Statistical Analysis Plan Title Page

Compound Name: **BL-3100-NBR03 multi-purpose solution**

Protocol Title: **A Safety and Effectiveness Study of a Contact Lens Cleaning and Disinfecting Solution**

Protocol and Version: **Study #914 Original**

Sponsor Legal Registered Address:

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Regulatory Agency Identifier Number(s)

Registry	ID
ClinicalTrials.gov	NCT05565937

Statistical Analysis Plan Version: **V2, 11APR2024**

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Confidential Information

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Version history

Table 1 documents the changes to the SAP. Details regarding protocol changes that resulted in changes to the SAP can be found in the respective protocol amendment.

Table 1 SAP Version History Summary

SAP Version Approval Date	Rationale	Changes to SAP
V1 09JUN2023	Original version	Not Applicable
V2 11APR2024	Corrections	Mapping of unscheduled visits for Trend Analysis Appendix 1, refraction parameter calculations corrections. Updates and clarifications to calculations and text throughout.

Abbreviations/Definitions

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
BSCVA	Best spectacle corrected visual acuity
CDISC	Clinical Data Interchange Standards Consortium
CSR	Clinical study report
D	Diopter
eCRF	Electronic case report form
ICF	Informed consent form
ICH	International Conference on Harmonization
ITT	intent to treat
LLT	Lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
PP	Per-protocol
PT	Preferred term
RTSM	Randomization and trial supply management
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Standard Data Tabulation Model
SOC	System organ class
TEAE	Treatment emergent adverse event
VA	Visual acuity
WHODD	World Health Organization Drug Dictionary

SAP Approval Signature Page

PROTOCOL TITLE	A Safety and Effectiveness Study of a Contact Lens Cleaning and Disinfecting Solution
SAP Version, Date	V2, 11APR2024
SAP AUTHOR	[redacted] Senior Biostatistician EMB Statistical Solutions, LLC
Investigational Product	BL-3100-NBR03 multi-purpose solution
Protocol Number	Study #914
Protocol Version, Date	Original 19JAN2023
Signature Statement	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Reviewers

Approver Signature [redacted]

Biostatistician
Bausch & Lomb

1. Introduction

The purpose of this SAP is to describe the analysis variables and statistical procedures that will be used to analyze and report the results from a study evaluating the safety and efficacy for the treatment of BL-3100-NBR03 multi-purpose solution for contact lens cleaning and disinfecting.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

Some of the analyses detailed here may be more explicit or in some respects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol, and the differences will be presented in the Section 4.10.

Changes to the protocol that impact the design, the data collected, or the statistical methods and that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the SAP, so long as the changes were implemented prior to database lock. Changes in planned analyses that are decided after database lock will be documented in the clinical study report (CSR).

The formats for the tables, listings, and figures (TLFs) described in this SAP (V2) were provided in a companion document to SAP V1. The companion document was not updated for SAP V2. Minor formatting changes to the output of TLFs do not require a SAP amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP and will instead be described in the CSR.

Please see the study protocol for details about the study design, procedures, and schedule of assessments and see the electronic case report form (eCRF) for details about variables collected and their possible values.

1.1. Objectives, Endpoints, and Estimands

Table 2 Objectives, Endpoints and Estimands

Primary		
Objective: The objective of this study is to evaluate the safety and effectiveness of BL-3100-NBR03 multi-purpose solution (Test) compared to renu® Advanced Formula multi-purpose solution (Control) when used by habitual contact lens wearers to clean and disinfect their contact lenses for approximately three months.	**Population:** Subjects who wear soft (hydrophilic) contact lenses which require daily conditioning, cleaning, chemical (not heat) disinfection and storage of soft contact lenses, regardless of gender, age, or ethnicity, and who do not have contraindications for the device.	**Safety Endpoint:** The proportion of eyes with any slit-lamp findings greater than Grade 2 at any follow-up visit. **Clinical Question:** Does BL-3100-NBR03 multi-purpose solution result in a non-inferior proportion of eyes with slit-lamp findings greater than Grade 2 compared to renu® Advanced Formula multi-purpose solution, when used over the course of 3 months in randomized eyes? **Estimand:** The difference in group proportion, between BL-3100-NBR03 and renu®, of [the proportion of eyes with any slit-lamp findings greater than Grade 2 at any follow-up visits], using all dispensed eyes. Missing values will be ignored when determining the presence of slit-lamp findings greater than Grade 2 for each eye and, subsequently, the difference in proportion between groups.
		Efficacy Endpoint (1): Overall comfort (at the eye level) averaged over all scheduled follow-up visits as measured via Lens Performance Rating Scale: Overall Comfort. **Clinical Question:** Does BL-3100-NBR03 multi-purpose solution result in non-inferior average overall comfort compared to renu® Advanced Formula multi-purpose solution, when used over the course of 3 months in randomized eyes? **Estimand:** The difference in group means, between BL-3100-NBR03 and renu®, of [the average (over each follow-up visit) of "overall comfort" for each eye], using all randomized eyes. Missing values will be ignored when computing average overall comfort and, subsequently, the difference in group means.
		Efficacy Endpoint (2): Vision (at the eye level) averaged over all scheduled follow-up visits as measured via Lens Performance Rating Scale: Vision. **Clinical Question:** Does BL-3100-NBR03 multi-purpose solution result in non-inferior average vision compared to renu® Advanced Formula multi-purpose solution, when used over the course of 3 months in randomized eyes?

		Estimand: The difference in group means, between BL-3100-NBR03 and renu®, of [the average (over each follow-up visit) of "vision" for each eye], using all randomized eyes. Missing values will be ignored when computing average vision and, subsequently, the difference in group means.
		Efficacy Endpoint (3): The proportion of eyes with a maximum degree of front surface deposits grade of ≤ 2 at any scheduled follow-up visit. **Clinical Question:** Does BL-3100-NBR03 multi-purpose solution result in a non-inferior proportion of eyes with maximum degree of front surface deposits (grade ≤2) compared to renu® Advanced Formula multi-purpose solution, when used over the course of 3 months in randomized eyes? **Estimand:** The difference in group proportion, between BL-3100-NBR03 and renu®, of [the proportion of eyes with a maximum degree of front surface deposits grade of ≤2 across all scheduled follow-up visits], using all randomized eyes. Missing values will be ignored when determining the maximum grade of front surface deposits for each eye and, subsequently, the difference in proportion between groups.
Secondary		
There are no predefined secondary endpoints		
Supportive Effectiveness		
Proportion of subjects treated with BL-3100-NBR03 agreeing with the consumer survey statements.		
Difference in group proportion, between BL-3100-NBR03 and renu®, of subjects agreeing with the consumer survey statements.		
Sensitivity Analyses: Best/worst case imputation analyses using best/worst imputation for primary endpoints.		
Sensitivity Analyses: Tipping-point analyses for primary endpoints.		
Sensitivity Analyses: Primary efficacy endpoints using only subjects without major protocol deviations (i.e. Per-Protocol analysis).		

1.2. Study Design

The study is designed to examine whether BL-3100-NBR03 multi-purpose solution cleaning and disinfecting solution is non-inferior to renu® Advanced Formula multi- purpose solution in several primary endpoints.

