-informative conjugate prior, inverse-gamma(0.001, 0.001) will be used. Starting values for the mean and variance of CLUE scores will be 60 and 400 (since standard deviation of CLUE is normalized to be 20), respectively. The Metropolis sampler algorithm as implemented in the SAS/STAT MCMC 14.2[14] procedure will be used to estimate the posterior distribution of the unknown parameters. Inferences will be made based on the 95% posterior credible intervals for relevant parameters.

Hypothesis Testing
The null and alternative hypotheses for CLUE comfort non-inferiority of the Test lens relative to the Control lens are as follows:

$$H_0: \beta_1 \leq -5$$
$$H_A: \beta_1 > -5$$

Non-inferiority will be declared if the lower bound of the 2-sided 95% credible interval of the difference between the Test lens and the Control lens is greater than -5, i.e., $P(\beta_1 > -5) \geq 0.975$.

Vision Satisfaction in Bright Lighting

The response set will first be reversed in order to appropriately analyze the data in order to provide the odds ratio of having a higher rating with the Test compared to the Control lens. Vision satisfaction in bright lighting at the 2-week follow-up evaluation will be analyzed using a Bayesian multinomial model for ordinal data. The regression model will include lens type as the only fixed effect. Clinical site will be included as a random effect. Other subject characteristics such as age, gender, race and iris category will be included when appropriate.

The Model:

Let y_{ijk}= (y_{ijk1} , y_{ijk2} , y_{ijk3}, y_{ijk4}, y_{ijk5}) denote the rating for the k^{th} subject, from the j^{th} site, assigned to the i^{th} study lens. Possible values of y_{ijk} are 1if the subject rating of vision satisfaction in bright lighting are X and 0 otherwise (x=1 for Strongly Agree and X=5 for Strongly Disagree, respectively). The likelihood is constructed as follows:

$$y_{ijk} \sim \text{Multinomial}\ (P_{ijk1},\ P_{ijk2}\ , P_{ijk3}, P_{ijk4}, P_{ijk5});$$

$$P_{ijk1} = \gamma_{ijk1}$$

$$P_{ijkX} = \gamma_{ijkX} - \gamma_{ijk(X-1)}\ 2 \leq X \leq 4$$

$$P_{ijk5} = 1 - \sum_{X=1..4} P_{ijkX}$$

$$\text{Logit}(\gamma_{ijkX}) = \theta_X + \beta_1 Lens_i + \delta_j$$

Where $\theta_X$is the intercept for levels X=1,2,3,4, We assume the random clinical site effects are i.i.d as δ_j~N(0, σ^2_{site}) for j=1, 2, 3, 4, 5, 6(site) .

In this model, we define $Lens_i$=0 for the Control lens and $Lens_i$=1 for the Test lens.

Independent non-informative N(0, 1000) priors for the regression coefficients β_1. For the variance of random effect of σ^2_{site} an independent non-informative conjugate prior, inverse-gamma(0.001, 0.001) will be used. For θ_X, we are considering the following priors

$$\pi 0(\theta 1) \sim N(0,100)$$
$$\pi 0(\theta 2|\ \theta 1) \sim N(0,100)I(\theta > \theta 1)$$
$$\pi 0(\theta 3|\ \theta 2) \sim N(0,100)I(\theta > \theta 2)$$
$$\pi 0(\theta 4|\ \theta 3) \sim N(0,100)I(\theta > \theta 3)$$

For the variance of random effects independent non-informative normal priors will also be used; σ^2_{site} ~inverse-gamma(0.001, 0.001). The Metropolis sample 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 the posterior credible interval for the relevant parameters.

If few subjects reported in category levels disagree and strongly disagree (less than 5%); the levels will be collapsed into one category level.

Hypothesis Testing

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

$$H_0\ p_T - p_C \leq -0.1$$
$$H_A\ p_T - p_C > -0.1$$

Where p_T *and* p_C are the proportions of patients with positive response (agree or strongly agree) in the Test group and Control group, respectively. Non-inferiority will be declared if the lower bound of the 2-sided 95% credible confidence interval is above -0.1 i.e. P($p_T - p_C > -0.1$)=0.975.

