

Johnson & Johnson Vision
Research & Development
Clinical Affair

Statistical Analysis Plan

Evaluation of Astigmatic Contact Lens

Protocol CR-5871

JJV Investigational Contact Lens ATLAS A

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

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AMENDMENT HISTORY

Not applicable.

ABBREVIATIONS

| | |
|------|---|
| AE | Adverse Event |
| AOA | Air Optix for Astigmatism® |
| CI | Confidence Interval |
| CLUE | Contact Lens User Experience |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| GCP | Good Clinical Practice |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| FDA | Food and Drug Administration |
| ICH | International Conference on Harmonization |
| IRB | Institutional Review Board |
| IRT | Item Response Theory |
| JJV | Johnson & Johnson Vision |
| PP | Per Protocol |
| PI | Principal Investigator |
| PRO | Patient Reported Outcome |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| VA | Visual Acuity |

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1. INTRODUCTION

1.1. Background

This document describes the data analysis specifications for the protocol CR5871 titled "Evaluation of Astigmatic Contact Lenses". The test lens is the Johnson & Johnson Vision (JJV) investigational contact lens Atlas A and the control lens is the Alcon Air Optix for Astigmatism® (AOA) which is currently marketed as a monthly replacement.

This Statistical Analysis Plan (SAP) will serve as the final guidance for all the statistical analyses for this study and will supersede the Section 9 in the protocol if there are any discrepancies.

1.2. Study Objectives

The objectives of the study are to demonstrate that the senofilcon C toric in its final lens design meets the design validation requirements related to corneal staining, lens fitting characteristics, visual acuity and rotational performance of senofilcon C toric contact lenses as well as subjective comfort and handling when worn for 30 (-2/±6) days on daily wear modality.

1.3. Study Design

This is a randomized, double-masked, multi-center, bilateral, 5-visit dispensing parallel group design study. Subjects will be randomly assigned to wear one of two study lenses bilaterally for approximately 30 days in a daily wear, monthly replacement modality. Approximately 270 eligible subjects will be enrolled to attain a minimum of 230 subjects to complete the study (115 subjects per arm).

This study consists 5 office visits including an initial visit and 4 subsequent follow-up visits as described in Table 1.

Table 1: Study Time Event Description

| Visit Number | Event | Description | Approximate Duration (Hour) |
|--------------|---|--|-----------------------------|
| 1 | Enrollment/ Baseline/ Dispensing | Execute informed consent process, determine eligibility criteria, collect demographics and baseline data, trial fitting/dispensing, and visual performance | 2.5 |
| 2 | 1-week Follow-up (6-9 days from Visit 1) | Follow-up visit to assess the study lens performance: subjective responses, visual acuity (VA), fitting characteristics, surface characteristics, and physiology | 1.0 |
| 3 | 2-week Follow-up (6-9 days from Visit 2) | Follow-up visit to assess the study lens performance: subjective responses, VA, fitting characteristics, surface characteristics, and physiology | 1.5 |
| 4 | 3-week Follow-up (6-9 days from Visit 3) | Follow-up visit to assess the study lens performance: subjective responses, VA, fitting characteristics, surface characteristics, and physiology | 1.0 |
| 5 | 4-week Follow-up (6-9 days from Visit 4) | Follow-up visit to assess the study lens performance: subjective responses, VA, fitting characteristics, surface characteristics, and physiology | 1.5 |

Subject will be advised to wear the study lenses for 8 hours each day and to the follow-up visit, after a minimum 8 hours of wear that day. Unscheduled visit(s) may occur during the course of the study if a

subject experiences any investigational device-related difficulties and/or problems requiring an unscheduled visit to the clinic.

1.4. Statistical Hypotheses for Study Objectives

1.4.1. Primary Hypotheses

The co-primary endpoints for this study are:

- Monocular distance visual acuity 20/40 or better,
- Lens fitting acceptability,
- Stability with blink,
- Absolute rotation, and
- Contact lens related corneal staining.

Monocular Visual Acuity (VA) 20/40 or better

The proportion of dichotomized monocular VA 20/40 or better in the Atlas A group will be compared to a historical control proportion (p_0) of 80%. The alternative hypothesis (denoted as H_a) is at least 80% of eyes in the Atlas A group will have monocular visual acuity 20/40 or better throughout all planned visits (Visits 1 through 5) whereas the null hypothesis (denoted as H_0) is less than 80% of eyes in the Atlas A group will have monocular visual acuity 20/40 or better. The following hypothesis testing for proportion will be assessed:

$$H_0: p < p_0 \text{ vs. } H_a: p \geq p_0,$$

where p represents the population proportion and p_0 represents a historical control proportion of 80%.

