Johnson & Johnson Vision

STATISTICAL ANALYSIS PLAN

Protocol CR-6283

Initial Evaluation of Investigational Lenses Manufactured on a New Production Line

Acuvue Oasys® with Tansitions™ (senofilcon A with new UV-blocker)

Version: 2.0

Date: 14 November 2018

VIS-TD-105131/2

[redacted]

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	*See Electronic Signature in Teamcenter* Name: [redacted] Title: Biostatistician II	DATE
Reviewers	*See Electronic Signature in Teamcenter* Name: [redacted]. Title: Senior Manager of Biostatistics	DATE
Approvers	*See Electronic Signature in Teamcenter* Name: John Buch, O.D., M.S., F.A.A.O. Title: Principal Research Optometrist	DATE

TABLE OF CONTENTS

AMENDMENT HISTORY

Version Number	Revision Date (DD/MM/YYYY)	Reasons for Revision
1.0	25 September 2018	Original Draft
2.0	14 November 2018	Updated details for sample size justification in section 8.4.

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-6283 Version 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.

2. STUDY OBJECTIVES

The primary objective of this study is to demonstrate non-inferiority of the Test lens compared to the Control lens with respect to CLUE comfort, vision satisfaction in bright lighting, Slit Lamp Findings (Grade 3 or higher) and Distance Monocular logMAR Visual Acuity. This study will also aim to show that the Fit Acceptance rate is at least 90% while wearing the Test lens. The secondary objective of this study is to demonstrate non-inferiority of the Test lens compare to the Control lens with respect to CLUE Overall quality of Vision and Handling and overall quality of vision outdoors.

This study also aims to explore the performance of Indoor, Outdoor and Driving performance using individual questionnaire items.

3. STUDY DESIGN

3.1. Overview

This study is a randomized, 4-visit, partially subject-masked, 2x3 bilateral crossover, dispensing trial. Approximately 120 subjects will be screened and enrolled to ensure that at least 105 subjects complete.

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 lens wear sequences (Test/Control/Control or Control/Test/Test).

If the subject is dispensed their first study lenses at the initial visit then 3 additional visits will be conducted. Their first follow-up visit will occur at approrimxately 2-weeks after intial dispensing (Visit 2). At visit 2, subjects will be dispensed their next lens as specified per the randomization. Subjects' follow-up for their second lens will occur approximately 2-weeks after visit 2 (Visit 3). Subjects will be dispensed their last study lens (per the randomization) at visit 3 and will return for their final follow-up visit (visit 4) approximately 2-week after visit 3. 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 each.

3.2. Test Articles

Table 1: Test Article Labels

Test Article	Label
ACUVUE OASYS® with Transitions™	Test
ACUVUE OASYS®	Control
All Test Articles	Total

3.3. Targeted Study Population and Sample Size

Approximately 120 subjects will be enrolled to ensure that at least 105 subjects will complete the study. 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 be randomized to either Test/Control/Control or Control/Test/Test. Each lens will be worn for approximately 2 weeks in a bilateral fashion as DW totaling in a study duration of approximately 42 days (6 weeks) per subject.

Table 2: Planned Enrollment Strategy by Lens type and Site

	Test	Control	Total
Enrolled	60	60	120
Randomized	57	57	114
Completed	54	54	108
Number of enrolled per site	10	10	20

3.4. Test Article Allocation and Masking

A computer-generated randomization scheme will be used to randomly assign subjects, in blocks of 2, to one of the two possible lens wear sequences (TEST/CONTROL/CONTROL or CONTROL/TEST/TEST). 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 / exclusion criteria
- Subject history and baseline information has been collected.

Complete masking is impossible due to the functioning nature of the Test lens.However, both the Test and Control were overlabeled in order to reduce bias as much as possible since the Control lens may be the subject's habitual lens by chance. Therefore, the study is partially-subject masked (Control lens only).

3.5. Time and Event Schedule

Table 3: Time and Events Schedule

Procedure	Baseline	Trial Fit & Dispense	Follow-up	Unscheduled	Exit
Visit	1	1, 2, 3	2, 3, 4	PRN	4
Visit Window	-	-	13-15 Days	-	-
Estimated Visit Duration	-	V1: 2 hours	V2, 3: 1 hour V4: 1.5 hours	-	-
Informed consent	✓	-	-	-	-
Eligibility screening	✓	-	-	-	-
CLUE Baseline Questionnaire	✓	-	-	-	-
GSI Background Questionnaire	✓				
Other Questionnaires	✓	-	✓	-	-
Subject demographics	✓	-	-	-	-
General health and medication history	✓	-	-	-	-
Subject's own contact lens information	✓	-	-	-	-
Habitual lens care	✓	-	-	-	-
Entrance visual acuity	✓	-	-	-	-
Spherocylindrical refraction and BVA	✓	-	-	✓	✓
Slit lamp biomicroscopy	✓	-	✓	✓	-
Expanded Conjunctival Redness	✓	-	✓	✓	-
Expanded Corneal Staining	✓	-	✓	✓	-
Trial fitting lens information	-	✓	-	-	-
Lens Damage	-	✓	-	-	-
Distance spherical over-refraction	-	✓	✓	-	-
Lens modification	-	✓	-	-	-
Visual acuity	-	✓	✓	✓	-
logMAR acuity	-	-	✓	-	-
Contrast sensitivity (site 1036)	-	-	✓	-	-
Lens fitting assessment	-	✓	✓	*	-
Lens dispensing information and criteria	-	✓	-	-	-
Patient instructions	-	✓	-	-	-
Lens information	-	-	✓	✓	-