Primary Safety Analysis:
Safety analysis will be conducted on safety population by actual treatment received by subjects.

Acceptable Lens Fit:

Acceptable lens fit will be analyzed using a Bayesian beta-binomial models for correlated binary data.

The Model:
Let Y1 and Y2 denote the binary outcomes of acceptable lens fit for the left and right eyes, respectively, when wearing the test lens. Considering the correlation, ρ, between Y1 and Y2, the distribution of the sum Y = Y1 + Y2 is obtained by the mixture of two variables. One of them follow a binomial distribution Bin(2, p) with mixing probability (1-ρ) and the other one follows a modified Bernoulli distribution MBern(p), taking value 0 and 2 rather than conventional 0 and 1, with mixing probability p:

$$P(Y = y| p, \rho) = (1- \rho)Bin(2, p)I_{A1} + \rho MBern(p)I_{A2}$$

Where $I_{A1} = \{0, 1, 2\}$ and $I_{A2} = \{0, 2\}$

To overcome the complexity of the mixture likelihood a latent variable Z_i, i = 1, 2 is introduced in the model to indicate in which component of the model the observation y_i, i=1, 2, belongs to, that is,

$$z_i = \begin{cases} 1, \text{if the observation belong to the MBern(p)}, \\ 0, \text{if the observation belong to the Bin(2,p)} \end{cases}$$

The joint distribution of the augmented data (Y_i, Z_i), i=1, 2, is given by

$$P(Y = y_i, Z = z_i| p, \rho) = \rho^{z_i} p^{y_i z_i/2} (1-p)^{(2-y_i)z_i/2} (1-\rho)^{1-z_i} \binom{2}{y_i} p^{y_i(1-z_i)} (1-p)^{(2-y_i)(1-z_i)}$$

The posterior distribution of (p, ρ) given (y, z) is

$$P(p, \rho | \mathbf{z}, \mathbf{y}) = P(\mathbf{y}, \mathbf{z}| p, \rho)\, \pi_0(p, \rho),$$

Where, π_0 is joint prior distribution of (p, ρ). Here we assume p and ρ to be independent with a prior beta(α,β) for p and uniform(0,1) for ρ. Hence the joint distribution of (p, ρ) is given by π_0 (p, ρ| α, β)$\propto p^{\alpha-1}(1-p)^{\beta-1}$. The Metropolis sampler algorithm as implemented in the SAS/STAT MCMC Procedure will be used to estimate the posterior distributions of the parameters (p, ρ). Inferences will be made based on a posterior credible interval for the relevant parameters.

Hypothesis Testing

With respect to Acceptable lens fit the null and alternative hypothesis for superiority is as follows:

$$H_o : p_T \leq 0.90$$
$$H_A : p_T > 0.90$$

Where, p_T represents the proportion of subject eyes that achieve acceptable fit for the Test lens. Success for acceptable fit will be declared if the lower bound of the 2-sided 95% credible interval of the proportion is greater than 0.90; i.e. $\mathbf{P(p_T > 0.90) \geq .975}$.
If the full planned model fails to converge, reduced versions may be considered.

Slit Lamp Findings

Grade 3 or higher slit lamp findings will be analyzed using a Bayesian Logistic regression random-effects model to compare the Test and Control lenses. The regression model will include baseline slit lamp findings and lens type. Site and subject will be included in the model as random effects.

Let y_{ijkl}=1 if a Grade 3 or higher SLF is observed and y_{ijkl} =0 otherwise for the l^{th} subject, from the k^{th} site, assigned to the i^{th} study lens for the j^{th} eye.

$$y_{ijkl} \sim \text{Binary}\ (p_{ijkl})$$

$$p_{ijkl} = \frac{\exp(\beta_0 + \beta_1 Lens_i + \beta_2 Baseline\ SLF_1 + \gamma_k + \delta_l)}{1 + \exp(\beta_0 + \beta_1 Lens_i + \beta_2 Baseline\ SLF_1 + \gamma_k + \delta_l)}$$

We assume the random effect for subject are i.i.d as $\delta_l \sim N(0, \sigma^2_{subject})$ for the random for clinical site are i.i.d as $\gamma_k \sim N(0, \sigma^2_{site})$ for i=1,2 (lens), j=1, 2 (eye), k=1, 2, 3, 4, 5, 6 (site) and l=1,…n (subject/site).