Lens Fitting Acceptability

The proportion of acceptable lens fit at fitting (Visit 1) in the Atlas A group will be compared to a historical control proportion (p_0) of 80%. The alternative hypothesis is at least 80% of eyes in the Atlas A group will have acceptable lens fit at fitting whereas the null hypothesis is less than 80% of eyes in the Atlas A group will have acceptable lens fit. The following hypothesis testing for proportion will be assessed:

$$H_0: p < p_0 \text{ vs. } H_a: p \geq p_0,$$

where p represents the population proportion and p_0 represents a historical control proportion of 80%.

Stability with Blink

The proportion of dichotomized adequate lens stability with blink (adequate stability is defined as lens stability with blink ≤ 5 -degree) at fitting (Visit 1) in the Atlas A group will be compared to a historical control proportion (p_0) of 80%. The alternative hypothesis is at least 80% of eyes in the Atlas A group will have adequate lens stability with blink at fitting whereas the null hypothesis is less than 80% of eyes in the Atlas A group will have adequate lens stability with blink. The following hypothesis testing for proportion will be assessed:

$$H_0: p < p_0 \text{ vs. } H_a: p \geq p_0,$$

where p represents the population proportion and p_0 represents a historical control proportion of 80%.

Absolute Rotation

The proportion of dichotomized acceptable absolute rotation (acceptable absolute rotation is defined as absolute rotation ≤ 10 -degree) at 15-minute post insertion (Visit 1) in the Atlas A group will be compared to a historical control proportion (p_0) of 80%. The alternative hypothesis is at least 80% of eyes in the Atlas A group will have acceptable absolute rotation at 15-minute post insertion whereas the null

hypothesis is less than 80% of eyes in the Atlas A group will have acceptable absolute rotation. The following hypothesis testing for proportion will be assessed:

$$H_0: p < p_0 \text{ vs. } H_a: p \geq p_0,$$

where p represents the population proportion and p_0 represents a historical control proportion of 80%.

Contact Lens Related Corneal Staining (CS)

The proportion of dichotomized unacceptable contact lens related CS (unacceptable CS is defined as CS grade 3 or higher) in the Atlas A group will be compared to the proportion of that in the AOA group throughout all planned and unplanned visits. The alternative hypothesis is the odds of unacceptable CS incidence rate in the Atlas A group ($OR_{\text{Atlas A}}$) is not statistically different from the odds of that in the AOA group (OR_{AOA}) throughout the wear period. The following hypothesis testing for odds ratio will be assessed:

$$H_0: OR = 1 \text{ vs. } H_a: OR \neq 1,$$

where OR represents the ratio of $OR_{\text{Atlas A}}$ over OR_{AOA} ($OR_{\text{Atlas A}}/OR_{\text{AOA}}$) and Ψ_0 represents a margin of 1 that reflects distribution similarity between the Atlas A and AOA groups.

1.4.2. Secondary Hypotheses

The secondary endpoints for this study are:

- Monocular distance visual acuity 20/20 or better,
- CLUE Comfort Score, and
- CLUE Handling Score.

Monocular Visual Acuity (VA) 20/20 or better

The proportion of dichotomized monocular VA 20/20 or better in the Atlas A group will be compared to the proportion of that in the AOA group at fitting (Visit 1). The alternative hypothesis is the odds of the proportion of eyes with monocular VA 20/20 or better in the Atlas A group ($OR_{\text{Atlas A}}$) is not inferior to the odds of that in the AOA group at fitting. The following hypothesis testing for odds ratio will be assessed:

$$H_0: OR \leq \Psi_0 \text{ vs. } H_a: OR > \Psi_0,$$

where OR represents the ratio of $OR_{\text{Atlas A}}$ over OR_{AOA} ($OR_{\text{Atlas A}}/OR_{\text{AOA}}$) and Ψ_0 represents a non-inferiority margin (0.5) that reflects 10% difference in distribution between the Atlas A and AOA groups using the reference rate of 89%.

