Short Title:

Statistical Analysis Plan
CLK027-P001

Full Title:

Statistical Analysis Plan
CLK027-P001 / NCT03118934

Protocol Title:	Assessing Fitting Guides in Alcon Multifocal Contact Lenses
Project Number:	CLK027-P001
Reference Number:	
Protocol TDOC Number:	TDOC-0053461
Author:	[redacted]
	[redacted]
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Approvals:	See last page for electronic approvals.
Job Notes:	

This is the first revision (Version 2.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

Executive Summary:

Key Objectives:

To demonstrate noninferiority of the alternative fitting guide compared to the current fitting guide as determined by the mean number of trial lenses needed to fit each eye at the Screening/Fitting visit for all Alcon multifocal (MF) lenses combined

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferior mean number of trial lenses needed to fit each eye of the alternative fitting guide compared to the current fitting guide, at Screening/Fitting visit for all Alcon MF lenses combined.

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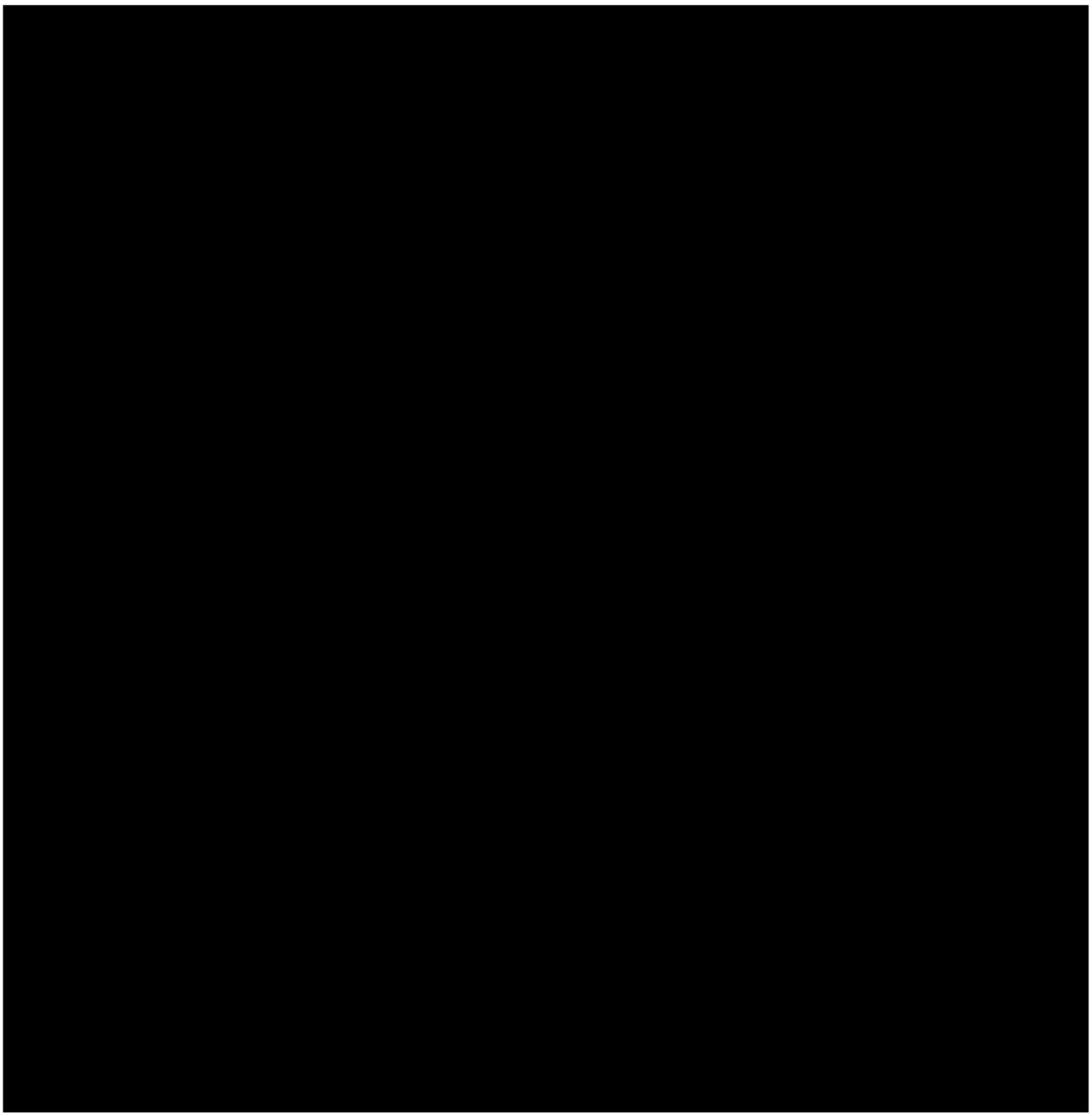
1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