Procedure	Baseline	Trial Fit & Dispense	Follow-up	Unscheduled	Exit
Visit	1	1, 2, 3	2, 3, 4	PRN	4
Visit Window	-	-	13-15 Days	-	-
Estimated Visit Duration	-	V1: 2 hours	V2, 3: 1 hour V4: 1.5 hours	-	-
Compliance	-	-	✓	✓	-
Wearing times	-	-	✓	✓	-
CLUE Follow-Up Questionnaire	-	-	✓	*	-
GSI Product Performance Questionnaire	-	-	✓	*	-
Symptoms	-	✓	✓	✓	-
Lens preference	-	-	V3	-	-
Surface characteristics	-	-	✓	*	-
Chief complaint, diagnosis, treatment	-	-	-	✓	-
* if wearing study contact lenses					

4. STUDY ENDPOINTS

4.1. Primary Endpoints

Primary Efficacy Endpoints:

CLUE Overall Comfort

Overall comfort scores will be assessed using the Contact Lens User Experience (CLUE™)[1] questionnaire at the two-week follow-up. CLUE is a validated patient-reported outcomes questionnaire to assess patient-experience attributes of soft contact lenses (comfort, vision, handling, and packaging) in a contact-lens wearing population in the US, ages 18-65. Derived CLUE scores, using Item Response Theory (IRT), follow a normal distribution with a population average score of 60 (SD 20), where higher scores indicate a more favorable/positive response. A 5 point increase in an average CLUE score translates into 10% shift in the distribution of scores for a population of soft contact lens wearers[1]. The handling 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 under two lighting conditions, (1) Bright illumination low contrast and (2) Dim Illumination High Contrast.

Vision Satisfaction in Bright Lighting

Vision satisfaction in bright lighting will be assessed using the individual item [redacted] "I was satisfied with the quality of my vision in bright lighting" from the CLUE™ questionnaire.

[redacted]

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 using the FDA Grading scale ranfing from 0 to 4, where Grade 0 represents the absence of findings and 1 to 4 representing successively worse findings (i.e. Grade 1=trace, Grade 2= mile, Grade 3=moderate and Grade 4= severe). The assessment will include conjunctival injection, corneal edema, corneal neovasluralization, corneal staining, tarsal abnormalities or any other complication. SLF assessements will be conducted for each subject eye at all scheduled study visits(Fitting [Visit 1] and 2-Week Follow-up [Visit 2]). The percentage of eyes with Grade 3 or higher slit lamp findings will be analyzed; eyes with multiple events will be counted only once.

Fit Acceptance Rate
Acceptable lens fit will be assessed for each subject eye at all scheduled study visits (fitting [visit 1] and follow-up [visit 2]). Fit acceptance rate will be based on the lens fit acceptance of eyes wearing the Test lens only. Fit rates of the Control lens will also be collected but are not a primary endpoint.

4.2. 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.

Overall Quality of Vision Outdoors
Overall quality of vision outdoors will be assessed using the individual item [redacted] "Overall quality of vision outdoors" from the market research questionnaire. This item uses the response scale, 0: Not Applicable, 1: Excellent, 2: Very Good, 3: Good, 4: Fair and 5: Poor.

4.3. Other Endpoints

Lens Preferences
Lens preferences will be assessed by individual items regarding lens preference at the two-week follow-up of the second wearing period (Visit 3). Subjects will be asked to choose for each preference item one of the following responses: Strongly Prefer the first lens, Prefer the first lens, no preference, prefer the second lens, strongly prefer the second lens. Lens preference questions consist of:

1. Overall lens preference [redacted]
2. Overall comfort [redacted]
3. Overall vision [redacted]
4. Overall reduction of glare [redacted]

[redacted]

5. Overall preference indoors [redacted]
6. Overall preference outdoors [redacted]
7. Overall preference while driving during the day [redacted]
8. Overall preference while driving at night [redacted]
9. Overall preference while using computer screens & digital devices [redacted]

Driving Performance

Driving performance will be assessed by two individual patient reported outcomes (PRO) questions at the two-week follow-up evaluation. The individual items are as follows:

1. Reduction in glare while driving during the day [redacted]
2. Reduction in glare while driving during the night [redacted]

Indoor Performance

Indoor performance will be assessed by three individual items at the two-week follow-up evaluation. The individual items are as follows:

1. Reduction in glare from the computer screen or digital devices [redacted]
2. Reduction in glare caused by bright indoor lights [redacted]
3. Reduction in glare caused by bright light coming through the window [redacted]

Outdoor Performance

Outdoor performance will be assessed by four individual itemsat the two-week follow-up evaluation. The individual items are as follows:

1. Ability to see comfortably in bright sunlight [redacted]
2. Reduction in glare in bright sunlight [redacted]
3. Reduction in squinting in bright sunlight [redacted]
4. Reduction in eye strain in bright sunlight [redacted]

All driving, indoor and outdoor (PRO) items above will be assessed using the same excellence scale of; 0: Not Applicable, 1: Excellent, 2: Very Good, 3: Good, 4: Fair and 5: Poor.

Contrast sensitivity will also be evaluated during this study.

5. STATISTICAL HYPOTHESES FOR STUDY OBJECTIVES

5.1. Primary Hypotheses

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

1. The Test lens will be non-inferior to the Control lens with respect to Distance Monocular logMAR Visual Acuity at the two-week follow-up evaluation under both lighting conditions (Bright illumination low contrast and dim illumination high contrast). A non-inferiority margin of 0.05 logMAR will be used.

[redacted]

2. The Test lens will be non-inferior to the Control lens with respect to the percentage of eyes with Grade 3 or higher Slit Lamp Findings (Biomicroscopy) across all follow-up visits (scheduled and unscheduled). A non-inferiority odds ratio margin of 2 will be used.

3. The proportion of eyes with acceptable fit will be greater than 90% across all visits (scheduled and unscheduled) for all subjects wearing the Test lens.