CLUE Score

The overall means of CLUE comfort and handling scores in the Atlas A group will be separately compared to the overall means of that in the AOA group considering all planned visits (fitting and 4 subsequent follow-up visits). The alternative hypothesis is the overall mean CLUE score in the Atlas A group is not inferior to that in the AOA group. The minimum clinically relevant difference (Δ , delta) between the Atlas A and AOA groups is set to -5 which translates into 10% shift in the CLUE score distribution. The following hypothesis testing for overall mean difference will be assessed:

$$H_0: \mu_{\text{Atlas A}} - \mu_{\text{AOA}} \leq \Delta \text{ vs. } H_a: \mu_{\text{Atlas A}} - \mu_{\text{AOA}} > \Delta,$$

where $\mu_{\text{Atlas A}}$ and μ_{AOA} represent overall means in the Atlas A and AOA groups, respectively.

1.5. Sample Size Justification

Sample size was calculated to attain the optimal number of subjects to demonstrate the statistical acceptance of the primary and secondary hypotheses using the historical data from CR5699 and CR5799. The incidence rates (%) of the primary endpoints from the historical data are presented in Table 2 below.

Table 2: Incidence Rate (%) from the Historical Data

| <i>Endpoints</i> | <i>Event</i> | <i>Atlas A Rate (%)</i> | <i>AOA Rate (%)</i> |
|---|--------------|-------------------------|---------------------|
| Monocular Visual Acuity 20/40 or better | Overall | 100 | 100 |
| Monocular Visual Acuity 20/20 or better | Overall | 93.2 | 92.9 |
| Corneal Staining < Grade 3* | Overall | 100 | 100 |
| Acceptable Lens Fit | Fitting | 100 | 100 |
| Absolute Rotation within 10-degree | 15-min | 97 | 96 |
| Stability with Blink within 5-degree | Fitting | 100 | 100 |
| *Corneal staining will be assessed to demonstrate no difference between the Atlas A and AOA lenses whereas the other primary endpoints will be assessed to demonstrate satisfying a minimum threshold (80%) of the Atlas A. | | | |

Primary Endpoints with a 80% Threshold:

The common reference rate of 95% was selected for the sample size calculation as all applicable primary endpoints are binary in nature. Assuming a correlation of 0.8 between eyes, 2000 trials (replicating 2000 trials) were simulated to attain a sample size with a minimum statistical power of 90%.

Primary Endpoints with No Difference:

The incidence reference rate of 0.005% was selected for the sample size calculation for no difference between two study lenses on corneal staining grade 3 or higher using the formula given by Diggle et al. (2002¹) for cluster binary data. The incidence rate of 0.005% was set considering the 5 previous Atlas studies (both sphere and astigmatism) including CR5417, CR5582, CR5726, CR5699 and CR5799. There were no incidences of corneal staining grade 3 or higher among all 5 studies, hence it was deemed that 0.005% is a reasonable incidence rate. The number of observations per subject (cluster) was set to 2 (2 eyes per subject) and a correlation between eyes within a subject was set to 0.3 to attain a sample size with a minimum statistical power of 80%.

Secondary Endpoint:

Sample size calculation for the overall CLUE comfort was also performed considering the effect size of 5 (Atlas A -AOA) to achieve a minimum statistical power of 90%. The 2000 trials were simulated for the repeated measurements from the multivariate normal distribution at a 5% significance level using the following covariance attained from the historical data:

Test:

u11 = 365.99
u21 = 214.84 u22 = 609.18
u31 = 176.06 u32 = 532.54 u33 = 637.19
u41 = 146.71 u42 = 514.08 u43 = 590.60 u44 = 714.34

Control:

u11 = 429.65
u21 = 245.51 u22 = 590.56
u31 = 210.38 u32 = 520.42 u33 = 603.15
u41 = 254.93 u42 = 533.15 u43 = 535.36 u44 = 643.20

Table 3: Sample Size Estimations

| <i>Endpoints</i> | <i>N per Arm</i> | <i>Power (%)</i> | <i>Total N*</i> |
|--|------------------|------------------|-----------------|
| Monocular Visual Acuity 20/40 or better | 90 | > 90 | 207 |
| Corneal Staining < Grade 3 | 116 | > 85 | 270 |
| Acceptable Lens Fit | 90 | > 90 | 207 |
| Absolute Rotation within 10-degree | 90 | > 90 | 207 |
| Stability with Blink within 5-degree | 90 | > 90 | 207 |
| CLUE Comfort | 90 | > 90 | 207 |
| *Total N includes ~15% dropout rate | | | |

Optimal sample size and its corresponding power for each study endpoint are presented in Table 3. It is determined that a total of 270 subjects (135 per arm) will be sufficient to demonstrate statistical acceptance of both primary and secondary hypotheses.