To demonstrate noninferiority of the alternative fitting guide compared to the current fitting guide as determined by the mean number of trial lenses needed to fit each eye at the Screening/Fitting visit for all Alcon MF lenses combined



1.2 Study Description

This is a multicenter, subject-masked, randomized, parallel, stratified, active-controlled evaluation to compare the fitting success (determined by the mean number of trial lenses needed to successfully fit each eye) using the current MF fitting guide compared to the alternative MF fitting guide for all three of the Alcon MF contact lenses (AIR OPTIX AQUA® Multifocal [AOA MF], DAILIES® AquaComfort Plus® Multifocal [DACP MF], and DAILIES TOTAL1® Multifocal [DT1 MF]).

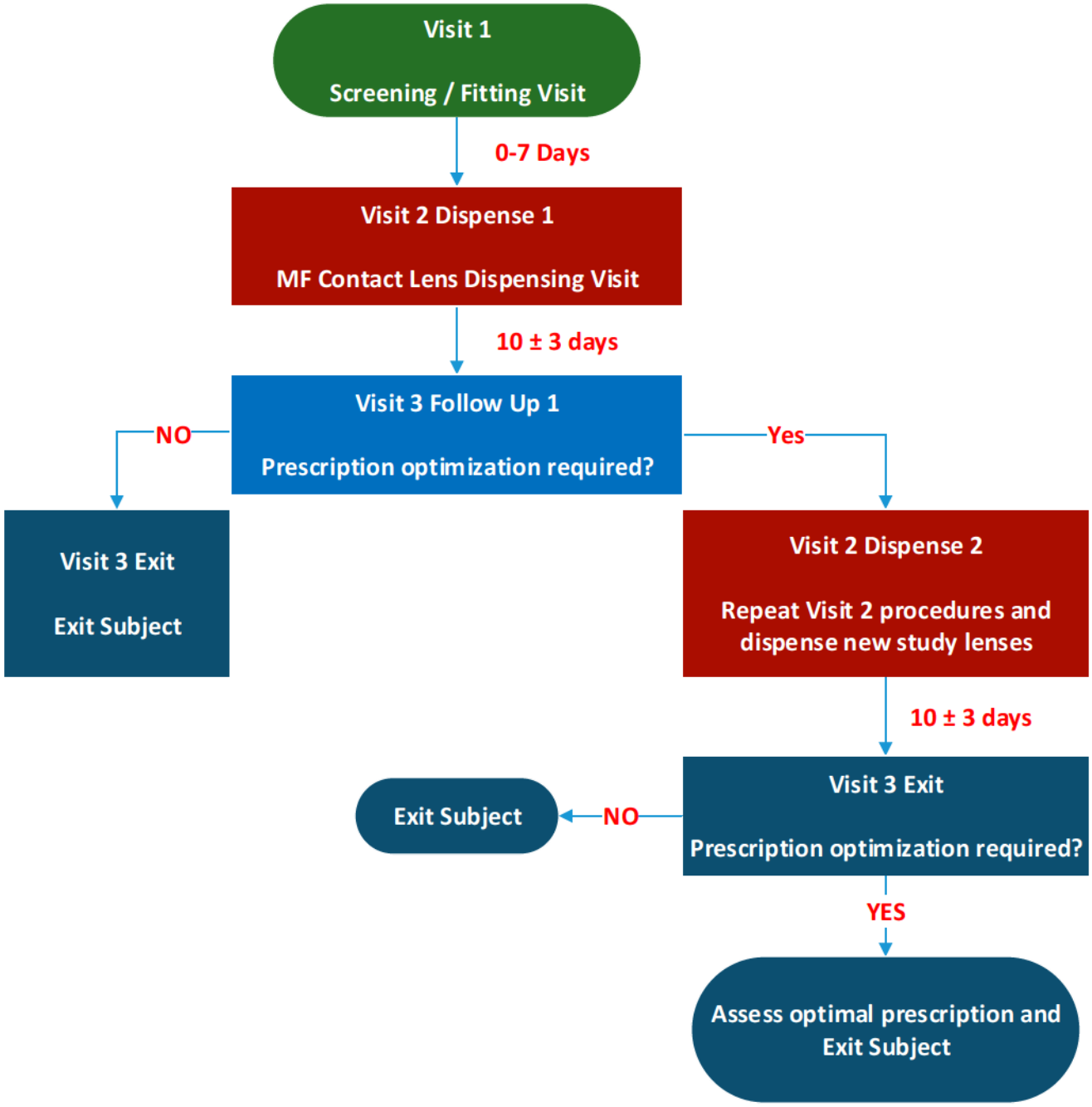
Approximately 180 subjects will be enrolled at approximately 20 sites. To participate in the study, subjects must be current soft contact lens wearers needing presbyopia-correction, with a near spectacle ADD of +0.50 D to +2.50 D (inclusive). Each site will enroll approximately 9 subjects (6 will be monthly/weekly habitual lens wearers and 3 will be daily disposable habitual lens wearers). [redacted]