Approximately 340 subjects (680 eyes) will be enrolled in this three-month multicenter, randomized, double-masked, parallel-group, bilateral study at approximately 22 investigative sites in the United States (US). Approximately one-half (50%) of the eligible subjects will be randomized to receive Bausch + Lomb investigational BL-3100-NBR03 multi-purpose solution (Test), and approximately one-half (50%) of the eligible subjects will be randomized to receive renu® Advanced Formula multi-purpose solution (Control). In addition, all subjects will be dispensed three new pairs (including two back-up pairs) of their habitual lenses at the beginning of the study for daily wear, and scheduled replacement lenses at the 1-Month and 2-Month Follow-up Visits.

All subjects will be seen for a Screening/Dispensing Visit, at which the informed consent form (ICF), including the Health Insurance Portability Accountability Act (HIPAA), will be obtained and eligibility will be assessed. If eligible, subjects will be dispensed three new pairs of their habitual lenses and a Study Kit containing a cleaning and disinfecting solution according to the subject's randomly assigned treatment. Subjects may also be dispensed a supply of Bausch + Lomb renu® Contact Lens Moisture Drops to be used on an as needed basis. Subjects must NOT use ANY other cleaning and disinfecting solution or rewetting drops during the study.

Subjects are to wear their study lenses on a daily wear basis and are to use the Test or Control multi-purpose solution and care regimen after removing the lenses each day. Subjects will return their worn lenses to the unmasked designee at each monthly follow-up visit and will return their used and unused study solutions to the unmasked designee at the three-month follow-up visit (or early study termination/suspension visit) for return to the Sponsor.

Eligible subjects will be enrolled into one of five lens groups based on their habitual contact lenses. Subjects will be randomized to receive either the Test or Control multi-purpose solution. The five lens groups will be comprised of habitual wearers of soft lenses based on lens material as indicated in the table below.

Table 3 Lens Groups

Lens Group	Lens Material	Trade Name	Manufacturer
4	Etafilcon A	Acuvue2	Vistakon
5-A	Balafilcon A	PureVision2	Bausch + Lomb
5-C	Samfilcon A	Ultra	Bausch + Lomb
5-Cm	Lotrafilcon B	Air Optix Aqua	Alcon

5-Cr	Senofilcon C	Vita	Vistakon

1.2.1. Masking/Unmasking

Study solutions will be provided in sealed opaque white boxes with Study Kit numbers preprinted on them.

This is a double-masked study. The Investigator and Sponsor or their representatives involved in the conduct of the study will be masked to the study cleaning and disinfecting solutions. These procedures are intended to reduce or eliminate bias that might impact study outcomes and their interpretation.

The randomization schedule will be created by an unmasked statistician not otherwise involved in the study and uploaded into the RTSM system. Personnel involved with any repackaging/ relabeling of clinical trial material will also be unmasked. A Clinical Monitor will become unmasked during product reconciliation, at the conclusion of each site's participation in the study and prior to locking the database. Unmasked designees at the site will manage dispensing and return of study solutions, study contact lenses and related supplies.

Study solutions will be provided in sealed opaque white boxes with Study Kit numbers preprinted on them. Subjects are not to show or discuss the study solution appearance with the Investigator or site staff unless instructed to do so. Subjects may discuss any questions they have with the unmasked designee at the site.

In the event that unmasking of a subject's randomly assigned treatment is required, the Investigator (or other designee) is required to contact the Medical Monitor to request permission to unmask. The Medical Monitor will contact the Sponsor designee and obtain approval to grant permission to unmask. Upon receipt of authorization from the Sponsor designee, the Medical Monitor will advise the Investigator (or other qualified designee) to log into the RTSM system and unmask the subject. If the Medical Monitor cannot be contacted, the Investigator (or other qualified designee) should then contact the Sponsor designee who can authorize the unmasking of a subject. In the event that the Medical Monitor or Sponsor designee cannot be contacted, and the Investigator (or other qualified designee) deems the unmasking emergent, the Investigator may log into the RTSM system without authorization and unmask the subject. Whether unmasking occurs inadvertently or intentionally, the Investigator must notify the Medical Monitor or Sponsor designee as soon as possible after unmasking. In addition, the Investigator must record the date, time, and reason for unmasking the study treatment in the source documentation.

1.2.2. Randomization

An unmasked statistician who is not otherwise involved in the trial will create the randomization schedule.

Each subject will be randomized to one of the treatment arms in a 1:1 ratio (Test to Control). Randomization will be managed using a RTSM system. The randomization will be stratified by lens group and investigational site.

Efforts will be made to enroll subjects in at least three of the lens strata within each site to minimize confounding between site and lens group. While the target enrollment for each lens group is approximately 68 subjects, some lens strata may be difficult to enroll.

2. Statistical Hypotheses and Testing

2.1. Statistical Hypotheses

The noninferiority margins that follow are commonly used values in the industry for the corresponding endpoints. The study will be statistically successful if the Test lens is statistically successful in all primary endpoints.

2.1.1. Overall Comfort Averaged Over All Follow-up Visits

The null hypothesis (H_0) is that the difference in mean overall comfort (Test group mean $[\mu_T]$ minus Control group mean $[\mu_C]$) is less than or equal to negative five points. The alternative hypothesis (H_1) is that the difference is greater than negative five points.

$$H_0: \mu_T - \mu_C \leq -5$$
$$H_1: \mu_T - \mu_C > -5$$

2.1.2. Vision Averaged Over All Follow-up Visits

The null hypothesis (H_0) is that the difference in mean vision (Test group mean $[\mu_T]$ minus Control group mean $[\mu_C]$) is less than or equal to negative five points. The alternative hypothesis (H_1) is that the difference is greater than negative five points.

$$H_0: \mu_T - \mu_C \leq -5$$
$$H_1: \mu_T - \mu_C > -5$$

2.1.3. Front Surface Deposits at All Follow-up Visits

The null hypothesis (H_0) is that the difference in proportion of eyes with maximum front surface deposits grade of ≤ 2 at all Follow-up Visits (Test group proportion $[\pi_T]$ minus Control group proportion $[\pi_C]$) is less than or equal to -0.1 (-10%). The alternative hypothesis (H_1) is that the difference is greater than -0.1 (10%).

$$H_0: \pi_T - \pi_C \leq -0.1$$
$$H_1: \pi_T - \pi_C > -0.1$$

2.1.4. Slit-Lamp Findings Greater than Grade 2

The null hypothesis (H_0) is that the difference in proportion of eyes with slit-lamp findings greater than Grade 2 at any follow-up visit (Test group proportion $[\pi_T]$ minus Control group proportion $[\pi_C]$) is greater than or equal to 0.05 (5%). The alternative hypothesis (H_1) is that the difference is less than 0.05 (5%).

$$H_0: \pi_T - \pi_C \geq 0.05$$
$$H_1: \pi_T - \pi_C < 0.05$$

2.1.5. Proportion of Test Group Respondents Agreeing

For each Subject Assessment statement, the null hypothesis (H_0) is that the proportion of respondents in the Test group agreeing with the statement (π_T) is less than or equal to 0.5. The alternative hypothesis (H_1) is that the proportion agreeing is greater than 0.5.

$$H_0: \pi_T \leq 0.5$$

$$H_1: \pi_T > 0.5$$

2.1.6. Comparison Between Groups of the Proportion of Respondents Agreeing

For each Subject Assessment statement, the null hypothesis (H_0) is that the proportion of respondents in the Test group agreeing with the statement (π_T) is less than or equal to the proportion of respondents in the Control group π_C). The alternative hypothesis (H_1) is that the proportion agreeing in the Test group is greater than the proportion agreeing in the Control group.

$$H_0: \pi_T \leq \pi_C$$

$$H_1: \pi_T > \pi_C$$

2.2. Sample Size Determination

Estimates of standard deviations and proportions were obtained from Bausch + Lomb Study #872.