1.6. Randomization and Masking

This study is a randomized, double-masked parallel group design. Each subject will be randomized to wear one of two study lenses during the study following the computer-generated randomization scheme prepared by the JJV biostatistician. The randomization will be stratified by study site and randomly permuted in blocks of 2 to achieve a 1:1 ratio of test and control assignments within each study site. The randomization assignment will be completed at the first visit prior to the first lens fitting.

The following procedures must have completed prior to randomize the subjects:

- Obtained Informed consent,
- Confirmed that the subject meets all the inclusion/exclusion criteria, and
- Collected the subject's history and baseline information.

This is a double masked study where the identity of the study lenses will be masked to both subjects and investigators involved in the data collection. The identity of the study lenses will be masked by over labeling the blister packs with a label containing the study number, lot number, sphere power, expiration date, and the randomization codes of T or D. Only the personnel involved in the over labeling and the statistician generating the randomization scheme will have access to the lens decode information translating the randomization codes into the test and control groups. The medical monitor will also have access to the lens decode information in case breaking the mask is necessary for the urgent medical treatment of a subject.

There is an inherent potential risk for unmasking. However, masking will be maintained as much as is logistically feasible. Under normal circumstances, the mask should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the mask should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may, in an emergency, contact the medical monitor. In the event the mask is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unmasking must be documented in the subject record.

Subjects who have had their treatment assignment unmasked are expected to return for all remaining scheduled evaluations. A replacement subject may be enrolled if a subject discontinues from the study prematurely. The decision to enroll replacement subjects will be made by the joint agreement of the Investigator and Sponsor.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

This is a 5-visit dispensing study. Each of subsequent visits should be scheduled approximately a week (6-9 days) following the preceding visit as shown below.

Table 4: Time and Event Schedule

| <i>Scheduled Visit</i> | <i>Time Event</i> | <i>Time Interval (Day)</i> | <i>Target Time Point (Day)</i> |
|------------------------|---------------------|----------------------------|--------------------------------|
| Visit 1 | Baseline/Dispensing | 0 | 0 |
| Visit 2 | 1-Week Follow-up | 6 to 9 from Visit 1 | 7 days from Visit 1 |
| Visit 3 | 2-Week Follow-up | 6 to 9 from Visit 2 | 7 days from Visit 2 |
| Visit 4 | 3-Week Follow-up | 6 to 9 from Visit 3 | 7 days from Visit 3 |
| Visit 5 | 4-Week Follow-up | 6 to 9 from Visit 4 | 7 days from Visit 4 |

2.2. Pooling Algorithm for Analysis Centers

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

2.3. Data Sets

2.3.1. Efficacy Analysis Set

Efficacy analysis set (a.k.a., Per-Protocol data set) includes all subjects who have successfully completed all required visits without any major protocol deviations that the cohort review committee documents as impacting the assessment of the hypotheses prior to the data hard-lock. Justification of excluding completed subjects due to major protocol deviations will be documented in a *Memo to File* and submitted to the trial master file by clinical operation manager.

The following efficacy secondary endpoints will be analyzed on the efficacy analysis set:

- Monocular distance visual acuity 20/20 or better,
- CLUE Comfort Score, and
- CLUE Handling Score.

2.3.2. Safety Analysis Set

Safety analysis set includes all subjects who are administered the test articles and have at least one observation after lens insertion. All safety endpoints will be summarized on the safety analysis set.

The following safety primary endpoints will be analyzed on the safety analysis set:

- Monocular distance visual acuity 20/40 or better,
- Lens fitting acceptability,
- Absolute rotation,
- Stability with blink, and
- Contact lens related corneal staining.

2.4. Definition of Subgroups

No subgroup analyses are planned in this study.

3. INTERIM ANALYSIS AND DATA MONITORING

3.1. Interim Analysis

There will be no interim analysis.

3.2. Data Monitoring

The study will be monitored in a manner consistent with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). The study monitors will maintain close contact with the Principal Investigator (PI) and the Investigator's designated staff.