Randomization for this study will be implemented in 2 parts. First, each site will be randomized to one fitting guide and will fit all subjects at their site using the assigned fitting guide (current or alternative). The purpose of this strategy is to reduce the likelihood that errors will be made in fitting the trial lenses if trying to use two similar fitting guides. Randomization of the fitting guide will be stratified by region.

Secondly, subjects who currently wear monthly/weekly contact lenses will be randomized to either AOA MF or DACP MF contact lenses (1:1 randomization). Subjects who currently wear daily disposable contact lenses will be fitted with DT1 MF contact lenses.

The expected duration of subject participation in the study is 10 ± 3 days (7 days minimum) and up to 33 days (maximum) for all subjects with a minimum of 2 scheduled visits, up to 5 scheduled visits, depending on necessity of refit dispensing and follow-up visits. The study design is presented in Figure 1–1.

Figure 1–1 Study Design



1.3 Randomization

A member of the Randomization Programming group at Alcon who is not part of the study team will generate the randomized allocation schedules applicable for the study. Each site will receive an envelope, based upon the randomization list, containing a card with the

respective fitting guide to use. Subsequently, randomization for habitual weekly/monthly lens wearers will be implemented.

1.4 Masking

This study is subject-masked. Subjects are masked only to the MF fitting guides.

1.5 Interim Analysis

Not applicable.

2 Analysis Sets

2.1 Safety Analysis Set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. As such, the safety analysis set will include all subjects/eyes exposed to study lenses evaluated in this study, except for the trial lenses used for parametrization and fitting at Visit 1. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study lenses exposed.

Subjects who are lost to follow-up and their exposure to dispensed study lenses is unknown will be included in the safety data set. The dispense date for these subjects will be assumed as the first exposure date (Visit 2 Dispense 1).

2.2 Full Analysis Set

The Full Analysis Set (FAS) will include:

1. all randomized subjects to AOA MF or DACP MF as well as subjects assigned to DT1 MF and
2. who are exposed to study lenses including those used for parametrization and fitting at Visit 1

All effectiveness analyses relevant to fitting guide will be conducted according to the randomized assignment. Effectiveness analyses based upon lens brand will be conducted according to the randomized or non-randomized assignment as applicable to the habitual lens wear.

2.3 Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will include:

1. all randomized subjects to AOA MF or DACP MF as well as subjects assigned to DT1 MF and

2. all data/subjects which have not met any of the critical deviation or non-evaluable criteria identified in the Deviations and Evaluability Plan

All effectiveness analyses relevant to fitting guide will be conducted according to the randomized assignment. Effectiveness analyses based upon lens brand will be conducted according to the randomized or non-randomized assignment as applicable to the habitual lens wear.

3 Subject Characteristics and Study Conduct Summaries

Demographic information (age, sex, ethnicity, and race) will be summarized on the safety, full and PP analysis sets. Baseline characteristics on habitual lens [redacted] will be summarized on the full and PP analysis sets. [redacted].

All descriptive summary statistics will be displayed with counts and percentage for categorical data, and with n, mean, standard deviation, median, minimum, and maximum for continuous data.