In this model, we define $Lens_i$=0 for the Control lens and $Lens_i$=1 for the Test lens.
For the β coefficients, independent non-informative priors $\mathbf{N(0, 1000)}$ will be used. For the variance of random effects of $\sigma^2_{subject}$ and σ^2_{site}, independent non-informative conjugate priors inverse-gamma (0.001, 0.001) will be used. The Metropolis-Hastings algorithm as implemented in the SAS/STAT 14.2 PROC MCMC procedure will be used to estimate posterior distributions of the unknown parameters. Inferences will be made based on the posterior credible interval for the relevant parameters.

Hypothesis Testing

The null and alternative hypothesis for Non-inferiority is as follows:

$$H_0\ p_T - p_C \geq 0.05$$
$$H_A\ p_T - p_C < 0.05$$

Where p_T *and* p_C are the proportions of eyes with Grade or higher SLFs for the Test group and Control group, respectively. Non-inferiority will be established if the upper limit of the 2-sided 95% credible interval is below 5%, i.e. Pr($p_T - p_C < \mathbf{0.05}$|y)=0.975.

If the full planned model fails to converge, reduced versions may be considered. In the event that the number of Grade 3 or higher SLFs is too small Grade 2 or higher SLFs will be analyzed and tested as described above.

10.2. Secondary Analysis

Secondary efficacy analysis:

CLUE Overall Quality of Vision and Handling

CLUE Overall Quality of Vision and Handling will be analyzed using the same statistical method described for CLUE Overall Comfort.

10.3. Other Analysis

Daily Average Wear Time, Subject reported ocular symptoms and lens fitting characteristics will be descriptively summarized at the two-week follow-up evaluation by lens type.

11. SAFETY EVALUATION

11.1. Adverse Events

Listings of all reported ocular and non-ocular AEs and SAEs will be reported and will include lens type, eye diagnosis, severity of the AE, the number of days the subject spent in the study, the slit lamp findings at discovery of the AE, whether or not it is lens related, the possible cause, and treatments provided to the patient, the outcome, the subjects final Snellen visual acuity, whether or not the subject eye had a scar at the resolution of the AE and the action taken. In addition, the total number of subjects and the total number of eyes with each type of AE (SAEs, ocular AEs and non-ocular AEs) will be tabulated and presented as a footnote in each summary.

11.2. Keratometry and Over Refraction

Keratometry will be assessed for each eye at Entrance (Visit 1) and Exit (Visit 2) for the following metrics: (1) Steep Dioptric Power, (2) Steep Degrees, (3) Flat Dioptric Power and (4) Flat Degree. Each keratometry metric will be summarized using n, mean, min, and max across eye type.

11.3. Contact lens Corrected Visual Acuity

Contact lens visual acuity will be assessed using Snellen visual acuity Charts at both the fitting evaluation and the 2-week Follow-up. CLVA will be assessed both monocularly and binocularly. Summaries for Monocular CLVA and binocular CLVA will be presented using counts and percentages of eyes and subjects, for monocular CLVA and binocular CLVA, respectively. A detailed listing of eyes that have worsened by 2 or more lines at final visit compared to baseline will be presented.

11.4. Reasons for Discontinuation

The number of discontinued subjects by the analysis time point will be displayed by visit. Reasons for discontinuation include the following:

1. Adverse Event
2. Unsatisfactory lens fitting due to test article
3. Unsatisfactory visual response due to test articles
4. Lens discomfort
5. Withdrew consent during study
6. Lost to follow-up
7. Subject no longer meet eligibility criteria
8. Subject withdrawn by PI due to non-compliance to protocol
9. Test article no longer available
10. Other

11.5. 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.

