Clinical Performance Evaluation of Two Frequent Replacement Silicone Hydrogel Multifocal Contact Lenses

STUDY ID

CLN705-C001

STATISTICAL ANALYSIS PLAN

NCT05338333

Statistical Analysis Plan for CLN705-C001
Title: Clinical Performance Evaluation of Two Frequent Replacement Silicone Hydrogel Multifocal Contact Lenses

[redacted]

Executive Summary:

Key Objectives:

The primary objective of this study is to demonstrate noninferiority (NI) in visual acuity (VA) at distance when wearing [redacted] Multifocal ([redacted] MF) contact lenses compared to AIR OPTIX® plus HydraGlyde® Multifocal (AOHG MF) contact lenses, after 30 days of wear.

[redacted]

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in VA with [redacted] MF contact lenses when compared to AOHG MF contact lenses, at Day 30, using a margin of 0.05 on the logMAR scale [redacted]

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1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate noninferiority in VA at distance when wearing [redacted] MF contact lenses compared to AOHG MF contact lenses, after 30 days of wear.

[redacted]

1.2 Study Description

Key components of the study are summarized in Table 1-1.

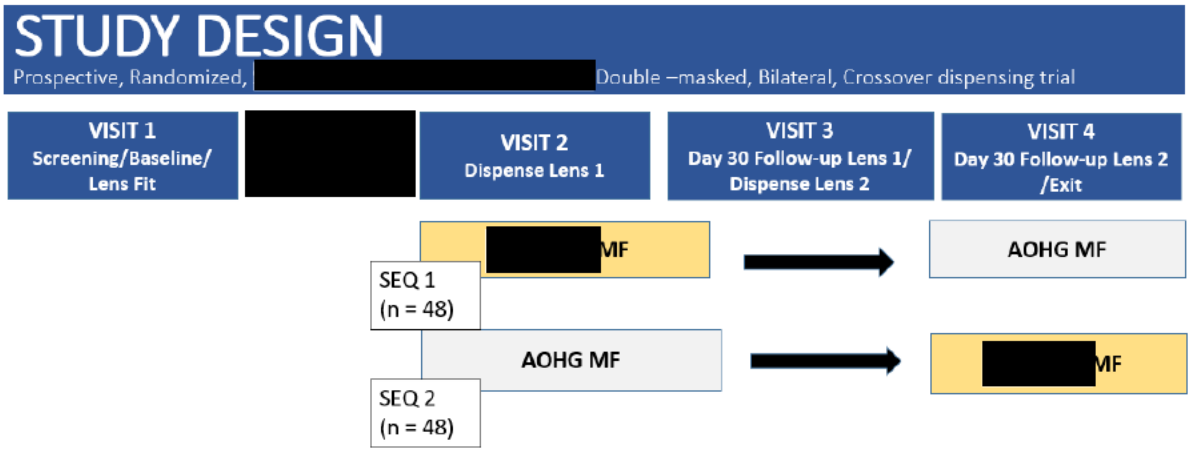
Table 1-1 Study Description Summary

Study Design	Prospective, randomized, [redacted] bilateral, crossover, double-masked
Study Population	The subject population consists of volunteer subjects aged ≥ 40 years, who are habitual daily disposable and biweekly/monthly replacement soft multifocal contact lens wearers for at least past 3 months and wear their habitual lenses at least 5 days per week and at least 8 hours per day. Target to complete: 84 Planned to enroll: ~96
Number of Sites	~8 US
Test Product	[redacted] Multifocal contact lenses ([redacted] MF; lehfilcon A; LID210464)
Comparator Product	AIR OPTIX® plus HydraGlyde® Multifocal contact lenses (AOHG MF; lotrafilcon B)

Planned Duration of Exposure	~60 days total duration (test and comparator): Test Product: 30 (-2/+1) days Comparator Product: 30 (-2/+1) days
Visits	Visit 1: Screening/Baseline/Lens Fit Visit 2: Dispense Lens 1 [3-5 days after Visit 1] Visit 3: Day 30 Follow-up Lens 1/Dispense Lens 2 [Day 30 (-2/+1)] Visit 4: Day 30 Follow-up Lens 2/Exit [Day 30 (-2/+1)] [redacted]

A study design schematic is depicted 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 schedule(s) for study lens sequence assignment. Randomization will be implemented in the Electronic Data Capture (EDC)/randomization integration system.