4 Effectiveness Analysis Strategy

This study defines one primary endpoint, [redacted]. All effectiveness evaluations will use the FAS as the primary analysis set. Supportive analyses of the primary [redacted] effectiveness endpoint will be conducted using the PP analysis set only if the number of subjects excluded from PP analysis set exceeds 5% of FAS. A summary of the planned analysis strategy is presented in Table 4–1 Summary of Inferential Analysis Strategy for Effectiveness Endpoints.

For all planned inferential analyses, alternative models/methods may be considered if convergence cannot be achieved.

[redacted]

2. [redacted]

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is the number of trial lenses needed to fit each eye at the Screening/Fitting visit (Visit 1), derived from number of on-eye lens prescriptions.

[redacted]

4.2 Effectiveness Hypotheses

4.2.1 Hypothesis for the Primary Endpoint

The primary hypothesis to be tested is the noninferiority of the alternative fitting guide when compared to the current fitting guide in fitting. The null and alternative hypotheses are formulated based on a pre-defined noninferiority margin of 0.5 as follows:

$$H_0: \mu_{(AFG)} - \mu_{(CFG)} \geq 0.5$$
$$H_a: \mu_{(AFG)} - \mu_{(CFG)} < 0.5$$

where $\mu_{(AFG)}$ and $\mu_{(CFG)}$ denote the mean number of trial lenses used to achieve fit in each eye using the alternative and current fitting guide, respectively, at the Screening/ Fitting visit. All Alcon MF lenses are to be included.