The sample size calculations assume that the unit of analysis will be the eye and that the outcomes from each subject's eyes will be independent.

Sample size calculations were completed using nQuery software, Version 9.

2.2.1. Overall Comfort

When the sample size in each group is 300 eyes (150 subjects), a two-group one-sided 0.025 significance level t-test will have 99% power to reject the null hypothesis that the Test group is not non-inferior to the Control group (the difference in means, $\mu_T - \mu_C$, is -5 or farther from zero in the same direction) in favor of the alternative hypothesis that the Test group is non- inferior, assuming that the expected difference in means is 0 and the common standard deviation is 13.264.

2.2.2. Vision

When the sample size in each group is 300 eyes (150 subjects), a two-group one-sided 0.025 significance level t-test will have 99% power to reject the null hypothesis that the Test group is not non-inferior to the Control group (the difference in means, $\mu_T - \mu_C$ is -5 or farther from zero in the same direction) in favor of the alternative hypothesis that the Test group is non-inferior, assuming that the expected difference in means is 0 and the common standard deviation is 11.7.

2.2.3. Front Surface Deposits

With 300 eyes (150 subjects) in each group, the observed one-sided 97.5% confidence interval will be expected to exceed -0.1 with 99% power when the Control proportion, π_C, is 0.942 and

the Test expected proportion, π_T, is 0.942; results are based on 100,000 simulations using the Newcombe-Wilson score method to construct the confidence interval.

2.2.4. Slit-Lamp Findings Greater than Grade 2

With 300 eyes (150 subjects) in each group, the observed one-sided 97.5% confidence interval will be expected to be less than 0.05 with 99% power when the Control proportion, π_C, is 0.008 and the Test expected proportion, π_T, is 0.008; results are based on 100,000 simulations using the Newcombe-Wilson score method to construct the confidence interval.

2.2.5. Lens Groups

For each lens group, at least approximately 30 test group subjects will complete the study. For a sample size of 30, the probability of observing at least one complication will be at least 95% when the true complication rate is 10% or greater.

2.2.6. Enrollment Targets

Approximately 300 subjects (150 in each treatment group) will complete the trial. Allowing for up to 10% losses and for equal enrollment across sites, the enrollment target will be approximately 340 subjects (680 eyes).

To allow for approximately 30 completed test group subjects per lens group, each lens group will enroll approximately 34 test group subjects.

2.2.7. Overall Power

If the four primary endpoints are independent, then the overall power of the study is 99% x 99% x 99% x 99% = 96%.

2.3. Multiplicity Adjustment

The overall Type I error will be controlled by requiring the four co-primary endpoints to all be statistically significant for overall success to be achieved. Failure of any one of the primary endpoints will invalidate the statistical significance of the primary objective as well as the consumer survey statements.

If the primary endpoints are met, then statistical testing of the supportive effectiveness endpoints concerning the consumer survey statements will proceed in two hierarchical families with Holm multiplicity adjustments applied within each family.

2.4. Interim Analyses

There will be no interim analysis of efficacy.

3. Study Populations

For the purposes of analysis, the following analysis sets are defined. For eye level analyses, a subject being included in a study population means both of their eyes will be included in the analysis.

Table 4 Study Populations

Subject Study Population	Description
Intent-to-Treat (ITT) Population	The ITT Population will consist of all randomized subjects for subject level summaries and, for eye level summaries, both of their eyes. Subjects will be included in ITT Population summaries according to the treatment group to which they were randomly assigned.
Per Protocol (PP) Population	The PP Population will consist of all ITT Population subjects without important (major) protocol deviations for subject level summaries and, for eye level summaries, both of their eyes. Subjects will be included in PP Population summaries according to the treatment group to which they were randomly assigned. The membership of the PP population will be determined prior to unmasking.
Safety Population	The Safety Population will consist of all dispensed subjects and, for eye level summaries, both of their eyes. Subjects will be included in Safety Population summaries according to the treatment that they received. If a subject receives more than one treatment and one of those treatments is the Test solution, then the subject will be included in Safety Population summaries under the Test treatment group.

The Safety Population is used to analyze the endpoints and assessments related to safety. The ITT Population is used to analyze endpoints related to the primary efficacy objectives and all other non-safety summaries (unless noted otherwise). The PP Population is used for a sensitivity analysis of the primary efficacy endpoints.

4. Statistical Analyses

4.1. General Considerations

EMB Statistical Solutions, LLC will generate the statistical analyses, including the associated datasets, detailed in this SAP. Programming for the creation of the datasets and for performing the statistical analyses will be performed using SAS® software, Version 9.4 or later, unless otherwise specified. Programs will be validated as stated in the Quality Control plan prior to finalization. In addition, all program outputs will be provided as portable document format (PDF) files and will be independently reviewed by a statistician. Upon completion of validation and quality review procedures, all programs and outputs will be retained.

Model assumptions will be checked. If model assumptions are sufficiently violated, then transformations or nonparametric methods of analysis may be used if warranted. Whenever alternative methods of analysis are implemented, the description of the new method along with the rationale for its use will be documented in the CSR. As is customary for contact lens solution trials, eyes will be treated as independent sampling units in eye level analyses unless otherwise noted.

Clinical Data Interchange Standards Consortium (CDISC) standards will be followed to facilitate potential electronic submission. All eCRF data and any externally provided data, such as laboratory data, will be retained in standard data tabulation model (SDTM) datasets. Plus, all data required for the planned analyses, including derived variables, will be provided in analysis data model (ADaM) data sets. The SDTM and ADaM datasets will be provided as SAS® transport files. Data listings will be provided for all relevant collected eCRF and derived data. All Data listings supplied as part of the CSR will be detailed in the relevant sections of this SAP. Each listing be sorted by intervention (first Test, then Control), study center number, subject number, assessment date and/or time point, if applicable.

4.1.1. Common Statistical Methods and Data Presentations

Unless otherwise specified, safety analyses will be based on the Safety Population and efficacy analyses will be based on the ITT Population or the PP Population (sensitivity analyses of primary efficacy analyses only). Other non-safety analyses (i.e. demographic information) will use the ITT Population (unless noted otherwise). Summaries will include results for each intervention separately. Some summaries will also include results for all subjects regardless of intervention (i.e. demographics and baseline characteristics).

All statistical tests will be 1-sided with a nominal alpha of 0.025 (2.5%). Endpoints relating to the Subject Assessment Questionnaire will include multiplicity adjustment of the p-value via a hierarchical two-family Holm procedure: type 1 error will remain at 0.025. Otherwise, there will be no adjustment for multiplicity.

The respective sections of this SAP will detail the statistical analyses, including use of the stratification variables (consisting of (1) lens group and (2) investigational site).

Categorical data will be presented using the total counts for each category and corresponding percentages. The denominator for each percentage will be the number of subjects or eyes with non-missing data unless otherwise indicated. Presentation will be of the form XXX (XX.X %), where the percentage is reported to one decimal place in parentheses. In the case of a frequency

of zero, the frequency and percentage will be presented as 0 rather than 0 (0%). Any single-arm confidence intervals on the proportion will be performed by exact methods, unless stated otherwise.