11.6. Physical Examination Findings

Slit lamp findings will be assessed for each subject eye at baseline, the 2-week follow-up and at any unscheduled visit using the FDA Grading scale (Grade 0=None, Grade 1=Trace, Grade2=Mild, Grade 3=Moderate, Grade 4=Severe). Slit lamp finding assessments include the following metrics:

- Corneal Infiltrates (Yes/No)
- Corneal Edema
- Corneal Neovascularization
- Corneal Neovascularization Location
- Corneal Staining
- Corneal Staining Location
- Conjunctival Injection
- Tarsal Abnormalities
- Other

11.7. Clinical Laboratory Tests

Not applicable.

11.8. Other Safety Parameters

Subject's Reported Ocular Symptoms

Frequency and severity by eye of subject's reported ocular symptoms and problems with the study lens at fitting and post-fitting evaluation visits including the 2-Week Follow-up and unscheduled visits. Severity of the symptoms can be:

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

The related procedure is explained in CTP-2009 in Appendix D of the study protocol.

Lens fitting characteristics

Frequency by eye of mechanical lens fitting characteristics at fitting and 2-Week Follow-up evaluations. Lens fitting characteristics to be reported are:

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

Contact Lens Deposits

Contact lens deposits will be assessed for each eye at the 2-week Follow-up on the front and back surface of the study lens; the amount of deposits will be Graded using the scale:

- None = Grade 0 (No deposition).
- Slight = Grade 1 (Deposition which occupies 1-5% of the lens surface area.)
- Mild = Grade 2 (Deposition which occupies 6-15% of the lens surface area.)
- Moderate = Grade 3 (Deposition which occupies 16-25% of the lens surface area.)
- Severe = Grade 4 (Deposition which occupies =26% of the lens surface area.)

Contact Lens Wettability

Contact lens Wettability will be assessed for each eye at both lens fitting and the 2-week Follow-up. Wettability will be Graded using the scale:

- Grade 0 = All regions of lens surface are wettable between blinks (a minimum of 6 seconds between blinks).
- Grade 1 = Discrete non-wetting area(s) after a minimum of 3 seconds post blink.
- Grade 2 = Single non-wetting area within 2-3 seconds of blink.
- Grade 3 = Several non-wetting areas within 2-3 seconds of blink.
- Grade 4 = Immediate area(s) of non-wetting after blink.

12. REFERENCES

1. Wirth RJ, et al. Development of the Contact Lens User Experience: CLUE Scales. Optom Vis Sci. 2016; 93(8): 801-808.
2. SAS Institute Inc: SAS® 9.4 Statements: Reference, Third Edition. Cary, NC: SAS Institute Inc; 2014.
3. Stroup, WS. *Generalized linear mixed models*. 2012, Boca Raton: CRC Press.

14. SAS CODE

14.1. Primary Endpoints

Distance Visual Acuity (logMAR)

```
PROC MCMC DATA =ads  vp NTHREADS=8 SEED=20180906 NBI=100000  NMC=800000
THIN=100 DIAG=ALL OUTPOST= simout DIC PLOTS(SMOOTH FRINGE)=ALL
MCHISTORY=BRIEF PROPCOV=QUANEW STATS=ALL STATS(ALPHA = (0.05)
PERCENTAGE=(2.5 50 97.5))
plots(smooth) = all monitor = (_parms_ mu_C mu_T diff);

  PARMS beta0 0;
  PARMS beta1 0 beta2 0 beta3 0 beta4 0;
  PARMS s2 1;
  PARMS s2g_site 1 s2g_subj 1;

  PRIOR beta: ~ NORMAL(0, var = 1000);
  PRIOR s2 ~ IGAMMA(.001, s =.001);
  PRIOR s2g_site s2g_subj ~ IGAMMA(.001, s =.001);

  RANDOM Gamma  site ~ NORMAL(0, var = s2g  site) SUBJECT=siteid;
  RANDOM Gamma  subj ~ NORMAL(0, var = s2g  subj) SUBJECT=site  subjid;
  mu = beta0 + beta1*TRTAN + beta3*age +beta4*sexn + Gamma_site + Gamma_subj;
  MODEL AVAL ~ normal(mu, var = s2);

  BEGINNODATA;
  mu  C    = beta0 + 0.5* beta4;
  mu  T    = beta0 + beta1 + 0.5* beta4;
  diff    = mu  T - mu_C;
  ENDNODATA;
RUN;
```