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

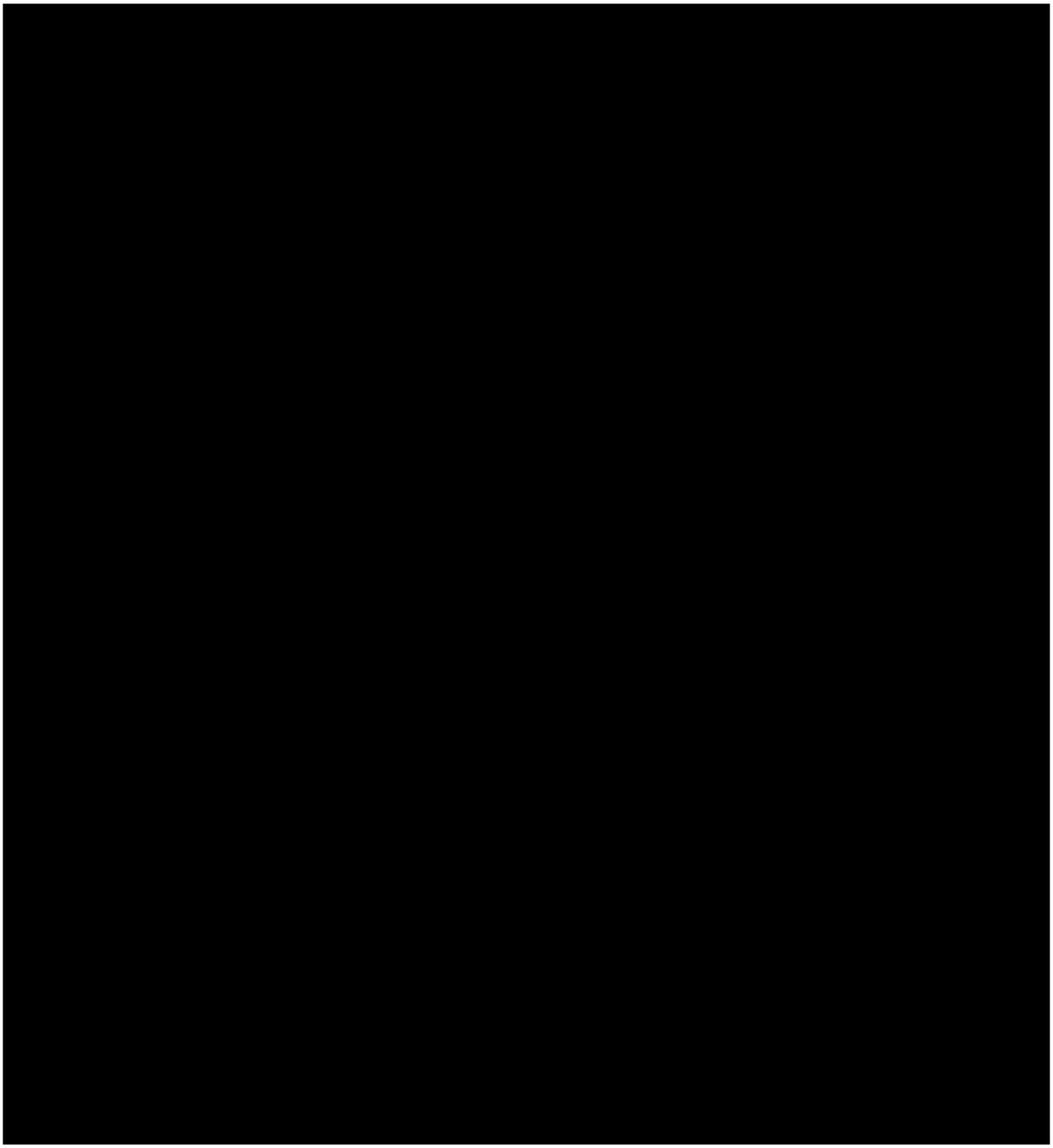
4.3.1 Primary Effectiveness Analyses

A mixed effect repeated measures model will be utilized to test these hypotheses, including terms for fitting guide, [redacted] Correlation between eyes will be accounted for. Fitting guide difference (Alternative minus Current) and the corresponding one-sided 95% upper confidence limit (UCL) will be computed. Noninferiority in fitting will be declared if UCL < 0.5 at Visit 1. The following SAS pseudo code will be used for the analysis:

proc sort data = one; by subject; run;

proc mixed data = one;

```
class subject fitting_guide lens ADD_power region eye ;
model y = fitting_guide lens fitting_guide*lens region ADD_power/ddfm = kr;
repeated eye /subject=subject  type=(to be determined);
lsmeans fitting_guide/ cl diff alpha=0.10 e;
run;
```



[redacted]

Table 4–1 Summary of Inferential Analysis Strategy for Effectiveness Endpoints

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method[b]	Analysis Set	Missing Data Approach
Primary				
Number of lenses needed for fit at Visit 1	M	Linear mixed model[c]	FAS (as randomized)	Observed data only
Number of lenses needed for fit at	S	Linear mixed	PPS (as	Observed

Visit 1		model[c]	randomized)	data only
[redacted]				

[a]M=Main analysis approach; S=Sensitivity analysis approach
[b]Further details on statistical models are:
[redacted]

[redacted]

4.4 Multiplicity Strategy

A sequential gatekeeping strategy will be implemented to control testing of multiple effectiveness endpoints. Therefore, the overall type I error will be controlled at one-sided 0.05 with the following testing order:

- Noninferiority of primary endpoint

[redacted]

4.6 Interim Analysis for Effectiveness

Not applicable.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are

- Adverse events
- Biomicroscopy findings
    - Limbal hyperemia
    - Bulbar hyperemia
    - Other findings
- Device deficiencies

5.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of safety endpoints listed in Section 5.1.

5.3 Statistical Methods for Safety Analyses

The analysis set for all safety analyses is the safety analysis set as defined in Section 2.1. Safety variables will be summarized descriptively.

5.3.1 Adverse Events

The applicable definition of an Adverse Event (AE) is in the study protocol. All AEs occurring from when a subject signs informed consent to when a subject exits the study will be accounted for in the reporting.

Analysis and presentation of pre-treatment and between-treatment AEs will be separated from treatment-emergent AEs occurring during the study period. A pre-treatment AE is an event that occurs after signing informed consent but prior to exposure to study lens not used for lens parametrization and fitting at Visit 1. A between-treatment AE is an event that occurs after last exposure to dispense 1 study lens but prior to exposure to dispense 2 study lens. The period for treatment-emergent AE analysis starts from exposure to study lens dispensed at Visit 2 (Dispense 1) until the subject completes or is discontinued from the study, excluding the between-treatment period.

Descriptive summaries (counts and percentages) for ocular and nonocular treatment-emergent AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Terms (PT). Serious AEs will be summarized separately. Additionally, relationship to lens will be identified in all AE tables. Unit of presentation for ocular AEs will be eyes and nonocular AEs will be subjects.

Individual subject's listings will be provided for pre-treatment, between-treatment and treatment emergent AEs, where any AE leading to study discontinuation will be indicated.