Summaries for continuous variables will include the number of subjects (or eyes) in the analysis, mean, standard deviation, median, minimum, and maximum. All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

Date variables will be formatted as DDMMMYYYY for presentation.

4.1.2. Missing Data, and Data Errors

For non-Safety Population analyses, subjects who receive a study intervention other than the one to which they were randomized will be presented according to their randomized intervention. Safety analyses will use the intervention actually dispensed: if a subject is ever given Test (even if they were initially dispensed Control), they will be treated as actually receiving Test for safety analyses. Data listings will clearly denote whether randomized or actual intervention is being used. These subjects will be noted in the CSR. Likewise, any other data errors identified in the final database will simply be noted in the CSR so long as the error does not impact the findings of the study.

The effect of missing data on the primary effectiveness endpoint analyses will be explored by considering best- and worst-case imputation scenarios and tipping point analysis with the ITT Set, which will be further described in this SAP.

Otherwise only observed data will be used for the study objective. All data summaries will identify the number of subjects (or eyes) with data, so the number of subjects (or eyes) with missing data for each variable can be deduced from the data summaries.

Handling of other types of missing data, e.g., missing attributes of an adverse event (AE), like start date or relatedness, will be addressed in the respective sections of this SAP.

4.1.3. Coding of Concomitant Medications and Adverse Events

Adverse events (AE) and medical/ocular history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™), and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD). The versions of the dictionaries used for reporting are specified in the Data Management Plan (DMP) and will be reported in the CSR.

4.1.4. Definition of Study Time Points

Visits will consist of the screening/dispensing visit, several follow-up visits, and the Exit visit. There is also the possibility for unscheduled visits. The following definitions will be used for classifying visits:

- Baseline (Day 1) will be defined as the screening/dispensing visit.
- Scheduled follow-up visits will include any of the following visits:
    - 2-Week Follow-up Visit
    - 1-Month Follow-up Visit

- 2-Month Follow-up Visit
- 3-Month Follow-up Visit

Any unscheduled visit (which may include the exit visit) which occurs after baseline will be considered a follow-up visit (but not a scheduled follow-up visit) for all analyses. For example, if a slit-lamp finding greater than Grade 2 occurs during an unscheduled visit after baseline, it will be included in the analyses for the primary safety endpoint.

4.2. Subject Disposition(s)

Study disposition of all subjects who sign the informed consent will be summarized. The summary will include:

- The overall number of subjects who sign informed consent (i.e., subjects screened).
- The following will be summarized for each intervention separately as well as overall.:
  - Subjects randomized.
  - Subjects dispensed.
  - Subjects who completed the 3-Month Follow-up Visit.
  - Subjects who discontinued the study.
  - Subjects assigned to each Study Population (ITT, PP, Safety).

A separate summary of eye accountability, including eyes enrolled but not dispensed, eyes completing each visit (active lens wearers), and discontinuation (with reasons), will be provided for the ITT Population, by treatment and overall.

Subject study disposition information will also be listed.

4.2.1. Protocol Deviations

In the event a protocol deviation occurs, the date of and reason for deviations must be documented in all cases. Significant or major protocol deviations impacting the rights or safety of the subject or the integrity of the study must be reported by the Investigator to the IRB/EC and Medical Monitor immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB/EC. Unless the protocol deviations put the subject at risk or the subject's condition requires that they be discontinued from the study, subjects may continue to participate until the end of the study.

Major protocol deviations will be summarized by subject. All protocol deviations will be provided in a corresponding listing.

4.3. Baseline Characteristics and Subject History

Demographics and baseline characteristics will be summarized descriptively by intervention and overall, for the ITT, PP, and Safety Populations. If the study populations are equivalent, then the PP and Safety Population summaries will not be produced. All relevant data will also be produced in a listing.

4.3.1. Demographics

Demographic variables collected during Day 1, including age (years), sex, childbearing potential, race, and ethnicity, will be summarized. Age will be based on the age of the subject on the date the informed consent is signed, and also summarized categorically by decade (<= 20, >20 <=30, >30 <=40, etc.).

4.3.2. Baseline Lens and Lens Care History

4.3.2.1. Subject Level Summary

A summary will be provided which includes the following baseline information from Day 1:

- Average Daily Wear Time (hours/day).
- Average Hours of Comfortable Wear (hours/day).
- Lens Care System Routinely Used.

4.3.2.2. Eye Level Summary

A summary will be provided which includes the following baseline information from Day 1:

- Current Lens Brand.
- Habitual Lens Power.
    - Sphere (D).
    - Base Curve (mm).
- Subject Wearing Lens at Screening (yes/no) and Time Worn (hours).

A separate summary of baseline refraction (without lenses, in minus cylinder notation) will be provided, and will include: sphere, cylinder, axis, and spherical equivalent.

4.4. Study Intervention and Concomitant Medications

4.4.1. Extent of Exposure

As is customary for contact lens solution trials, treatment exposure will not be summarized.

4.4.2. Treatment Compliance

As is customary for contact lens solution trials, treatment compliance will not be summarized.

4.4.3. Concomitant Medications

All medications for conditions taken within 30 days of signing the informed consent and any ongoing medication(s) taken during the study/medical treatment given for the treatment of an adverse event (AE) during the study should be recorded.

For reporting purposes, concomitant medications will be defined as medications taken on or after the Day 1. This includes all medications initially taken prior to Day 1 but with a stop date that is either missing or after Day 1. Those medications where the stop date is documented as prior to Day 1 will be classified as prior medications. The prior medications will be in the study database but will not be included in any summary reports nor listed.

When only a missing or partial date for a medication is available, the following rule will be applied for classifying the medication as concomitant or prior and for deriving duration, if necessary:

- For the start date:
    - If year, month, and day are missing then use the minimum of the subject's first visit date or the consent date.
    - If year is present and month is missing, then use January 1.
    - If only day is missing, impute the first day of the month.
- For the end date:
    - If year, month, and day are missing then use the subject's last visit date.
    - If year is present and month is missing, then use December 31.
    - If only day is missing, then use the last day of the month.
    - Do not expand the record past the subject's last visit.
- The original missing or partial date, the imputed complete date, and the indicator variable that indicates which dates were imputed will be retained in the database.

Concomitant medications will be reported by Anatomical Therapeutic Chemical classification system Level 2 (main therapeutic group) and preferred drug name (often the generic drug name) from the WHODD. The report of all concomitant medications taken during the study will be provided as listings only.

4.4.4. Study Lens Dispensation

The number and proportion of subjects with lenses dispensed at each visit will be summarized, along with type of lens dispensed at each visit. A separate summary will be provided that summarizes the lens power (i.e sphere and base curve) of the dispensed lenses by visit at the eye level.

4.4.5. Lens Replacement

The number and proportion of eyes with any lenses replaced will be summarized for each treatment group individually by subjects who (1) completed the study, (2) discontinued the study, and (3) either completed or discontinued the study (i.e., overall). This summary will include a categorical summary counting the number of replacement lenses needed for each eye. Additionally, the primary reason and type of lens dispensed as replacement will be reported by count and percentage (using the total number of lenses replaced as the denominator). Finally, this summary will include the lens power across all replaced lenses.

4.5. Primary Estimand Analyses

The primary objective of the study will depend on successfully demonstrating non-inferiority of Test vs. Control in four different primary estimands, one of which is safety-related and the other three of which are efficacy-related.