4. The Test lens will be non-inferior to the Control lens with respect to CLUE Overall Comfort at the two-week follow-up evaluation. A non-inferiority margin of -5 points will be used.

5. The Test lens will be non-inferior to the Control lens with respect to Vision satisfaction in bright lighting at the two-week follow-up evaluation. A non-inferiority cumulative odds ratio margin of 0.67 will be used.

5.2. Secondary Hypotheses

1. The Test lens will be non-inferior to the Control lens with respect to CLUE Overall quality of vision at the two-week follow-up evaluation. A non-inferiority margin of -5 points will be used.

2. The Test lens will be non-inferior to the Control with respect to CLUE Handling at the two-week follow-up evaluation. A non-inferiority margin of -5 points will be used.

3. The Test lens will be non-inferior the Control lens with respect to Overall quality of vision indoors at the 2-week follow-up evaluation. A non-inferiority cumulative odds ratio margin of 0.67 will be used.

5.3. Other Hypotheses

1. The Test lens will be superior to the Control lens in all 9 of the following lens preference items at the two-week follow-up evaluation of the second wearing period.
    a) Overall lens preference
    b) Overall comfort
    c) Overall vision
    d) Overall reduction of glare
    e) Overall preference indoors
    f) Overall preference outdoors
    g) Overall preference while driving during the day
    h) Overall preference while driving at night
    i) Overall preference while using computer screens & digital devices

2. The Test lens will be superior to the Control lens in at least 2 of the following 4 indoor performance measures at the two-week follow-up evaluation.
    a) Reduction in squinting while using computer screens or digital devices

b) Reduction in glare from the computer screen or digital devices
c) Reduction in glare caused by bright indoor lights
d) Reduction in glare caused by bright light coming through the window

3. The Test lens will be non-inferior to the Control lens with respect to both of the following driving performance metrics at the two-week follow-up evaluation. A cumulative odds ratio margin of 0.67 will be used.
    a) Reduction in glare while driving during the day
    b) Reduction in glare while driving during the night

4. The Test lens will be superior to the Control lens in at least 2 of the following 4 outdoor performance measures at the two-week follow-up evaluation.
    a) Ability to see comfortably in bright sunlight
    b) Reduction in glare in bright sunlight
    c) Reduction in squinting in bright sunlight
    d) Reduction in eye strain in bright sunlight

5. At the 2-week follow-up evaluation, the difference in the area under the contrast sensitivity function curve (measured by the quick Contrast Sensitivity Function (qCSF) method) between the Test lens and the Control lens is more than -0.3 log unit.

6. ANALYSIS SETS

6.1. All Enrolled

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

6.2. Intent-to-Treat (ITT)

Intent-to-treat will include all the subjects who were randomized to study treatment. Subject will be analyzed as per randomized treatment (Planned Arm).

6.3. Safety Population

This analysis population will include all subjects who are randomized and administered any test article. Safety analyses will be based on the safety population.

6.4. 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.

7. DEFINITIONS AND DERIVED VARIABLES

7.1. 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]

7.2. Iris Color

Iris color will categorized into either dark or light based on the subjects hue and lightness of their iris using Johnson & Jonsons 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 suject will be classified as having a light iris; otherwise subjects will be classified as having a dark iris.

7.3. 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 FU	13 to 15	14
2	Fitting	13 to 15	14
3	2-Week FU	13 to 15	21
3	Fitting	13 to 15	21
4	2-Week FU	13 to 15	28

[a] The first treatment day is Day 1.

8. GENERAL STATISTICAL CONSIDERATIONS

8.1. 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].

8.2. 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 statistical analysis.

Summary tables (descriptive statistics and/or frequency tables) will be provided for all baseline variables, efficacy variables and safety variables, as appropriate, by study lens at each time event (fitting and follow-up). 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.

8.3. 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.

8.4. 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), CLUE comfort, handling and overall quality of vision. It was assumed there was no difference between the Test and Control lens with respect to visual acuity and slit lamp findings. Based on data from 3 historical studies, it was assumed there was a 5-, 3- and 4-point difference between the Test and Control lenses with respect to CLUE comfort, handling and overall quality of vision, respectively.

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, overall quality of vision indoors 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

[redacted]

CLUE Domain [Mean(SD)[1]]	Test	Control
Comfort	66.46 (22.20)	61.19 (24.20)
Handling	69.61 (19.18)	66.79 (20.01)
Overall Quality of Vision	64.15 (18.83)	60.33 (22.29)

[1]SD = Standard Deviation

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

Visual Acuity High Illumination High Contrast	Test	Control
[Mean(SD)[1]]	-0.0928 (0.08253)	-0.0726 (0.08011)

[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	1 (0.05)	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	55 (8.09)	59 (21.85)
Tarsal Abnormalities	51 (5.93)	24 (8.89)
Corneal Neovascularization	0 (0.0)	0 (0.0)
Corneal Staining	2 (0.29)	0 (0.0)
Other Findings	0 (0.0)	0 (0.0)
Total Eyes (N)	680	270
Any SLF Grade 2[2]	108 (15.8)	83 (33.74)
Any SLF Grade 3+	0 (0.0)	0 (0.0)
Total Unique Eyes	680	270

[redacted]

Total Unique Subjects	340	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 Items from [redacted] – 2-Week Follow-up

Questionnaire Item/ Response	Test	Control
Vision Satisfaction in Bright Light [n(%)]		
Strongly Agree	65 (35.9)	35 (19.2)
Agree	89 (49.2)	95 (52.2)
Neither Agree Nor Disagree	24 (9.92)	17 (9.3)
Disagree	13 (7.2)	29 (15.9)
Strongly Disagree	0 (0.0)	6 (3.3)
Overall Quality of Vision Indoors [n (%)]		
Excellent	100 (55.2)	80 (44.0)
Very Good	55 (30.4)	62 (34.1)
Good	23 (12.7)	30 (16.5)
Fair	3 (1.7)	7 (3.9)
Poor	0 (0.0)	3 (1.65)

CLUE Comfort

Sample size calculation for CLUE comfort 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[3].