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

- **Adverse Event:** An AE is any untoward (unwanted) medical occurrence in a patient or clinical investigation subject administered a test article whether or not caused by the test article or treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of the test article whether or not related to the test article.
- **Protocol Deviation:** An unanticipated instance when the clinical protocol, as approved by Institutional Review Board (IRB), is not followed.
- **Product Quality Complaint (PQC):** Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for clinical trial use. PQC is associated with any investigational product (i.e., product manufactured or supplied specifically for a clinical trial).

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Healthy males and females aged between 18 and 40 years will be enrolled in this study. Enrolled subjects must be habitual soft toric contact lens wearers in both eyes. Approximately 50% of study subjects will be habitual monthly replacement modality toric wearers including Air Optix for Astigmatism and Biofinity Toric.

Demographic characteristics including gender, race, ethnicity and age will be summarized by study lens and overall for all enrolled subjects. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) whereas categorical variables will be summarized using frequency table (number and percentage of each category).

4.2. Disposition Information

Accountability (disposition) of all enrolled subjects will be presented by study lens and overall in each of the following subgroups.

- **Completed:** Randomized subjects who are eligible to participate in the study and have successfully completed all required visits.
- **Discontinued:** Randomized subjects who are prematurely discontinued from the study due to any reasons described in the *Protocol Section 5.1*.

- **Total Dispensed:** Subjects who administered the test article at least once (i.e., lens insertion occurred in at least one eye).
- **Enrolled Not Dispensed:** Subjects who are (i) enrolled in the study (provided informed consent) but failed to satisfy the eligibility criteria (inclusion/exclusion criteria), (ii) randomized but discontinued or drop out prior to administering the test article, or (iii) not randomized to treatment for any reason.
- **Total enrolled:** Subjects who signed the informed consent form (i.e., completed + discontinued + enrolled not dispensed).

Efficacy and Safety data sets are defined in Section 2.3.

4.3. Treatment Compliance

Subjects are advised to wear the study lenses for 8 hours each day as daily wear for approximately thirty days. Subject compliance with wearing the study lenses will be recorded at each follow-up visit via electronic data capture (EDC).

Subject's wear time, comfort wear time and percentage of comfort wear time will be descriptively summarized.

4.4. Protocol Deviations

All protocol deviations will be reviewed during the cohort meeting upon study soft-lock. During the cohort meeting, every protocol deviation will be reviewed and classified as either minor or major deviation by cohort committee. Those subjects who deemed to make a major protocol will be excluded from the efficacy analysis set.

All reported protocol deviations will be listed.

4.5. Prior and Concomitant Medications

All reported prior or/and concurrent medications will be listed.

4.6. Discontinuation

All reasons for discontinuation will be summarized.

5. PRIMARY ANALYSIS

All primary analyses will be conducted on the safety analysis set.

5.1. Analysis Specifications

5.1.1. Level of Significance

All planned primary analyses for this study will be conducted with an overall type I error rate of 5%.

The primary analyses (multiple endpoints) will be performed using the intersection-union principal; all primary hypotheses will be simultaneously evaluated using $\alpha = 0.05$. All primary hypotheses must be met in order to claim the success of the study objectives.

5.1.2. Data Handling Rules

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

5.2. Primary Endpoint(s)

The co-primary endpoints for this study are:

- Monocular distance visual acuity 20/40 or better,
- Contact lens related corneal staining,
- Lens fitting acceptability,
- Absolute rotation
- Stability with blink.

5.2.1. Definition

Monocular Visual Acuity (VA) 20/40 or better

Monocular VA with the study lenses will be assessed using a Snellen distance VA chart at an optical distance of 20 feet throughout the study. Observed monocular VA collected during the planned visits (Visits 1 through 5) will be dichotomized whether VA was '20/40 or better' (refer as 'acceptable VA') or 'worse'. VA of 20/40 with a negative modifier will consider to be worse than 20/40. Each eye/subject will be categorized into two groups such that 'response=1' if an eye had acceptable VA or 'response=0' otherwise.

Lens Fit Acceptance

Lens fit characteristics will be assessed via slit lamp in terms of lens position, movement and tightness. Each lens fit collected at fitting (Visit 1) will be judged as being either 'acceptable' or 'unacceptable' based on the static and dynamic fit characteristic.