4.5.1. Definition of Endpoints

The safety-related endpoint is as follows:

- The proportion of eyes with any slit-lamp findings greater than Grade 2 over all follow-up visits (scheduled and unscheduled).
    - At each follow-up visit, graded slit-lamp findings will be assessed for each eye using Grades 0 through 4. Using only the non-missing observations from all follow-up visits, each eye will be classified with respect to findings greater than Grade 2 at any visit (Absent, Present).

The efficacy-related endpoints are as follows:

- Overall comfort averaged over all scheduled follow-up visits.
    - At each follow-up visit, overall comfort will be assessed for each eye on a scale from 0 to 100, with 100 denoting the most favorable response. For each eye, mean overall comfort over all follow-up visits will be computed as the average of the non-missing values over all scheduled follow-up visits
- Vision averaged over all scheduled follow-up visits.
    - At each follow-up visit, vision will be assessed for each eye on a scale from 0 to 100, with 100 denoting the most favorable response. For each eye, mean vision over all follow-up visits will be computed as the average of the non-missing values over all scheduled follow-up visits.
- The proportion of eyes with a maximum degree of front surface deposits grade of ≤ 2 over all scheduled follow-up visits.
    - At each follow-up visit, the degree of front surface deposits will be graded for each eye as 0, 1, 2, 3, or 4. Using only the non-missing observations from scheduled follow-up visits without imputation, each eye will be classified with respect to the maximum grade of front surface deposits (≤ 2, > 2) observed over all follow-up visits.

4.5.2. Main Analytical Approach

All contrasts and differences will be calculated as Test – Control. All observations will be treated as independent (e.g. each eye and/or each subject).

4.5.2.1. Graded Slit-Lamp Findings > Grade 2

Greater than Grade 2 findings (Absent, Present) overall all follow-up visits will be summarized at the eye level by treatment using categorical summary statistics for the Safety Population. A one-sided upper 97.5% confidence limit around the difference in "Present" proportions between the Test and Control treatment groups will be constructed using the Newcombe-Wilson score method.

If the upper confidence limit is less than 5.0% or if no findings greater than Grade 2 are observed in either treatment group, then the null hypothesis that the Test solution is not noninferior will be rejected, and the Test solution will be statistically successful in this outcome.

4.5.2.2. Overall Comfort

Mean overall comfort over all follow-up visits will be summarized at the eye level by treatment using continuous summary statistics for the ITT Population. A one-sided lower 97.5% confidence limit around the difference in means between the Test and Control treatment groups, computed using an analysis of variance model including the fixed factors of treatment, site, and lens group will be displayed.

If the lower confidence limit is greater than -5.0, then the null hypothesis that the test solution is not noninferior will be rejected, and the test solution will be statistically successful in this outcome.

4.5.2.3. Vision

Vision will be analyzed using the methods described above for overall comfort.

4.5.2.4. Front Surface Deposits

Maximum Front Surface Deposits Over All Follow-up Visits (≤ 2, > 2) will be summarized at the eye level by treatment using categorical summary statistics for the ITT Population in a table. A one-sided lower 97.5% confidence limit around the difference in "≤ 2" proportions between the Test and Control treatment groups will be constructed using the Newcombe-Wilson score method.

If the lower confidence limit is greater than -10.0% or if no deposits with grade greater than 2 are observed in either treatment group, then the null hypothesis that the Test solution is not noninferior will be rejected, and the Test solution will be statistically successful in this outcome.

4.5.3. Sensitivity Analyses

The four primary endpoints (>Grade 2 slit-lamp findings, overall comfort, vision, and front surface deposits) will each have the following sensitivity analyses performed:

- **PP Analysis:** the original analyses will be repeated using the PP Population (efficacy endpoints only: overall comfort, vision, and front surface deposits).
- **Best/Worst-Case Imputation Analysis:** each eye with missing values at any scheduled follow-up visit will have their missing values imputed and analyzed twice (analyzed repeating the original analysis using the ITT Population), once using the best- and once using the worst-case scenarios. Following Yan et al. (2009), the worst-case imputation imputes the worst response observed among the test group for the missing responses in the test group, and imputes the best response observed in the control group for the missing responses in control group. The best-case imputation is the reverse of this: impute the best response observed among the test group for the missing responses in the test group, and impute the worst response observed in the control group for the missing responses in control group.

  For slit-lamp findings, the best response is "Absent" (i.e. no findings >Grade 2), and worst is "Present". For overall comfort / vision, the best response is the equivalent to the largest response, and worst is equivalent to the smallest response (scale of 0-100). For

frontal surface deposits, the best response is no grade greater than 2, while the worst is a grade of 2 or greater.

- **Tipping-point Analysis:** If any observed-cases primary efficacy analysis conclusion is different than either the best-case or worst-case imputation conclusion (i.e. the observed-cases primary efficacy analysis concludes non-inferiority, but the worst-case imputation fails to conclude non-inferiority), then an additional tipping-point analysis will be performed for that endpoint using the ITT Population.

  The tipping-point analysis will follow the spirit of the algorithms for continuous and binary data, as appropriate, as described in Yan et al. (2009).

  Continuous outcomes (overall comfort and vision): The tipping point analysis will iteratively (1) impute all missing values in the dataset and then (2) perform the primary analysis (e.g. determine the non-inferiority of test vs. control via an analysis of variance model including the fixed factors of treatment, site, and lens group) on the imputed dataset. Iterations continue until the outcome of the analysis using the imputed dataset results in the opposite conclusion as observed in the observed cases primary analysis.

  For example, an observed cases primary analysis that results in the rejection of non-inferiority will iteratively impute better and better scores within the Control group (and worse and worse scores within the Test group), until non-inferiority fails to be rejected.

  The algorithm is as follows. For the first iteration: if an eye is missing all scheduled follow-up visits, then their endpoint (i.e. the average over all visits) will be imputed using the observed group (i.e. Test or Control) mean. Otherwise, all visit-specific missing values for the given eye will be imputed using the observed eye-level mean (meaning the average over all observed visits for that eye). This will create the first iteration of the imputed dataset. The primary analysis will then be run on this imputed dataset. If this analysis contradicts the observed cases analysis, then the tipping point has been found, and the imputed dataset will be called the tipping point dataset, and the tipping point analysis is completed.

  Otherwise, iterate as follows: for each group, imputed values will be perturbed by 0.005 as either a worsening (i.e. -0.005) or an improvement (i.e. +0.005), depending on the direction of the tipping point, and the primary analysis will be performed on this new imputed dataset. If this analysis contradicts the observed cases analysis, then the tipping point has been found, the imputed dataset will be declared the tipping point dataset, and the tipping point analysis is completed. Otherwise, continue to perturbate the imputed values by increments 0.005 until the tipping point is reached.

  The tipping point dataset's group means, and the estimated difference in group means, will be reported.

Binary outcome (proportion of eyes with any slit-lamp findings >Grade 2 and proportion of eyes with a maximum degree of front surface deposits grade of ≤ 2 at any scheduled follow-up visit.): All missing values will be imputed as some combination of either successes or failures, across all possible combinations. Combinations that result in a tipping point (i.e., a result contrary to what was determined by the primary analysis) will be flagged as such, and displayed as a plot showing the tipping points.

4.6. Secondary Endpoint Analysis

There are no predefined secondary endpoints.