5.3.2 Biomicroscopy Findings

Biomicroscopy assessment will be performed at all study visits, including scheduled visits and unscheduled visits. If Visit 1 and Visit 2 Dispense 1 occur on the same day, biomicroscopy will only be performed once at the visit. Similarly, if Visits 3 Follow-up 1 and Visit 2 Dispense 2 occur on the same day. The reporting unit for each biomicroscopy finding will be eyes. A summary of grade category counts and percentages will be presented for each parameter by visit. A shift table showing grade at baseline relative to follow-up visits will be presented by visit for each parameter. Baseline will be defined as Visit 2, except if Visit 2 occurs on the same day as Visit 1, Baseline will be obtained from Visit 1.

For each biomicroscopy parameter, counts and percentages of eyes which experience an increase of ≥2 grades from baseline to any subsequent visit (including unscheduled visits) will be presented. A listing will be provided which presents all eyes with an increase of ≥2 grades in any biomicroscopy parameter at any visit compared to the grade for the same eye at baseline. The listing will include all biomicroscopy data from all visits for these eyes and will

be presented by lens, investigator, subject, age, sex, visit, eye, parameter, baseline value, and value at the visit.

5.3.3 Device Deficiencies

The applicable definition of a device deficiency is in the study protocol. A frequency table showing counts for each Device Deficiency category will be presented. In addition, listings for treatment-emergent and pre-treatment (prior to exposure to study lenses not used for lens parametrization and fitting at Visit 1) device deficiencies will be provided.

6 Analysis Strategy for Other Endpoints

Not applicable.

7 Sample Size and Power Calculations

Sample size calculation for the primary effectiveness hypothesis on fit success is based on results [redacted] With an assumed common standard deviation of 0.6 and expected difference of 0.25, a sample size of 80 (160 eyes) in each group will provide 83% power for a noninferiority margin of 0.5, at one-sided α=0.05, based on a two group t-test.

8 References

9 Revision History

This is the first revision (Version 2.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

Summary of changes:

- To update the definition of safety analysis set in order to include subjects who are lost to follow-up and their exposure to dispensed study lenses is unknown

[redacted]

[redacted]

Itemized Changes:

Section	Information Changed
Section 2.1	The following was added: Subjects who are lost to follow-up and their exposure to dispensed study lenses is unknown will be included in the safety data set. The dispense date for these subjects will be assumed as the first exposure date (Visit 2 Dispense 1).

[redacted]

[redacted]

10 Appendix

Table 10–1 Overview of Study Plan

	Visit 1	Visit 2 Dispense 1 / Visit 2 Dispense 2	Visit 3 Follow Up 1 / Visit 3 Exit	USV
Procedure/ Assessment	**Screening and Fitting**	**Dispensing 0-7 days from Visit 1**	**Day 10 ± 3 – Follow-up / Exit**	**Unscheduled Visit**
Randomization • Site to Fitting Guide	✓ *			
Informed Consent	✓			
Demographics	✓			
Medical History	✓			
Concomitant Medications/ Changes in Concomitant Medications	✓	✓	✓	✓
Subjective (Manifest) refraction	✓	(✓)	(✓)	(✓)
BCVA † (with manifest refraction)	✓	(✓)	(✓)	(✓)
[redacted]				

Study contact lens parameters optimization and fitting †	✓			
[redacted]				
Inclusion/Exclusion	✓			
Randomization Weekly/Monthly Subject to study lens	✓ **			
Dispense study lenses		✓ **		
[redacted]				
Biomicroscopy	✓	✓	✓	✓
[redacted]				
Assess optimal prescription			✓ [e]	(✓)
Assess AEs	✓ [f]	✓	✓	✓
Assess device deficiencies	✓	✓	✓	✓
[redacted]				
Exit Form	(✓)	(✓)	✓	(✓)

AE = Adverse Event; BCVA = Best Corrected Visual Acuity; logMAR = logarithmic Minimum Angle of Resolution; USV = Unscheduled Visit; VA = Visual Acuity

[redacted]

If subject needs a new prescription, perform Visit 2 Dispense 2 and Visit 3/Exit

[f] AEs are collected from the time of informed consent

[redacted]

(✓) as needed, or if a 2-line change in contact lens corrected VA is observed (Manifest refraction and BCVA only)

* Prior to Visit 1

** per randomization scheme, if weekly/monthly lens wearers

[redacted]

† Source only

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]