Model details:

CLUE comfort was analyzed using a linear mixed model. Lens type was included as the only fixed effect. An unstructured (UN) covariance matrix was used to model the correlation between measurements on the same subject across study periods. Below is the variance-covariance matrix used in the CLUE Comfort model.

$$\sum_{comfort} \begin{pmatrix} 397.18 & 142.48 & 144.55 \\ 142.48 & 411.89 & 210.90 \\ 144.55 & 210.90 & 370.83 \end{pmatrix}$$

[redacted]

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[3].

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 on the same subject across study periods. Below is the variance-covariance matrix used in the visual performance model.

$$\sum_{visual\ performance} \begin{pmatrix} 0.003518 & 0.000374 & 0.000374 \\ 0.000374 & 0.003518 & 0.000374 \\ 0.000374 & 0.000374 & 0.003518 \end{pmatrix}$$

Acceptable Lens Fit

Acceptable lens fit is a binary response as y=1 if a subject eye has an acceptable fit and y=0 otherwise. Indicated by the historical data there was only 1 observed unacceptable lens fittings for the Test lens therefore, the common reference rate of 95% was selected for the sample size calculation, since this is considered to be a more conservative reference proportion. Assuming a correlation 0.80 between measurements within the same subject and period (intra-eye correlation); and assuming a correlation of 0.50 between measurements within the same subject across periods. A total of 2000 replicating trials were simulated to estimate a sample size with a minimum statistical power of 80%.

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 0.80 between left and right eyes within the same subject and period; and a correlation of 0.50 between measurements within the same subject across periods (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 50 was chosen to achieve a minimum statistical power of 80%.

The non-inferiority odds ratio margin of 2 corresponds to no more than a 5% difference between the Test and Control lenses assuming the Control reference rate does not exceed 5%.

Individual Questionnaire Items

Overall quality of vision outdoors and vision satisfaction in bright lighting sample size estimates were calculated using historical data from [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 sequence, lens type, period and first order carryover effect were included in the model as fixed effects. A variance component (VC) covariance structure was used to model the measurements between subjects across study periods.

The non-inferiority cumulative odds ratio margin of 0.67 corresponds to no more than a 10% difference between the Test and Control lenses assuming there is no difference between study lenses.

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

Endpoint	Number per Subjects to Complete	Power
Distance Monocular Visual Acuity (logMAR)	4	80%
SLFs (Grade 3 or Higher)	50	80%
Acceptable lens Fit	65	80%
CLUE Comfort	30	87%
Vision Satisfaction in Bright Lighting	48	81%

Table12: Sample Size Estimates and Power Calculations for Secondary Endpoints

Endpoint	Number per Subjects to Complete	Power
CLUE Handling	30	81%
CLUE Overall Quality of Vision	30	82%
Overall Quality of Vision Indoors	95	81%

As indicated in Table 11 and 12 above, the sample size chosen for this study was primarly driven by overall quality of vision indoors. The plan is to enroll 120 eligible subjects with a target of 105 subjects to complete 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 105 subjects complete the study.

8.5. 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.

8.6. 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-atrandom. To evaluate the impact of missing data, sensitivity analysis will be conducted using multiple imputation methods if the proportion of subject dropout is greater than the 15%. The SAS/STAT procedures PROC MI and PROC MIANALYZE will be utilized with a parametric regression method used to make at least 10 imputations.

9. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An interim analysis will be conducted after the first 75 subjects complete the first wearing period or 4-weeks post first subject first visit. The interim analysis will consist of descriptively summarizing safety and efficacy parameters. The results will be reviewed with historical data with lenses from the pilot line before the design validation study, [redacted] is initiated. The results will be communicated to study responsible clinician, project lead and platform lead. No statistical analysis will be conducted on the interim data.

10. SUBJECT INFORMATION

10.1. 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) subject's death during the study period (b) subject withdrawal of consent and/or assent (c) subject not compliant to protocol (d) subject lost to follow-up (e) subject no longer meets eligibility criteria (e) subject develops significant or serious adverse events causing discontinuation of study lens wear (f) subject who have experience a Corneal Infiltrative Event (g) investigator's clinical judgement regarding the subject safety reasons (that it is in the best interest of the subject to stop treatment) (h) subject missed any scheduled visit.

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.

10.2. 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.

10.3. Demographics and Baseline Characteristics

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

10.4. 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.

10.5. 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: Oral retinoid isotretinoin (e.g. Accutane), oral tetracyclines, topical scopolamine, oral (e.g. Seldane, Chlor-Trimeton and Benadryl) and ophthalmic antihistamines, oral phenothiazines (e.g. Haldol, Mellaril, Thorazine, Elavil, Pamelor and Compazine), oral and ophthalmic Beta-Adrenergic blockers (e.g. Propranolol, Timolol and Practolol), systemic steroids and any prescribed or over the counter (OTC) ocular medication.

There are no disallowed concomitant therapies in this study.