Qualifying subjects will be randomized in a 1:1 ratio to receive treatment (lens) in crossover sequence [redacted]

Sequence	EDC/randomization integration system	Lens Name
Sequence 1	LID210464/AOHG MF	[redacted] MF/AOHG MF
Sequence 2	AOHG MF/LID210464	AOHG MF/[redacted] MF

1.4 Masking

This study is double-masked.

[redacted]

1.5 Interim Analysis

There are no plans to conduct an interim analysis and no criteria by which the study would be terminated early based upon statistical determination.

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 any study lenses evaluated in this study. [redacted] any adverse event (AE) or device deficiency occurring after Informed Consent and prior to the initial exposure to the study lenses (test or comparator) under evaluation in this clinical protocol will be listed as pre-treatment.

For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study lenses exposed in the corresponding lens sequence.

Adverse events occurring from the time of informed consent but prior to first exposure to study lenses will be summarized in subject listings.

2.2 Full Analysis Set

The full analysis set (FAS) is the set of all randomized subjects who are exposed to any study lenses evaluated in this study. [redacted]

2.3 Per Protocol Analysis Set

The per protocol (PP) analysis set is a subset of FAS and excludes all data/subjects that have met any of the critical deviation or evaluability criteria identified in the Deviation and Evaluability Plan (DEP).

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

The following tables will be presented:

- Subject Disposition by Lens Sequence
- Analysis Sets by Lens
- Analysis Sets by Lens Sequence
- Subject Accounting by Lens Sequence
- Demographics Characteristics by Lens Sequence
- Baseline Characteristics by Lens Sequence [lens brand, lens power: sphere, ADD]

Subject accounting and demographics characteristics tables will be summarized on the safety, full, and per protocol analysis datasets. Baseline characteristics will be summarized on the full and per protocol analysis datasets.

In addition, the following subject listings will be provided:

- Listing of Subjects Excluded from Protocol Defined Analysis Sets
- Listing of Lens Sequence Assignment by Investigator
- Listing of Subjects Discontinued from Study

4 EFFECTIVENESS ANALYSIS STRATEGY

This study defines 1 primary, [redacted] endpoint. Unless otherwise specified, effectiveness evaluations will use the FAS as the primary analysis set, [redacted]

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum, as well as confidence intervals/limits as applicable. Categorical variables will be summarized with frequencies and percentages from each category.

All data obtained in evaluable subjects/eyes will be included in the analysis. No imputation for missing values will be carried out for the primary [redacted]

For all planned inferential analyses, alternative models/methods may be considered, for instance, if convergence cannot be achieved. Furthermore, if significant carryover effects are noted (confounded with sequence effect), results will be examined by period to ensure the overall conclusion is valid.

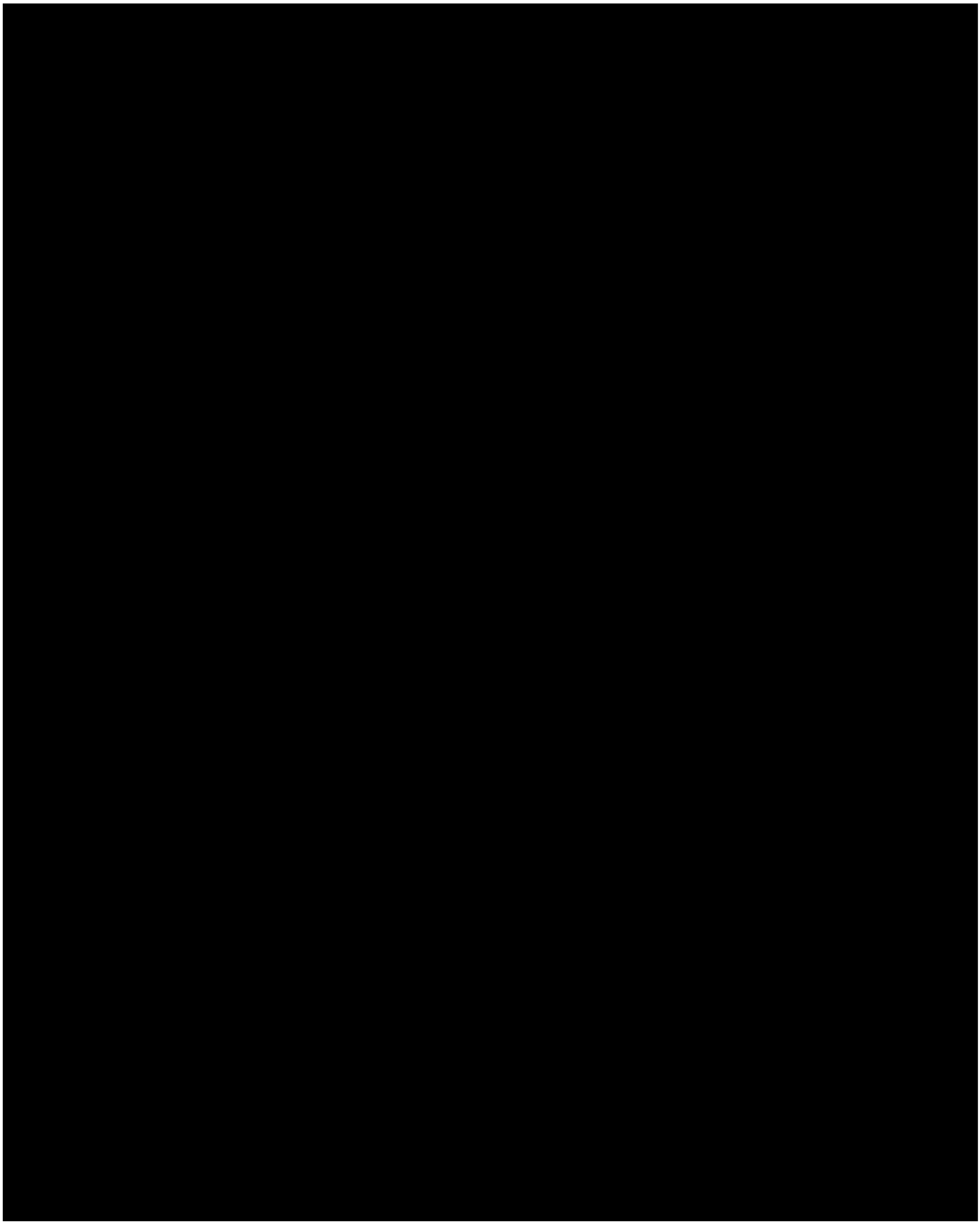
[redacted]