Where,
ads vp =analysis data set for Distance Monocular Visual Acuity (logMAR)
trtan= numerical representation of treatment, where Test=1 and Control=0
bASE= Baseline CLUE comfort score
age= Age of subject at time of consent
sexn= Numerical representation of sex, where Female=1 and Male=0;
siteid= Site Number
site_subjid=Unique Subject ID

CLUE Comfort

```
PROC MCMC DATA = ads  cmt NTHREADS = 8 SEED=198756325 nbi=100000 nmc
=800000  thin=100 DIAG =ALL OUTPOST=simout DIC PLOTS(SMOOTH FRINGE)= ALL
MCHISTORY = BRIEF PROPCOV =QUANEW    STATS=ALL STATS(ALPHA=(0.05)
PERCENTAGE=(2.5 50 97.5))plots(smooth)=ALL MONITOR=(_parms_ mu_C mu_T diff);
  PARMS beta0 60;
```

```
  PARMS beta1 0 beta2 0 beta3 0 beta4 0;
  PARMS s2 400;
  PARMS s2g_site 1;

  PRIOR beta: ~ NORMAL(0, var = 1000);
  PRIOR s2 ~ IGAMMA(.001, s =.001);
  PRIOR s2g_site ~ IGAMMA(.001, s =.001);

  random Gamma_site ~ NORMAL(0, var = s2g_site) SUBJECT=SITEID;

  mu = beta0 + beta1*TRTAN + beta2*base + beta3*age + beta4*sexn +  Gamma_site;

  MODEL AVAL ~ normal(mu, var = s2);

  BEGINNODATA;
  mu  C    = beta0 + 0.5* beta4;
  mu  T    = beta0 + beta1+ 0.5* beta4;
  diff    = mu_T - mu_C;
  ENDNODATA;
RUN;
```

Where,
ads_cmt=analysis data set for CLUE Comfort
trtan= numerical representation of treatment, where Test=1 and Control=0
bASE= Baseline CLUE comfort score
age= Age of subject at time of consent
sexn= Numerical representation of sex, where Female=1 and Male=0;
siteid= Site Number

Vision Satisfaction in Bright Lighting

```
PROC MCMC DATA =ads  VS SEED=20181019 nbi =100000  nmc =500000  thin=100
DIAG=ALL OUTPOST=simout DIC PLOTS(SMOOTH FRINGE) = ALL
MCHISTORY=BRIEF PROPCOV=QUANEW STATS=ALL STATS(ALPHA=(0.05)
PERCENTAGE = (2.5 50 97.5))
plots(smooth)=ALL MONITOR=(_parms_ OR);

  ARRAY theta[4] theta1-theta4;
  ARRAY gamma[4] gamma1-gamma4;

  PARMS theta1-theta4 beta0 0 beta1 0 beta2 0 beta3 0;
  PARMS s2g 1;

  PRIOR beta: ~ NORMAL(0,VAR=1000);
  PRIOR theta1 ~ NORMAL(0,VAR=100);
  PRIOR theta2 ~ NORMAL(0,VAR=100,lower=theta1);
```

```
PRIOR theta3 ~ NORMAL(0,VAR=100,lower=theta2);
PRIOR theta4 ~ NORMAL(0,VAR=100,lower=theta3);
PRIOR s2g ~ IGAMMA(.01, s =.01);

RANDOM Gamma  site ~ NORMAL(0, VAR = s2g) SUBJECT=SITEID;
mu = beta0 + beta1*TRTAN + beta2*age + beta3*sexn + Gamma_site;
DO j = 1 to 4;
  gamma[j] = logistic(theta[j] + mu);
END;
pi1 = gamma1;
pi2 = gamma2 - gamma1;
pi3 = gamma3 - gamma2;
pi4 = gamma4 - gamma3;
pi5 = 1 - sum(of pi1-pi4);

llike = logmpdfmultinom(of y1-y5, of pi1-pi5);
MODEL DGENERAL(llike);

BEGINNODATA;
 array gammac[5];
 array gammat[5];
 array pc[5];
 array pt[5];
  DO i = 1 to 5;
   gammac[i] = logistic(theta[i] + beta0 + 0.5*beta3);
   gammat[i] = logistic(theta[i] + beta0 + beta1 + 0.5*beta3);
 END;
pc1 = gammac1;
pc2 = gammac2 - gammac1;
pc3 = gammac3 - gammac2;
pc4 = gammac4 – gammac3;
pc5 = 1 - sum(of pc1-pc4);
pt1 = gammat1;
pt2 = gammat2 - gammat1;
pt3 = gammat3 - gammat2;
pt4 = gammat4 – gammat3;
pt5 = 1 - sum(of pt1-pt4);
p2box_c = pc1 + pc2;
p2box  t = pt1 + pt2;
diff = p2box  t - p2box_c;
ENDNODATA;
RUN;
```