10.6. Medical History

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

11. STATISTICAL ANALYSIS

11.1. Primary Analysis

Primary efficacy analysis:

Visual Acuity

Distance monocular visual acuity (logMAR) will be tested under two conditions (bright illumination low contrast and dim illumination high contrast). Each condition will be analyzed separately using a Bayesian multivariate normal random-effects model to compare the Test and Control lenses. The regression model will include sequence of lens wear, lens type and first-order carryover effect as fixed effects. Clinical site and subject nested within clinical site 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_{ijklm}= ($y1_{ijklm}$, $y2_{ijklm}$, $y3_{ijklm}$) denote the visual acuity (logMAR) for the m^{th} subject at the l^{th} site, assigned to the i^{th} lens for the j^{th} eye using the k^{th} sequence at periods 1, 2, 3, respectively. The likelihood for y_{ijklm} is constructed as follows:

$$y_{ijklm} \sim \mathrm{N}(\mu_{ijklm}, \Sigma)$$

Where μ_{ijklm} = ($\mu 1_{ijklm}$, $\mu 2_{ijklm}$, $\mu 3_{ijklm}$)^T and Σ is a 3X3 variance-covariance matrix. Here,

$$\mu 1_{ijklm} = \mu_0 + \pi_1 + \beta_1 Lens_{[i,k]} + \beta_2 Sequence_k + \gamma_l + \alpha_j$$
$$\mu 2_{ijklm} = \mu_0 + \pi_2 + \beta_1 Lens_{[i,k]} + \beta_2 Sequence_k + \beta_3 Carry1_{[i,k]} + \gamma_l + \alpha_j$$
$$\mu 3_{ijklm} = \mu_0 + \pi_3 + \beta_1 Lens_{[i,k]} + \beta_2 Sequence_k - \beta_3 Carry1_{[i,k]} + \gamma_l + \alpha_j$$

In this model π_1, π_2, π_3 represent the effect of period with the constraint $\pi_1 + \pi_2 + \pi_3 = 0$. Lens will be determined by sequence k therefore lens i is denoted as a function of k. We define $Lens_i$=0 for the Control lens and $Lens_i$=1 for the Test lens, sequence is defined as: Sequence=0 for the order Control/Test/Test and Sequence=1 for order Test/Control/Control. The first-order carryover effect will be defined as carry=0 for the Control lens and carry=1 for the Test lens. So β_1 stands for the difference between the Test and Control lens with respect to visual performance. A negative β_1 indicates the Test performed better than the Control lens.

We assume random subject eye effects are independent and identically distributed (i.i.d) as $\alpha_j \sim$ N(0, σ^2_{eye}) and the random subject effect is i.i.d. as $\delta_m \sim$ N(0, $\sigma^2_{subject}$) and the random site effect is i.i.d as $\gamma_l \sim$ N(0, σ^2_{site}) for i=1,2 (lens), j=1, 2 (eye), k=1, 2 (sequence), carry1=1, 2 (first-order carryover effect) and l=1…| m_l(subject/site) and l=1,2, 3, 4, 5 and 6 (site).

For the β coefficients, independent non-informative priors N(0, 1000) will be used. For the variance of random effects σ^2_{eye} and σ^2_{site} independent non-informative conjugate priors inverse-gamma(0.001, 0.001) will be used. For Σ, non-informative conjugate priors inverse-wishart(3,S) will be used where S is a 3X3 variance-covariance matrix of y_{ijklm}. 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:

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

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. $P(\beta_1 < 0.05) \geq 0.975$.

CLUE Overall Comfort

CLUE Comfort scores will be analyzed using a Bayesian multivariate normal random-effects model to compare the Test and Control lenses. The regression model will include baseline CLUE comfort scores, sequence of lens wear, lens type and first-order carryover effect 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 when appropriate.

The Model:

Let $y_{ijkl} = (y1_{ijkl}, y2_{ijkl}, y3_{ijkl})$ denote the CLUE Comfort score for the l^{th} subject at the k^{th} site, assigned to the i^{th} lens using the j^{th} sequence at periods 1, 2 and 3. The likelihood for y_{ijkl} is constructed as follows:

$$y_{ijkl} \sim N(\mu_{ijkl}, \Sigma)$$

Where $\mu_{ijkl} = (\mu 1_{ijkl}, \mu 2_{ijkl}, \mu 3_{ijkl})^T$ and Σ is a 3X3 variance-covariance matrix. Here,

$$\mu 1_{ijkl} = \mu_0 + \pi_1 + \beta_1 Lens_{[i,j]} + \beta_2 \text{baseline} + \beta_3 Sequence_j + \gamma_k$$
$$\mu 2_{ijkl} = \mu_0 + \pi_2 + \beta_1 Lens_{[i,j]} + \beta_2 \text{baseline} + \beta_3 Sequence_j + \beta_4 Carry1_{[i,j]} + \gamma_k$$
$$\mu 3_{ijkl} = \mu_0 + \pi_3 + \beta_1 Lens_{[i,j]} + \beta_2 \text{baseline} + \beta_3 Sequence_j - \beta_4 Carry1_{[i,j]} + \gamma_k$$

In this model π_1, π_2, π_3 represent the effect of period with the constraint $\pi_1 + \pi_2 + \pi_3 = 0$. Lens will be determined by sequence j, therefore i is denoted as a function of j. We define Lens=0 for the Control lens and $\text{Lens} = 1$ for the Test lens, sequence is defined as: Sequence=0 for the order Control/Test/Test and Sequence=1 for order Test/Control/Control. The first-order carryover effect will be defined as carry=0 for the Control lens and carry=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 $\gamma_k \sim N(0, \sigma^2_{site})$ for site for i=1, 2 (lens), j=1, 2 (sequence), k=1, 2, 3, 4, 5 and 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. For Σ, non-informative conjugate priors inverse-wishart(3,S) will be used where S is a 3X3 variance-covariance matrix of y_{ijkl}. 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:

$$H_o: \beta_1 \leq -5$$

$$H_A: \beta_1 > -5$$

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

Vision satisfaction in bright lighting will be analyzed using a Bayesian multinomial model for ordinal data. The regression model will include sequence of lens wear, lens type, period and first order carryover effect. Clinical site and subject nested within clinical site will be included as random effects. Other subject characteristics such as age, gender, race and iris category will be included when appropriate.