Lens Stability with Blink

Rotational stability with blink will be assessed via slit lamp with beam that can be rotated. The stability of the scribe mark rotational position during a series of normal (unforced) blinks will be observed. Observed rotational stability with blink will be dichotomized whether stability was ' ≤ 5 -degree' or 'worse' at fitting (Visit 1).

Absolute Rotation

Lens rotation will be assessed via slit lamp with beam that can be rotated. The rotational error (assume shortest distance) and direction (base towards the nose or based towards temple)] will be calculated. Absolute rotation will be dichotomized such that 'response=1' if absolute rotation was less than equal to 10-degree (refer as 'acceptable rotation') or 'response=0' otherwise upon 15-minute post insertion at fitting (Visit 1).

Contact Lens Related Corneal Staining (CS)

Contact lens related corneal staining will be assessed via slit lamp throughout the study. Corneal staining will be graded using a 5-level scale; 0=no staining, 1=trace, 2=mild, 3=moderate and 4=severe. Observed corneal staining collected during planned and unscheduled visits will be dichotomized whether the corneal staining is 'grade 2 or lower' or 'Grade 3 or higher'.

5.2.2. Analysis Methods

Monocular Visual Acuity (VA) 20/40 or better Analysis

Each eye/subject will be categorized into two groups such that 'response=1' if VA was 20/40 or better (refer as 'acceptable VA') throughout all planned visits or 'response=0' otherwise. The generalized linear mixed model (Liang and Zeger, 1986²), as implemented in the SAS/STAT procedure GLIMMIX⁷, will be

used to assess the overall acceptable VA for each lens type utilizing binomial distribution with logit link function. The model will include lens type as a fixed effect and site, subject and eye nested within subject as random effects. Baseline characteristics such as age and gender may be also included in the model as covariates if appropriate.

The model based proportion of eyes with acceptable VA with its corresponding 95% confidence interval (CI) will be constructed for each lens type from the generalized linear mixed model. Overall acceptable VA will be concluded if the lower limit of the 95% CI is greater than or equal to 0.80 (80%).

Lens Fit Acceptance Analysis

Lens fit acceptance at fitting (Visit 1) will be evaluated by lens type if at least 80% of eyes have acceptable lens fit (response=1) using the generalized linear mixed model (Liang and Zeger, 1986²), as implemented in the SAS/STAT procedure GLIMMIX⁷, with binomial distribution and logit link function. The model will include lens type as a fixed effect and site, subject and eye nested within subject as random effects. Baseline characteristics such as age and gender may be also included in the model as covariates if appropriate.

The model based proportion of eyes with acceptable lens fit with its corresponding 95% CI will be constructed for each lens type from the generalized linear mixed model. Acceptable lens fit will be concluded if the lower limit of the 95% CI is greater than or equal to 0.80 (80%).

Lens Stability with Blink Analysis

Observed rotational stability with blink will be dichotomized such that 'response=1' if stability was less than or equal to 5-degree (refer as 'adequate stability') or 'response=0' otherwise. The dichotomized adequate stability at fitting (Visit 1) will be evaluated by lens type if at least 80% of eyes have adequate stability (response=1). The generalized linear mixed model (Liang and Zeger, 1986²), as implemented in the SAS/STAT procedure GLIMMIX⁷, will be used to assess adequate stability for each lens type separately utilizing binomial distribution with logit link function. The model will include lens type as a fixed effects and site, subject and eye nested within subject as random effects. Baseline characteristics such as age and gender may be also included as covariates in the model if appropriate.

The model based proportion of eyes with adequate stability with its corresponding 95% CI will be constructed for each lens type from the generalized linear mixed model. Adequate stability will be concluded if the lower limit of the 95% CI is greater than or equal to 0.80 (80%).

Absolute Rotation Analysis

Acceptable absolute rotation upon 15-minute post insertion at fitting (Visit 1) will be evaluated by lens type if at least 80% of eyes have acceptable absolute rotation (response=1) using the generalized linear mixed model (Liang and Zeger, 1986²), as implemented in the SAS/STAT procedure GLIMMIX⁷, with binomial distribution and logit link function. The model will include lens type as a fixed effect; site, subject and eye nested within subject will be considered as random effects. Baseline characteristics such as age and gender may be considered as covariates in the model when appropriate. The model based proportion of eyes with acceptable absolute rotation with its corresponding 95% confidence interval (CI) will be constructed for each lens type from the generalized linear mixed model. Acceptable absolute rotation will be concluded if the lower limit of the 95% CI is greater than or equal to 0.80 (80%).