4.1 Effectiveness Endpoints

Primary Effectiveness Endpoint

The primary endpoint is binocular High Contrast/High Illumination (HC/HI) VA at distance (4 m or 3 m) at Day 30. This VA is collected with study lenses, on the logMAR scale.

[redacted]



4.2 Effectiveness Hypotheses

Primary Effectiveness

The null and alternative hypotheses are formulated in terms of the predefined margin of 0.05 for noninferiority:

H_0: $\mu_{(T)} - \mu_{(C)} \geq 0.05$
H_a: $\mu_{(T)} - \mu_{(C)} < 0.05$

where $\mu_{(T)}$ and $\mu_{(C)}$ denote the mean distance binocular HC/HI VA at Day 30 for [redacted] MF and AOHG MF, respectively, on the logMAR scale.

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

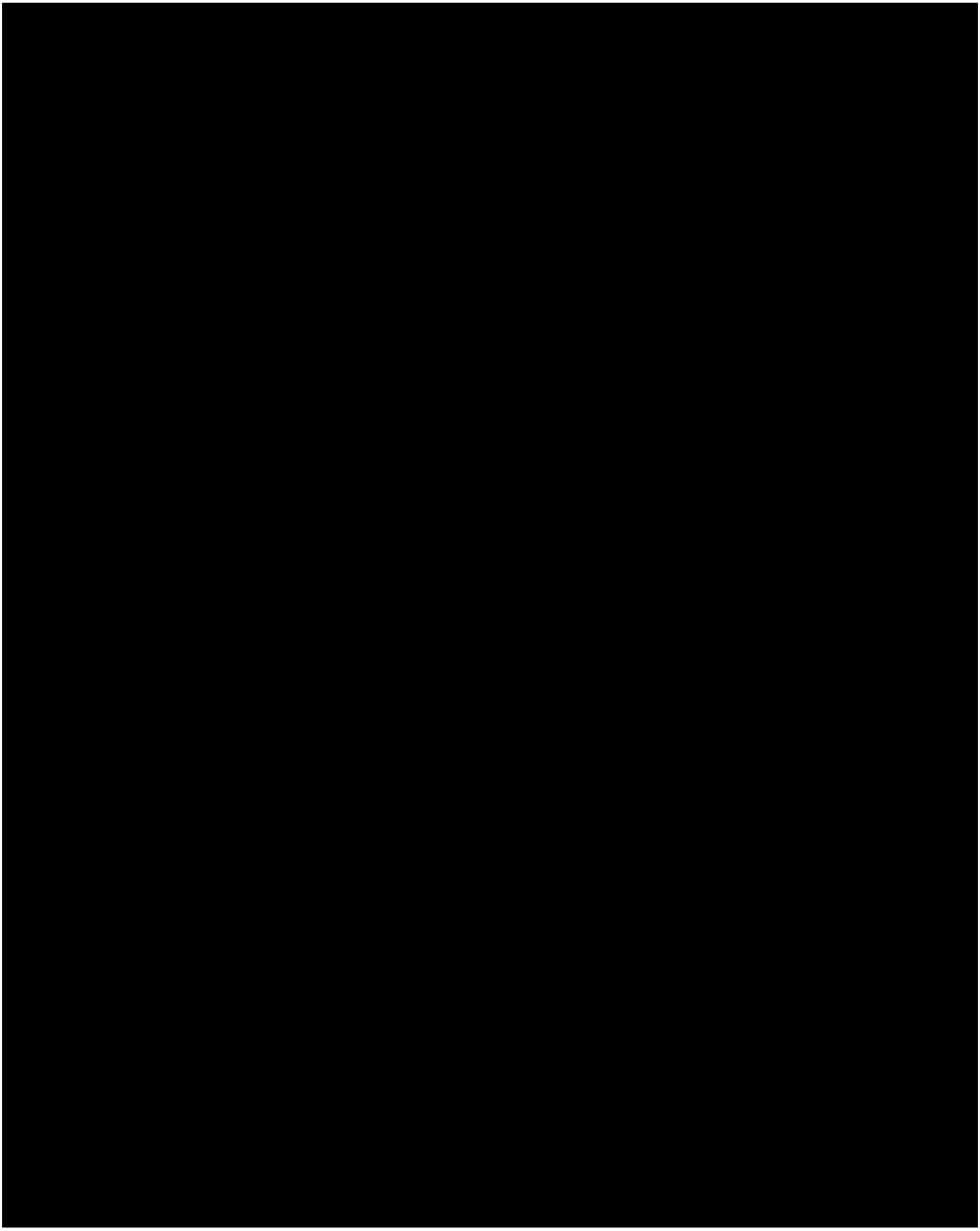
4.3.1 Primary Effectiveness Analysis

A mixed effects repeated measures model will be utilized to test these hypotheses. The model will include terms for lens, visit, lens by visit interaction, period, sequence, and habitual lens stratum. Within-subject correlation due to the crossover design will also be accounted for in

the model. Lens difference ([redacted] MF minus AOHG MF) and the corresponding one-sided 95% upper confidence limit will be computed at Day 30. Noninferiority in distance VA will be declared if upper confidence limit is less than 0.05.

[redacted]

[redacted]



5 SAFETY ANALYSIS STRATEGY

5.1 Safety Endpoints

The safety endpoints are

- AE
- Biomicroscopy Findings/Slit Lamp Examinations
    - Limbal hyperemia

  - Bulbar hyperemia
  - Corneal staining
  - Conjunctival staining
  - Palpebral conjunctival observations
  - Corneal epithelial edema
  - Corneal stromal edema
  - Corneal vascularization