4.7. Supportive Effectiveness Analysis

4.7.1. Definition of Endpoints

Subject Assessment Questionnaire: The supportive effectiveness endpoints are based on each question of the Subject Assessment Questionnaire. At the Exit visit, subjects will report their level of agreement with each of a series of twelve statements in the Subject Assessment Questionnaire. Responses will be on a scale of one (strongly disagree) through six (strongly agree). These values will be dichotomized for analysis, with responses of one through three being mapped to the category of "Disagree" and responses of four through six being mapped to "Agree."

4.7.2. Analytical Approach

For each statement, the proportion of subjects who "Agree" with the statement will be determined for Test and Control. Statistical testing will proceed in two hierarchical families of twelve statistical tests each (one test per statement), with the null hypotheses of the first family eligible for rejection if all the primary endpoints are met.

- The first family will employ a one-sided exact binomial test to compare the proportion of respondents in the Test group agreeing with each statement to 0.5.
- The second family will employ a one-sided chi-square test to compare the proportion of respondents agreeing with each statement between the treatment groups.

Within each family of hypothesis tests, the *P*-values will be adjusted for multiplicity using the Holm method; specifically, the raw (i.e. unadjusted) one-sided *P*-values will be adjusted using SAS PROC MULTTEST with the Holm option. Adjusted one-sided *P*-values less than 0.025 will show statistical significance. The second family will only be analyzed for significance if the entirety of the first family is statistically significant. This gatekeeping strategy will preserve the overall type I error rate of 0.025 across both families.

The responses to each statement will be summarized categorically by treatment group in a table for the ITT Set. The adjusted *P*-values from the statistical tests will also be displayed along with an indicator of statistical significance. If the statistical tests in a family are not eligible for rejection due to hierarchy, then the adjusted *P*-values for that family will not be displayed.

4.8. Other Safety Analyses

4.8.1. Adverse Events

AEs will be collected from the day the subject gives informed consent until the subject withdraws (or completes) the study. All AEs will be followed until the event resolves or stabilizes (which may result in follow-up continuing after the subject has left the study). Investigators will assess whether each AE is related to study device (study solution) and/or rewetting drops using the categories not related or related, as well as the severity of each AE -- using the categories mild, moderate, severe.

Unless specified otherwise summaries of AEs will be presented in two ways, (1) counts (percentages) of subjects using the Safety Population, including all ocular and non-ocular AEs and (2) counts (percentages) of eyes using the Safety Population, including only ocular AE. The number of events will be reported as appropriate.

Summaries will be based on the coded system organ class (SOC) and preferred term (PT) using the latest MedDRA dictionary. The summaries will display the SOC in alphabetical order, while PTs within the SOC will be presented in order of overall decreasing frequency of occurrence in the Test arm. A subject/eye with multiple AEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for the different PTs within that SOC. A subject/eye with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT.

A summary overview of AEs will be provided that gives the number of subjects/eyes with

- Any AE
- Any Treatment-Emergent AE (TEAE)
- Any Related (Study Solution or Rewetting Drops) TEAE
    - Any Related (Study Solution) TEAE
    - Any Related (Rewetting Drops) TEAE
- Any Severe TEAE

- Any Serious TEAE
- Any Related (Study Solution or Rewetting Drops) Serious TEAE
    - Any Related (Study Solution) Serious TEAE
    - Any Related (Rewetting Drops) Serious TEAE

- Any Non-Serious AE occurring in >=1%, >=2%, >=3%, >=4%, >=5% subjects/eyes

- Any Significant Non-Serious TEAE
- Any Non-Significant Non-Serious TEAE

- Any Adverse Device Effect
- Any Severe Adverse Device Effect
- Any Unanticipated Serious Adverse Device Effect
    - Any Severe Unanticipated Serious Adverse Device Effect

- Any Anticipated Serious Adverse Device Effect
    - Any Severe Anticipated Serious Adverse Device Effect

All information pertaining to AEs noted during the study will be listed by subject/eye, detailing verbatim given the Investigator, PT, SOC, start date, stop date, severity, action taken, and device relatedness. The AE onset will also be shown relative (in number of days) to the day of initial use of the randomized study device.

No statistical testing will be performed for comparisons of AEs.

4.8.1.1. Treatment Emergent Adverse Events

Those AEs that emerge or worsen on or after Day 1, i.e., treatment emergent adverse events (TEAEs), will be the primary type of AEs reported in the CSR. Determination whether an AE emerged or worsened will be based on the coded lower-level term (LLT) from MedDRA.

For AEs with incomplete start or stop dates, the following rules will be used to impute start and/or stop dates for the sole purpose of determining if an AE is treatment emergent. Both the recorded partial dates and the associated imputed dates will be saved in the database.

- For partial stop dates, the latest possible date per the provided information will be used as the imputed AE stop date subject to the provision that the imputed AE stop date is not later than the subject's date of study completion or withdrawal.
- For partial start dates:
    - If the complete AE stop date, even if imputed, is prior to the date of Day 1, the imputed AE start date will be the complete AE stop date, and the AE is not treatment emergent.
    - Else if the month and year of AE onset/worsening are provided but day is missing, then
        - If the month and year match the month and year of Day 1, then the date when study intervention is first administered will be the imputed AE start date, and the AE will be considered treatment emergent.
        - Otherwise, the first day of the month provided will be the imputed AE start date, and treatment emergent status will be assessed relative to the date of Day 1.
    - Else if the year of AE onset is provided, but the month and day are missing
        - If the year matches the year of Day 1, then the date of Day 1 will be the imputed AE start date, and the event will be classified as treatment emergent.
        - Otherwise, January 1st for the provided year will be the imputed AE start date, and treatment emergent status will be assessed relative to the date of Day 1.
    - If the AE start date is completely missing, then the date of Day 1 will be the imputed AE start date., and the event will be classified as treatment emergent.

Events with missing relationship to study device will be considered related for statistical summaries, and events with unrecorded severity will be considered severe for statistical summaries. Any preferred terms with a missing relationship or severity will be described in the table footnotes.

4.8.1.2. Treatment-Related TEAE

All AEs will be determined as either related or not related:

Related: There is at least a reasonable possibility that the AE is related to the study device (study solution) and/or rewetting drops. Reasonable possibility means that there is evidence to suggest a causal relationship or association between the study device and/or rewetting drops and the AE.

Not related: There is little or no reasonable possibility that the AE is related to the study device (study solution) and/or rewetting drops. This assessment implies that the AE has no evidence to suggest either a causal relationship or association to the study device and/or rewetting drops and a more likely or certain alternative etiology exists.

A summary of related TEAEs will be provided by relationship to (1) study device, (2) rewetting drops, or (3) both study device and rewetting drops.

4.8.1.3. Serious Treatment-Emergent Adverse Events

An SAE is an AE that (related or not related to the investigational test articles, comparator products or study procedures):

- Led to death
- Led to serious deterioration in the health of the subject, that resulted in:
    - A life-threatening illness or injury; or
    - A permanent impairment of a body structure or a body function (e.g., blindness); or
    - Inpatient or prolonged hospitalization; or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

Serious adverse events may include but are not limited to any hazardous, sight-threatening conditions occurring after exposure to the investigational test article or control product including, but not limited to, the following:

- A presumed infectious ulcer (defined as a progressive erosion of the corneal tissue). For the purposes of reporting, this includes:
    - Central or para-central location
    - Penetration of Bowman's membrane
    - Infiltrate ≥2 mm diameter
    - Associated with iritis

- Associated with any increase in intraocular pressure
- Culture positive for microorganisms
- Increasing size or severity at subsequent visits

  NOTE: Signs of a presumed infectious corneal ulcer may include irregular focal infiltrates, active lesions with raised edges, significant diffuse infiltration, anterior corneal to mid-stromal involvement, erosion with overlying staining, conjunctival and lid edema, anterior chamber reaction (iritis), and severe bulbar and limbal redness. Symptoms associated with a presumed infectious ulcer (microbial keratitis) may include pain of rapid onset, severe redness, purulent or mucopurulent discharge, tearing, and photophobia.