Contact Lens Related Corneal Staining (CS) Analysis

Each eye/subject will be categorized into two groups such that 'response=1' if an eye had acceptable corneal staining (CS) (i.e., CS grade 2 or lower) throughout all planned and unscheduled visits or 'response=0' otherwise. The incidence rate of the Atlas A lens will be compared to the AOA lens using a generalized linear mixed model (Liang and Zeger, 1986²), as implemented in the SAS/STAT procedure GLIMMIX⁷, with binomial distribution and logit link function. The model will include lens type as a

fixed effect and site, subject and eyes nested within subject as random effects. Baseline characteristics such as age and gender may be considered as covariates in the model when appropriate.

The incidence rate of CS for the Atlas A lens will be compared to the AOA lens using the two-sided 95% CI constructed for odds ratios (Atlas A over AOA). No difference between the Atlas A and AOA lenses will be concluded if the 95% CI of the odds ratio contains 1.

In case a full model does not converge for any reasons (likely due to small incidence rate) for any of the primary analyses, a reduced model will be considered.

Additional post-hoc analysis may be conducted if necessary at the discretion of the project leader.

6. SECONDARY ANALYSIS

All secondary analyses will be conducted on the efficacy analysis set.

6.1. Analysis specifications

6.1.1. Level of Significance

The secondary analyses will be performed only if all the primary hypotheses are met using a gate keeping strategy. Adjustment of multiple pairwise-comparisons between Atlas A and AOA across different time will be conducted using a simulated-based method (Edward and Berry, 1987²).

6.1.2. Data Handling Rules

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

6.2. Secondary Endpoints

The secondary endpoints are:

- Monocular distance visual acuity 20/20 or better,
- Subjective CLUE comfort score, and
- Subjective CLUE handling score

6.2.1. Definition

Monocular Visual Acuity (VA) 20/20 or better

Monocular visual acuity (VA) with the study lenses will be assessed using a Snellen distance VA chart at an optical distance of 20 feet throughout the study. Observed monocular VA collected at fitting (Visit 1) will be dichotomized whether VA was '20/20 or better' (refer as 'suitable VA') or 'worse'. VA of 20/20 with a negative modifier will consider to be worse than 20/20. Each eye/subject will be categorized into two groups such that 'response=1' if an eye had suitable VA at fitting or 'response=0' otherwise.

CLUE Score

Subjective CLUE comfort and handling score will be assessed using the Contact Lens User Experience™ (CLUE) questionnaire (Wirth and Houts, 2016⁴). CLUE is a validated patient-reported outcomes (PRO) questionnaire to assess patient-experience attributes of soft contact lenses (comfort, vision, handling, and packaging) in a contact-lens wearing population in the US, ages 18-65. Derived CLUE scores using Item

Response Theory (IRT) follow a normal distribution with a population average score of 60 (SD 20), where higher scores indicate a more favorable/positive response. A 5-point increase in an average CLUE score translates into 10% shift in the distribution of scores for population of soft disposable contact lens wearers.

6.2.2. Analysis Methods

Monocular Visual Acuity (VA) 20/20 or better Analysis

Dichotomized suitable VA at fitting (Visit 1) will be compared between the Atlas A and AOA lenses using a generalized linear mixed model (Liang and Zeger, 1986²), as implemented in the SAS/STAT procedure GLIMMIX⁷, with binomial distribution and logit link function. The model will include lens type as a fixed effect and site, subject and eyes nested within subject as random effects. Baseline characteristics such as age and gender may be considered as covariates in the model when appropriate.

The model based proportion of eyes with suitable VA at fitting will be compared between the Atlas A and AOA lenses using the two-sided 95% CI constructed for odds ratios (Atlas A over AOA). Non-inferiority will be concluded if the lower limit of the two-sided 95% CI of the odds ratio is above 0.5. The odds ratio margin of 0.4 corresponds to a 10% difference in proportion between the Atlas A and AOA lenses assuming a reference rate of 89%.