Where,
ads_VS =analysis data set for Vision Satisfaction in Bright Lighting
trtan= numerical representation of treatment, where Test=1 and Control=0

age= Age of subject at time of consent
sexn= Numerical representation of sex, where Female=1 and Male=0;
siteid= Site Number

Lens Fit

```
PROC MCMC DATA=ads_LF DIC MCHISTORY=brief
NBI=50000 NMC=200000 THIN = 50 STATS=ALL plots(smooth)  MONITOR=(_parms_ )
OUTPOST =post STATS(ALPHA=(0.05) PERCENTAGE=(2.5 25 50 75 97.5) ) SEED=53457  ;
ODS OUTPUT PostSummaries = PostSummaries ;
ODS OUTPUT PostIntervals  = PostIntervals ;
BY trta;
PARM p 0.5  ;
PARM ro .6 ;
PRIOR ro ~uniform(0,1);
PRIOR p ~ beta(0.5, 0.5);
;
llike = log( (1-ro)*PDF('BINOMIAL', y, p, 2) + z*ro*(PDF('BINOMIAL',y,p,2)**0.5));
MODEL y ~ GENERAL(llike);
RUN;
```

Slit lamp Findings (Grade 3 or higher)

```
PROC MCMC DATA=ads  SLF DIC MCHISTORY=brief
NBI=100000 NMC=500000 THIN =100 STATS=ALL plots(smooth)  MONITOR=(_parms_
P  C P  T)
OUTPOST =post STATS(ALPHA=(0.05) PERCENTAGE=(2.5 25 50 75 97.5) ) SEED=53457  ;
ODS OUTPUT PostSummaries = PostSummaries ;
ODS OUTPUT PostIntervals  = PostIntervals ;
PARMS (beta0 beta1 beta2 beta3) 0 sigma_site 1 sigma_subject 1;
PRIOR beta: ~NORMAL(0, var=1000);
PRIOR sigma_site~ IGAMMA(shape=0.01, scale=0.01);
PRIOR sigma_subject ~UNIFORM(0,100);

RANDOM gamma  site ~NORMAL(0, var=sigma  site) SUBJECT=siteid;
RANDOM gamma_subject ~NORMAL(0, sd=sigma_subject) SUBJECT=site_subjid;

mu = beta0 + beta1*trtan + beta2*age + beta3*sexn + gamma_site + gamma_subject;

p = logistic(mu);

MODEL y  ~ BINARY(P);

BEGINNODATA;
P  C = logistic(beta0 + 0.5*beta3);
P_T = logistic(beta0 + beta1 + 0.5*beta3);
```

```
Diff = P  T - P  C;
ENDNODATA;
run;
```

Where,
ads SLF =analysis data set for Slit Lamp Findings
trtan= numerical representation of treatment, where Test=1 and Control=0
age= Age of subject at time of consent
sexn= Numerical representation of sex, where Female=1 and Male=0;
siteid= Site Number
site_subjid=Unique Subject ID

14.2. Secondary Endpoints

CLUE Overall quality of vision and Handling will be analyzed and Tested using the same SAS code described for CLUE Comfort in section 14.1 above.