- Any central or paracentral (within the central 6 mm of cornea) corneal event that results in permanent opacification (such as corneal scar or vascularization)
- Any serious adverse ophthalmic events including hypopyon and/or hyphema
- Any neovascularization within the central 6 mm of the cornea
- Permanent loss of ≥2 lines of BSCVA
- All cases of iritis.

All SAEs will be listed. A summary of SAEs by SOC and PT will be provided.

4.8.1.4. TEAE Resulting in Death

Any TEAEs resulting in death will be included in the listing of SAEs and clearly marked as such.

4.8.1.5. TEAE Leading to Study Treatment Discontinuation

For every AE the investigator will indicate if the subject discontinued from the study due to the AE. A listing of all such subjects/eyes, along with their TEAE information, will be provided.

4.8.1.6. TEAE by Maximal Severity

A summary of TEAEs by maximal severity will be provided, where severity is either mild, moderate, or severe:

Mild: Subject awareness of a sign or symptom that is easily tolerated, requires no treatment, and does not interfere with subject's daily activities.

Moderate: Subject awareness of a sign or symptom which may be a low level of concern to the subject and may interfere with daily activities but can be relieved by simple therapeutic care.

Severe: A sign or symptom that interrupts the subject's daily activity and requires systemic therapy or other treatment.

4.8.1.7. Significant Non-Serious TEAEs

A summary of significant non-serious TEAEs will be provided. A significant non-serious adverse event is an AE that does not meet the serious criteria, is considered significant by the Sponsor, and requires expedited reporting to the Sponsor. These events include but are not limited to:

- Peripheral non-progressive non-infectious corneal ulcers.
- All symptomatic corneal infiltrative events.
- All cases of corneal staining greater than or equal to Grade 3.
- A temporary loss of two or more lines of BSCVA (for greater than or equal to 2 weeks).
- Neovascularization cases Grade 2 or greater (if not within 6 mm of the cornea).
- Any ocular event that necessitates temporary lens discontinuation of greater than or equal to 2 weeks.

4.8.1.8. Non-Significant Non-Serious TEAEs

A summary of non-significant non-serious TEAEs will be provided. A non-significant non-serious adverse event may include but are not limited to the following and does not require expedited reporting:

- Bacterial Conjunctivitis.
- Viral Conjunctivitis.
- Allergic Conjunctivitis.
- Corneal Edema.
- Contact Lens Related Papillary Conjunctivitis.
- Loss of Contrast Sensitivity.

4.8.1.9. Additional Summaries of TEAEs

Additional summaries of TEAEs will be provided:

- Related SAEs by relationship to (1) study device, (2) rewetting drops, or (3) both study device and rewetting drops.
- Severe TEAEs.
- TEAEs that are considered Adverse Device Effects.
- Serious TEAEs that are considered Adverse Device Effects by (un)anticipated status.
- Non-serious TEAEs occurring in 1% or more, 2% or more, 3% or more, 4% or more, and 5% or more of subjects/eyes

4.8.2. Trend Analysis Profile

For each treatment arm, a Trend Analysis Profile will be created to assist in the identification of trends, as per FDA guidance for contact lens care products. This will include summaries of the following, for each scheduled visit individually and overall:

- Total # of eyes (active or discontinued)
- Number of discontinued eyes
- Average wear time
- Number of lens replacements
- Number of total TEAEs
- Number of corneal ulcers
- Number of iritis episodes
- Corneal staining reports:

    - Total number
    - Total > Grade 2
    - Total # of eyes
- Edema reports (for each of epithelial edema and epithelial microcysts):
    - Total number
    - Total > Grade 2
    - Total # of eyes
- Injection reports (for each of limbal and bulbar injections):
    - Total number
    - Total > Grade 2
    - Total # of eyes
- Upper lid tarsal conjunctival abnormalities reports:
    - Total number
    - Total > Grade 2
    - Total # of eyes
- Corneal neovascularization reports:
    - Total number
    - Total > Grade 2
    - Total # of eyes
- Corneal infiltrates reports:
    - Total number
    - Total > Grade 2
    - Total # of eyes
- Total visits
- Total missed visits

For mapping purposes, and for accounting for unscheduled events, the following assignments will be used, which maps a given day to its closest visit:

Visit	Target	Mapping Unscheduled Visits
2-Week Follow-up Visit	14 Days	0 – 22 Days
1-Month Follow-up Visit	30 Days	23 – 45 Days
2-Month Follow-up Visit	60 Days	46 - 75 Days
3-Month Follow-up Visit	90 Days	76 or more Days

The number of corneal ulcers and number of iritis are a subset of TEAE, which will be identified by qualified study personnel. The number of staining, edema, injection, and neovascularization reports come from the slit-lamp examination (note edema and injection both have two reports each per slit-lamp examination).

4.8.3. Clinical Laboratory Analyses

Cultures for determining corneal ulcer or suspected ocular infection will be taken. The results of such cultures will be summarized and provided as listings. The summary will include the number of eyes with any positive culture, as well as the number and percentage of positive cultures by type (cul-de-sac, lower eyelid margin, corneal lesion, lenses, lens case, or lens case solution).

4.9. Other Analyses

The following analyses will, unless otherwise specified, also be provided as listings that will include all visits. Unless stated otherwise, summaries and listings will utilize the Safety Population and be by treatment group. For summaries by visit, the "worst" measure across visits and typical measure across all follow-up visits (using the average for continuous measures, or the mode for categorical measures, as appropriate), will be summarized as well, and denoted in the listings.

Unless stated otherwise, these summaries will be by eye, rather than subject, and no comparisons between treatment group and/or baseline will be made for these analyses. Only observed cases will be used.

Keratometry

The absolute change in keratometry parameters (horizontal/vertical focusing power) at the exit visit vs. the screening/dispensing visits (diopters) will be summarized and will include a by-eye summary of the largest (absolute) change between vertical and horizontal power. This summary will be done in two ways:

- Continuous change in horizontal/vertical/largest.
- Categorical change in 1 diopter bins (i.e. 0-0.99D, 1 – 1.99D, … , >= 5.00D).

Refraction

Refraction parameters without lenses will be summarized at each visit. These parameters (in minus cylinder notation) will include sphere, cylinder, axis, and spherical equivalent.

Additionally, the change in spherical equivalent from baseline to the exit visit will be summarized both continuously and categorically by binning the change into 1-diapter bins (i.e. 0-.99D, 1 – 1.99D, …, >=5.00D).