The Model:

Let y_{ijklm}= (y_{ijklm1} , y_{ijklm2} , y_{ijklm3}, y_{ijklm4}, y_{ijklm5}) denote the rating for the m^{th} subject, from the l^{th} site, assigned to the i^{th} study lens in the j^{th} period using the k^{th} sequence. Possible values of y_{ijklm} 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:

$$y_{ijklm} \sim \text{Multinomial } (P_{ijklm1}, P_{ijklm2}, P_{ijklm3}, P_{ijklm4}, P_{ijklm5})$$

$$P_{ijklm1} = \gamma_{ijklm1}$$

$$P_{ijklmX} = \gamma_{ijklmX} - \gamma_{ijklm(X-1)} \; 2 \leq n \leq 4$$

$$P_{ijklm5} = 1 - \sum_{x=1,..4} P_{ijklmX}$$

$$\text{Logit}(\gamma_{ijklmX}) = \theta_n + \beta_1 Lens_{i[j,k]} + \beta_2 Period_{j1} + \beta_3 Period_{j2} + \beta_4 Sequence_k + \beta_5 Carry_{i[j,k]} + \gamma_l + \delta_{m_{(l)}}$$

Where $\theta_n$is the intercept for levels n=1,2,3,4, $P_{ijklm1} = \Pr(\gamma_{ijklm1} = 1)$ with respect to the vision satisfaction in bright lighting item. We assume the random subject effects are independent identically distributed (i.i.d) as $\delta_{m_{(l)}} \sim N(0, \sigma^2_{subject})$ for subject m nested within clinical site l and

the random clinical site effects are i.i.d as γ_l~N(0, σ^2_{site}) for i=1,2 (lens), j=1, 2, 3 (Period) k=1, 2(Sequence) l=1, …6 (Site) m=1, …n_l(subject/site).

In this model, the lens I will be determined by the period j and sequence k, therefore i is denoted as a function of j and k. We define $Lens_i$=0 for the Control lens and $Lens_i$=1 for the Test lens. The cumulative odds ratio for having higher rating can be written as OR=$e^{\beta 1}$.

Independent vague N(0, 1000) priors for the regression coefficients β_i i=1,…5. For θ_n, 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 vague normal priors will also be used; σ^2_P ~inverse-gamma(0.001, 0.001) and σ^2_s ~inverse-gamma(0.001, 0.001). The Metropolis sample algorithim 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.

Hypothesis Testing

The null and alternative hypotheses for superiority are as follows:

$$H_o \quad OR \leq 0.67$$
$$H_A \quad OR > 0.67$$

Where OR represent the cumulative odds ratio of having higher rating of the Test lens compared to the Control lens. Non-inferiority will be declared if the lower bound of the 2-sided 95% credible confidence interval is above 0.67, i.e. P(OR=$e^{\beta 1}$>0.67|y)=0.975.

Primary Safety Analysis:

Lens Fit Acceptance

Lens fit acceptance will be analyzed using a Bayesian Logistic regression random-effects model to estimate the proportion of subjects' eyes wearing the Test lens having acceptable lens fitting. The regression model will include period, sequence of lens wear and first order carryover effect as fixed effects. Site and subject will be included in the model as random effects.

Let y_{ijklm}=1 if an acceptable lens fit is observed for eyes wearing the Test lens only and y_{ijklm} =0 otherwise for the m^{th} subject, from the l^{th} site, for the i^{th} eye in the j^{th} period using the k^{th} sequence.

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

$$p_{ijklm} = \frac{\exp(\mu_{ijklm})}{1+\exp(\mu_{ijklm})}$$

$\mu_{ijklm} = \beta_0 + \beta_1 Lens_{i[j,k]} + \beta_3 period_{j1} + \beta_4 period_{j2} + \beta_5 \text{sequence}_k + \beta_6 Carry1_{i[j,k]} + \gamma_l + \delta_{m_{(l)}} + \alpha_{j_{(m(l))}}$

We assume the random subject eye effects are i.i.d as $\alpha_{j_{(m(l))}} \sim N(0, \sigma^2_{eye})$ for eye nested within subject within clinical site, the random effect for subject are i.i.d as $\delta_{m_{(l)}} \sim N(0, \sigma^2_{subject})$ for subject nested within clinical site and the random clinical site effects are i.i.d as $\gamma_m \sim N(0, \sigma^2_{site})$ for i=1, 2 (eye) , j=1, 2, 3 (period) k=1, 2(Sequence) l=1, …6 (Site) m=1, …n_l(subject/site).

For the β coefficients, independent non-informative priors $N(0, 10000)$ will be used. For the variance of random effects of σ^2_{eye},$\sigma^2_{subject}$ andσ^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

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

$$H_0 = p \leq 0.90$$
$$H_1 = p > 0.90$$

Where, p represents the proportion of subject eyes that achieve acceptable fit for the Test lens. Where p is calculated as:

$$p = \frac{\exp(\mu)}{1 + \exp(\mu)}$$

And $\mu = \beta_0 + \beta_1 + \frac{\beta_3}{3} + \frac{\beta_4}{3} + \frac{\beta_5}{2} + \frac{\beta_6}{2}$

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. $P(p > 0.90) \geq .975$.
If the full planned model fails to converge, reduced versions may be considered.

Primary safety analysis:

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, lens type, period, sequence of lens wear and first order carryover effect. Site and subject will be included in the model as random effects.
Let y_{ijklmn}=1 if a Grade 3 or higher SLF is observed and y_{ijklm} =0 otherwise for the n^{th} subject, from the m^{th} site, assigned to the i^{th} study lens for the j^{th} eye in the k^{th} period using the l^{th} sequence.