CLUE Score Analysis:

CLUE scores including comfort, vision, handling and packaging will be analyzed separately using a linear mixed model (Liang and Zeger, 1986²), as implemented in the SAS/STAT procedure GLIMMIX⁷, adjusting for baseline values as a fixed covariate when appropriate. Each model will include the following experimental design factors: lens type, time event (i.e., fitting, 1-, 2-, 3- and 4-week follow-up), and lens type by time event interaction as fixed effects; and site as a random effect when appropriate. Baseline characteristics such as age and gender may be considered as covariates when appropriate.

The covariance between residuals between the same subject at different time events will be selected based on the finite-sample corrected Akaike's information Criterion (Keselman et al. 1998³). The following covariate structures will be considered:

- Homogenous compound symmetry (CS)
- Heterogeneous compound symmetry (CSH)
- Ante-dependence (ANTE(1))
- Unstructured (UN)
- Spatial Power (SP(POW))

For ANTE(1) and SP(POW) covariance structures, site and subject will be included as random effects. For the remaining covariate structures, only site will be included as a random effect. The covariate structure that returns the lowest Akaike Information Criteria Corrected (AICC) will be considered as the structure best fits for the data. Heterogeneous residuals covariance structure (R-side) across the lens types may be considered when appropriate. The log-likelihood ratio test will be used to assess homogeneity between covariance structures across lens types.

The overall CLUE comfort scores across all study visits will be compared between the Atlas A and AOA lenses using the two-sided 95% CI constructed for the LS means differences (Atlas A minus Atlas A) from the repeated measures analysis. The non-inferiority will be concluded if the lower limit of the 95% CI for the LS mean difference is greater than -5. If the lower confidence limit is greater than 0, the statistical superiority will be concluded.

The overall CLUE handling scores across all study visits for the Atlas A lens will be assessed whether subjective handling score is adequate using a margin of 50. The adequate subjective handling will be concluded if the lower limit of the 95% CI for the LS mean is greater than 50.

The Kenward and Roger method (Kenward and Roger, 1997⁴) will be used for the calculation of the denominator degree of freedom for the all above statistical models if applicable. If a spatial power covariance structure is selected, the first order option will be used.

Additional post-hoc analysis may be conducted if necessary at the discretion of the project leader.

7. OTHER PARAMETERS

7.1. Average Wear Time

Subjects' current lens wear time and comfort wear time in hour will be descriptively summarized at each visit by lens type using n, mean, standard deviation, median, minimum and maximum.

7.2. Adverse Events

Adverse events (AEs) will be listed for each eye/subject. The listing will include subjects' demographics information, test article received, AE reported term, seriousness (yes/no), type of AE (ocular/non-ocular), severity, causality, etc. Corneal inflammatory events (CIEs) will be listed separately.

7.3. Reason for Discontinuation

Reason for discontinuation will be listed for each subject. The listing will include subjects' demographics information, test article received, and reason for discontinuation.

8. OTHER SAFETY PARAMETERS

The other safety parameters for this study are:

- Biomicroscopy,
- Corneal Staining,
- Conjunctival Staining,
- Conjunctival Hyperemia, and
- Ocular symptoms.

Safety parameters will be tabulated using frequency distribution tables or/and descriptive statistics as appropriate.

REFERENCES

1. Diggle, P. J., Heagerty, P., Liang, K.-Y., & Zeger, S. L. (2002). *Analysis of Longitudinal Data*. 2nd edition. *Oxford University Press*.
2. Liang, K.Y. & Zeger, S.L. (1986). Longitudinal Data Analysis using Generalized Linear Models, *Biometrika*, 1986(73): 13 -22.
3. Edward, D. G., & Berry, J. J. (1987). The Efficiency of Simulation-Based Multiple Comparison. *Biometrics*, 43, 913-928
4. Wirth, R. J., Edwards, M. C., Henderson, M. C., Henderson, T., Olivares, G., & and Houts, C. R. (2016). Development of the Contact Lens User Experience: CLUE Scales. *Optometry and Vision Science*, 93(8): 801-808.
5. Keselman, H. J., Algina, J., Kowalchuk, R. K., & Wolfinger, R. D. (1998). A comparison of two approaches for selecting covariance structures in the analysis of repeated measurements. *Communications in Statistics-Simulation and Computation*, 27, 591-604.
6. Kenward, M. G., & Roger, J. H. (1997). Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics*, 53, 983-997.
7. SAS Institute Inc., SAS/STAT Version 9.4., Cary, NC, USA: SAS Institute Inc. 2002-2012