Best Spectacle Corrected Visual Acuity (BSCVA)

The BSCVA (without lenses) will be summarized at the screening/dispensing visit and the exit visit. In addition to the letters correct, the logMAR and Snellen category parameters (see appendix) will also be summarized. The difference between the exit and screening/dispensing visit will be calculated for:

1) Continuous change in logMAR
2) Number and proportion of eyes that decrease by >=10 letters

Visual Acuity (VA)

Separate summaries for VA will be done for worn lenses (all follow-up visits) and dispensing evaluations (1 and 2-Month Follow-Up Visits only). Summaries for worn lenses and dispensing evaluations will be summarized by subjects who (1) completed the study and (2) discontinued the study. VA will be summarized at each visit. Summaries will be done as:

1) LogMAR
2) Snellen

Additionally, the change in VA from the screening/dispensing visit will be calculated at each follow-up visit (for worn lenses). These differences will include:

- Number and percentage of eyes with a loss of >=2 lines (note 1 line is equal to 5 letters or 0.1 logMAR)
- Categorical summary of the #lines as +4, +3, … , -3, -4
- Continuous change in logMAR

For the final visit only, a shift table in Snellen categories from the screening/dispensing visit will be provided.

For the dispensing visit and final visit only, a summary comparing BSCVA to worn lenses VA will be provided. This will include the number and percentage of eyes with 1 or more line loss from BSCVA to worn lenses VA, and the continuous change in logMAR. A shift table comparing the initial BSCVA to final-visit worn lens VA (in logMAR increments of 0.1) will also be provided for test/control eyes who completed/discontinued the study (4 shift tables total).

Dispensed Lens Characteristics

The following lens characteristics will be categorically summarized at each scheduled visit:

- Lens centration
- Lens movement
    - Josephson push up test
- Lens wettability

Worn Lens Characteristics

The following lens characteristics will be categorically summarized at each scheduled visit, and will include the number of subjects who came in wearing their study lenses:

- Lens centration
- Lens movement
    - Josephson push up test
- Lens wettability
- Lens deposit type
- Lens deposit percent coverage
- Degree of front surface deposit
- Degree of back surface deposit

Lens Wear Parameters

The following lens wear parameters will be summarized at each scheduled visit for each eye:

- Average daily wear time since last visit (hours per day)
- Average comfortable wear time since last visit (hours per day)
- Hours worn on day of visit (hours)
- Replaced lens (yes / no)
    - Among those with replaced lenses, time since lens replacement (days) as calculated by current visit date– date of lens replacement + 1.

A separate summary will also include summaries of the number of days on study that the subject did not wear the study lenses and the percentage of days on study that the subject used the study solution and wore their study lenses, on average (as < 80% or >=80%).

An additional summary of average wear time per visit will be provided for test/control eyes that completed/discontinued the study.

Over-Refraction and Distance VA for Non-Plano Eyes

The number and percentage of eyes that are not Plano will be summarized by visit, along with their recorded sphere (D) and distance VA (total number of letters correct). This will be done by dispensed or worn lens for the appropriate visits.

Lens Performance Assessment

In addition to primary endpoints "Overall comfort" and "Vision", each of the following categories will also be summarized using the ITT Population by visit and over all scheduled follow-up visits:

- Burning and stinging upon lens insertion
- Comfort upon insertion
- **Overall comfort**
- Comfort at the end of the day
- Ease of handling/insertion
- Ease of handling/removal
- Dryness
- Vision upon insertion
- **Vision**
- Vision in low light
- Vision at end of day
- Lens cleanliness upon removal
- Overall impression

A summary of rewetting drop usage by visit and by highest (i.e., most) use over all scheduled follow-up visits will be provided.

Symptoms/Complaints

For each visit, each symptom/complaint will be summarized as follows:

1) Categorically by rating (i.e. 0 – None, …, 4- Severe)
    a. This summary will include the number and proportion of eyes experiencing any symptoms of problems with the lenses

2) Positive reports (i.e. symptoms/complaints reported as > 0 None) by visit for each of test/control by study completion/discontinuation status.
3) By favorable / unfavorable, where favorable is defined as a rating < 3 or choosing "No" symptoms or problems with the lenses, and unfavorable is defined as a rating of 3 or 4.

Note this will include the symptoms/complaints for the habitual lenses as collected at the screening visit

Slit-Lamp Examination

Results from the slit-lamp examination will be summarized categorically (typically grade 0 – 4 or absent/present, depending on category) for each slit-lamp examination category at each scheduled visit. Additionally, for each visit, the total findings across categories of each grade (for categories graded 0 – 4) will be summarized categorically. This will be done for each of test/control by study completion/discontinuation status.

Corneal Scars

The number and percentage of eyes with pre-existing corneal scars will be summarized, as well as the number percentage of eyes developing new corneal scars or experienced changes to their pre-existing scars. The locations of the scars will be summarized by visit and overall (categorical) along with the size in millimeters of the largest scar observed at that visit (or overall).

A corresponding listing with details of each pre-existing, new, or changed corneal scar will be produced.

Corneal Infiltrates

Corneal infiltrates will be summarized at each scheduled visit. This summary will include:

- Size of largest infiltrate (mm)
- Depth of deepest infiltrate (as epithelial, anterior stroma, or mid/posterior stromal)
- Infiltrate density (Grade 0 – 4)
- Infiltrate type
- Degree of pain (categorically as 0 – 10)
- Size of any overlying defect (mm)
- Location

Pregnancy Status

A listing of subjects who become pregnant will be provided.

4.9.1. Subgroup analyses

Several analyses will be repeated for each lens group. The groups are the same as described in Table 3. The analyses which will be repeated as subgroup analyses on these lens groups include:

- All primary analyses
    - Slit-lamp findings > Grade 2 over all follow-up visits
    - Front Surface Deposits with grade of ≤ 2 over all follow-up visits

  - Overall comfort over all follow-up visits
  - Vision over all follow-up visits
- Symptoms/complaints

4.10. Changes to Protocol-Planned Analyses

Included a tipping point analysis to primary safety endpoint of proportion of eyes with any slit-lamp findings greater than Grade 2 over all follow-up visits. There are no other planned changes to the protocol-planned analyses.

5. Supporting Documentation

5.1. Appendix 1: Algorithms for Refraction Parameters and LogMAR

Refraction Parameters

Results originally given in positive cylinder notation (i.e., with a cylinder value > 0) can be converted to minus notation by the following algorithms:

- Sphere = original sphere + original cylinder
- Cylinder = $-1 \times$ (original cylinder)
- Axis:
    - If original axis is between 1 and 90, inclusive ($1 \leq$ original axis ≤ 90), then new axis = original axis + 90
    - If original axis is between 91 and 180 ($91 \leq$ original axis ≤ 180), then new axis = original axis – 90

Spherical equivalent is calculated as sphere + 0.5*cylinder, where cylinder and sphere are in minus notation.

Determining LogMAR from the number of letters correct.

- Let X be the number of letters entered on the case report form. Then logMAR is as follows:

  If $X \geq 7$ then logMAR = 0.8 – (0.02*[X – 7]);
  Else if $X < 3$ then logMAR = 1.0 – 0.0333*X;
  Else if $3 \leq X < 7$ then logMAR = 0.9 – (0.025*[X – 3]);

6. References

Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. J Biopharm Stat. 2009 Nov;19(6):1085-98. doi: 10.1080/10543400903243009. PMID: 20183466.

BAUSCH + LOMB

Memo-To-File

Date: 03 February 2025

Re: Statistical Analysis Plan Version Number Discrepancy

Protocol Number: 914

Protocol Title: A Safety and Effectiveness Study of a Contact Lens Cleaning and Disinfecting Solution

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The Statistical Analysis Plan Version 2.0 was finalized on April 11, 2024, with the updates from Version 1.0 summarized in Table 1. However, the footer was not updated, and incorrectly indicates "Version 1".

[redacted]

Signature | Date

[redacted]

Printed Name | 914 Clinical Trial Manager

CC: [914 TMF]