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

$$p_{ijklmn} = \frac{\exp(\mu_{ijklmn})}{1 + \exp(\mu_{ijklmn})}$$

$\mu_{ijklmn} = \beta_0 + \beta_1 Lens_{ij[k,l]} + \beta_2 \text{Baseline SLF}_l + \beta_3 period_{k1} + \beta_4 period_{k2} + \beta_5 \text{sequence}_k + \beta_6 Carry1_{i[k,l]} + \gamma_m + \delta_{n_{(m)}} + \alpha_{j_{(n(m))}}$

We assume the random subject eye effects are i.i.d as $\alpha_{j_{(n(m))}} \sim N(0, \sigma^2_{eye/subject/site})$ for eye nested within subject within clinical site, the random effect for subject are i.i.d as $\delta_{n_{(m)}} \sim N(0, \sigma^2_{subject/site})$ for subject nested within clinical site and the random clinical site effects are i.i.d as $\gamma_m \sim N(0, \sigma^2_{site})$ for i=1,2 (lens), j=1, 2 (eye) , k=1, 2, 3 (period) l=1, 2(Sequence) m=1, …6 (Site) m=1, …n_m(subject/site).

In this model, the lens I will be determined by the period k and sequence l, therefore i is denoted as a function of j and k. We define $Lens_i$=0 for the Control lens and $Lens_i$=1 for the Test lens. The odds ratio for having a lower rate of SLFs can be written as OR=$e^{\beta 1}$.

For the β coefficients, independent non-informative priors $N(0, 10000)$ will be used. For the variance of random effects of σ^2_{eye},$\sigma^2_{\text{subject}}$ andσ^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_o: OR ≥ 2

H_A: OR< 2

Where OR represents the cumulative odds of the Test lens having a lower rate of Grade 3 SLFs compared to the Control lens and is calculated as OR=$e^{\beta 1}$. Non-inferiority will be established if the upper limit of the 2-sided 95% credible interval is below 2, i.e. P($OR < 2$ |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.

11.2. Secondary Analysis

Secondary efficacy analysis:

CLUE Overall Quality of Vision and Handling

CLUE Overall Quality of Vision and Handling will be analyzed and test in the exact same manner as CLUE Overall Comfort.

Overall Quality of Vision Indoors

Overall quality of vision indoors will be analyzed and tested in the same manner as vision satisfaction in bright lighting. The only difference between the two models are the response set used to assess each item. For this model,

Let y_{ijklm}= (y_{ijklm1} , y_{ijklm2} , y_{ijklm3}, y_{ijklm4}, y_{ijklm5}) denote the rating for the m^{th} subject, from the l^{th} site, assigned to the i^{th} study lens in the j^{th} period using the k^{th} sequence. Possible values of y_{ijklm} are 1if the subject rating of overall quality of vision indoors are X and 0 otherwise (x=1 for Excellent and X=5 for Poor, respectively).

Secondary safety analysis:
Not Applicable

11.3. Other Analysis

Other efficacy analysis:

Lens Preferences:

Lens preference items listed below will be analyzed separately using Bayesian multinomial models for nominal data.

1. Overall lens preference
2. Overall comfort
3. Overall vision
4. Overall reduction of glare
5. Overall preference indoors
6. Overall preference outdoors
7. Overall preference while driving during the day
8. Overall preference while driving at night
9. Overall preference while using computer screens & digital devices

The regression models will include lens wearing sequence, age and gender as fixed covariates when appropriate. Investigational site will be included as random effect if the variation across sites is not negligible.

Let $\mathbf{y_{ijkl}}$ = (y_{ijk1}, y_{ijk2}, y_{ijk3}, y_{ijk4}) denote subject lens preference for the i^{th} subject from the j^{th} site with regard to the k^{th} preference item. Possible values of y_{ijkl} are: y_{ijk1} = 1 if the subject preferred the Test lens, 0 otherwise; y_{ijk2} = 1 if the subject preferred the Control lens, 0 otherwise; y_{ijk3} = 1 if the subject preferred both the Test and Control lenses, 0 otherwise and y_{ijk4} = 1 if the subject preferred neither Test nor Control lenses, 0 otherwise. The likelihood of $\mathbf{y_{ijkl}}$ is constructed as follow:

$$\mathbf{y_{ijkl}} \sim \text{Multinomial}\ (p_{ijk1}, p_{ijk2}, p_{ijk3}, p_{ijk4})$$
$$p_{ijkl} = \theta_{ijkl} / \Sigma_m \theta_{ijkl}$$
$$\log(\theta_{ijkl}) = \mu_{0kl} + \beta_{1k}\text{Sequence}_{ij} + \beta_{2k}\text{Age}_{ij} + \beta_{3k}\text{Female}_{ij} + \delta_j,$$

where μ_{0kl} are the intercepts with μ_{0k4} set to 0, $p_{ijkl} = P(Y_{ijkl} = 1)$ and $\gamma_j \sim N(0, \sigma_s^2)$. We will use independent vague N(0,1000) priors for the regression coefficients μ_{0kl}, β_{1k}, β_{2k} and β_{3k}, and IG(0.001, 0.001) for σ_s^2.

Hypothesis Testing:

For each preference item, the null and alternative hypotheses for superiority are as follows:
Ho: $OR_k \leq 1$ Ha: $OR_k > 1$; where OR_k represents the odds ratio of comparing the Test lens to the Control lens with regard to item k. The odds ratio is calculated as:

$$OR_k = p_{.k1}(1- p_{.k2})/p_{.k2}(1-p_{.k1}),$$

where $p_{.kl}$ is the mean estimate p_{ijkl} for k=1, ..., 5 and l = 1, …, 4.

For each item k, the superiority will be declared if the lower bound of the 2-sided 95% credible interval of OR_k is greater than 1: $Pr(OR_k > 1| \mathbf{y}) \geq .975$.

Outdoor Glare Reduction

Outdoor Glare reduction consists of 4 individual questionnaire items.

1. Ability to see comfortably in bright sunlight
2. Reduction in glare caused by bright sunlight
3. Reduction of squinting in bright sunlight
4. Reduction of eyestrain in bright sunlight

All outdoor glare items are assessed using the same ordinal scale (1=Excellent …5=Poor). Outdoor Glare reduction items will be analyzed separately using a Bayesian multinomial model for ordinal data adjusting for baseline. The regression model will include sequence of lens wear, lens type, period and first order carryover effect. Clinical site and subject nested within clinical site will be included as random effects. Other subject characteristics such as age, gender, race and iris category will be included when appropriate.

The Model:

Let y_{ijklm}= (y_{ijklm1} , y_{ijklm2} , y_{ijklm3}, y_{ijklm4}, y_{ijklm5}) denote the rating for the m^{th} subject, from the l^{th} site, assigned to the i^{th} study lens in the j^{th} period using the k^{th} sequence. Possible values of y_{ijklm} are 1if the subject rating of outdoor glare items are X and 0 otherwise (x=1 for Excellent and X=5 for Poor, respectively). The likelihood is constructed as follows:

$$y_{ijklm} \sim \text{Multinomial } (P_{ijklm1},\ P_{ijklm2}\ , P_{ijklm3}, P_{ijklm4}, P_{ijklm5})$$

$$P_{ijklm1} = \gamma_{ijklm1}$$

$$P_{ijklmX} = \gamma_{ijklmX} - \gamma_{ijklm(X-1)}\ 2 \leq n \leq 4$$

$$P_{ijklm5} = 1 - \sum_{x=1,..4} P_{ijklmX}$$

Logit(γ_{ijklmX})= $\theta_n + \beta_1 Lens_{i[j,k]} + \beta_2 Period_{j1} + \beta_3 Period_{j2} + \beta_4 Sequence_k + \beta_5 Carry_{i[j,k]} + \gamma_l + \delta_{m_{(l)}}$

Where $\theta_n$is the intercept for levels n=1,2,3,4, $P_{ijklm1} = \Pr(\gamma_{ijklm1} = 1)$ with respect to outdoor glare preference. We assume the random subject effects are independent identically distributed (i.i.d) as $\delta_{m_{(l)}}$~N(0, $\sigma^2_{subject/site}$)for subject m nested within clinical site l and the random clinical site effects are i.i.d as γ_l~N(0, σ^2_{site}) for i=1,2 (lens), j=1, 2, 3 (Period) k=1, 2(Sequence) l=1, …5 (Site) m=1, …n_l(subject/site).

In this model, the lens I will be determined by the period j and sequence k, therefore i is denoted as a function of j and k. We define $Lens_i$=0 for the Control lens and $Lens_i$=1 for the Test lens. The odds ratio for having higher rating can be written as OR=$e^{-\beta 1}$.

Independent vague N(0, 1000) priors for the regression coefficients β_i i=1,…5. For θ_n, 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 vague normal priors will also be used; σ^2_P ~inverse-gamma(0.001, 0.001) and σ^2_s ~inverse-gamma(0.001, 0.001). The Metropolis sample algorithim 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.

Hypothesis Testing

The null and alternative hypotheses for superiority are as follows:

$$H_o \ \ OR \leq 1$$
$$H_A \ OR > 1$$

Where OR represent the cumulative odds ratio of having higher rating of the Test lens compared to the Control lens where the OR is calculated as OR=$e^{-\beta 1}$. Superiority will be declared if the lower bound of the 2-sided 95% credible confidence interval is above 1, i.e.
P(OR=$e^{-\beta 1}$>1|y)=0.975.

Indoor Glare Reduction

Indoor Glare reduction consists of 4 individual questionnaire items:

1. Reduction in squinting while using computer screens or digital devices
2. Reduction in glare from the computer screen or digital devices
3. Reduction in glare caused by bright indoor lights
4. Reduction in glare caused by bright light coming through the window

Each item will be analyzed individually and tested in the exact same manner as the Outdoor Glare Reduction Items described above.

Driving Measures

Driving measure consists of two individual questionnaire items:

1. Reduction in glare while driving during the day
2. Reduction in glare while driving during the night

Each item will be analyzed individually in the exact same manner as the Outdoor Glare Reduction Items described above. However, the hypothesis test will be as follows:

Hypothesis Testing

The null and alternative hypotheses for superiority are as follows:

$$H_o \ \ OR \leq 0.67$$
$$H_A \ OR > 0.67$$

Where OR represent the cumulative odds ratio of having higher rating of the Test lens compared to the Control lens. Non-inferiority will be declared if the lower bound of the 2-sided 95% credible confidence interval is above 0.67, i.e. P(OR=$e^{-\beta 1}$>0.67|y)=0.975. Superiority will be declared if the lower bound of the 2-sided 95% credible interval is above 1, i.e. P(OR=$e^{-\beta 1}$> 1|y)=0.975. Superiority will only be tested in the event that non-inferiority is established.

12. SAFETY EVALUATION

12.1. Adverse Events

Listings of all reported ocular and non-ocular AEs and SAEs will be reported.

12.2. Physical Examination Findings

Slit lamp findings will be summarized by lens type. The slit lamp assessment will evaluate the following

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

12.3. Other Safety Parameters

Corneal Staining Area, Type and Depth as well as Conjunctival Redness (Bulbar and Limbal) will be descriptively summarized by lens type. Expanded corneal staining will be assessed in the following locations:

- Central
- Nasal
- Temporal
- Inferior
- Superior

13. 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.