  - Conjunctival compression/indention
  - Chemosis
  - Corneal infiltrates
  - 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 defined in Section 2.1. Baseline will be defined as the last measurement prior to exposure to study lenses. For biomicroscopy data, baseline will be defined as Visit 2. Safety variables will be summarized descriptively.

5.3.1 Adverse Events

The applicable definition of an AE is in the study protocol. All AEs occurring from when a subject signs informed consent to the time of their study exit will be accounted for in the reporting.

Pre-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 lenses. The period for treatment-emergent AE analysis starts from exposure to study lenses until the subject completes or is discontinued from the study. Each AE will be summarized under the exposed lens based upon the event onset date/time, up until the start of the next lens in the crossover sequence.

The following tables and supportive listings will be provided:

- Incidence of All Ocular Treatment-Emergent Adverse Events

- Incidence of Ocular Serious Treatment-Emergent Adverse Events
- Incidence of Ocular Significant Nonserious Treatment-Emergent Adverse Events
- Incidence of All Nonocular Treatment-Emergent Adverse Events
- Incidence of Nonocular Serious Treatment-Emergent Adverse Events
- Listing of All Ocular Treatment-Emergent Adverse Events
- Listing of All Nonocular Treatment-Emergent Adverse Events
- Listing of All Ocular Pre-Treatment Adverse Events
- Listing of All Nonocular Pre-Treatment Adverse Events

5.3.2 Biomicroscopy Findings/Slit Lamp Examination

The following tables and supportive listings will be provided:

- Frequency and Percentage for Biomicroscopy Findings by Visit
- Incidence of Increased Severity by 2 or More Grades in Biomicroscopy Findings
- Listing of Subjects with Other Biomicroscopy Findings
- Listing of Subjects with Conjunctival Compression/Indentation or Chemosis
- Listing of Subjects with Increased Severity by 2 or More Grades in Biomicroscopy Findings
- Listing of Subjects with Infiltrates

5.3.3 Device Deficiencies

The following tables and supportive listings will be provided:

- Frequency of Treatment-Emergent Device Deficiencies
- Listing of Treatment-Emergent Device Deficiencies
- Listing of Device Deficiencies Prior To Treatment Exposure

[redacted]

7 SAMPLE SIZE AND POWER CALCULATIONS

[redacted]

Sample size required for [redacted] the primary effectiveness [redacted], at 90% power and one-sided α=0.05, is summarized below:

Endpoint	SD (Paired Difference)	N/Sequence (NI margin = 0.05)
Distance VA	0.0845	13/Sequence
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]nce

8 REFERENCES

Not applicable.

[redacted]

10 APPENDIX

Table 10-1 Schedule of Study Procedures and Assessments

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screening / Baseline / Lens Fit	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 3 Dispense Lens 2**	**Visit 4 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled Visit**	**Early Exit**
Procedure/ Assessment		**Day 1 [3-5 days after Visit 1** [redacted]	**Day 30 (-2/+1) Days**	**Day 1 [same day as Lens 1 Day 30 Follow-up visit]**	**Day 30 (-2/+1) Days**	**N/A**	**N/A**
Informed Consent	X						
Demographics	X						
Medical History∞	X	X	X		X	X	X
Concomitant Medications∞	X	X	X		X	X	X
Habitual lens information (brand, power, lens solution*)	X						
VA with habitual correction (OD, OS, Snellen distance)*	X				X	(X)	X
Keratometry (OD, OS)*	X						

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screening / Baseline / Lens Fit	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 3 Dispense Lens 2**	**Visit 4 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled Visit**	**Early Exit**
Procedure/ Assessment		**Day 1 [3-5 days after Visit 1 [redacted]**	**Day 30 (-2/+1) Days**	**Day 1 [same day as Lens 1 Day 30 Follow-up visit]**	**Day 30 (-2/+1) Days**	**N/A**	**N/A**
Manifest refraction*	X	(X)	(X)	(X)	(X)	(X)	(X)
BCVA (OD, OS, Snellen distance with manifest refraction)*	X	(X)	(X)	(X)	(X)	(X)	(X)
Biomicroscopy	X	X	X		X	X *Optional with Unplanned Lens Replacement only*	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion/Exclusion criteria	X						
Randomize	X						
Study lens parameters optimization and fitting per randomization scheme (Test and Comparator)*	X						
[redacted]	[redacted]						

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screening / Baseline / Lens Fit	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 3 Dispense Lens 2**	**Visit 4 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled Visit**	**Early Exit**
Procedure/ Assessment		**Day 1 [3-5 days after Visit 1 [redacted]**	**Day 30 (-2/+1) Days**	**Day 1 [same day as Lens 1 Day 30 Follow-up visit]**	**Day 30 (-2/+1) Days**	**N/A**	**N/A**
[redacted]							
Study lens power to be dispensed	X						
[redacted]	[redacted]						
Dispense study lenses per randomization scheme		X		X		(X)	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LogMAR HC/HI VA at: • Distance (4 m or 3 m; [redacted] OU)		X	X	X	X	(X)	X

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screening / Baseline / Lens Fit	Visit 2 Dispense Lens 1	Visit 3 Day 30 Follow-up Lens 1	Visit 3 Dispense Lens 2	Visit 4 Day 30 Follow-up Lens 2 / Exit	Unscheduled Visit	Early Exit
Procedure/ Assessment		Day 1 [3-5 days after Visit 1 [redacted]	Day 30 (-2/+1) Days	Day 1 [same day as Lens 1 Day 30 Follow-up visit]	Day 30 (-2/+1) Days	N/A	N/A
[redacted]							
[redacted]		■	■	■	■		■
[redacted]		■	■	■	■		■
[redacted]		■		■			
[redacted]			■		■		■
[redacted]			■		■		■
[redacted]			■		■		(X)

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screening / Baseline / Lens Fit	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 3 Dispense Lens 2**	**Visit 4 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled Visit**	**Early Exit**
Procedure/ Assessment		**Day 1 [3-5 days after Visit 1** [redacted]	**Day 30 (-2/+1) Days**	**Day 1 [same day as Lens 1 Day 30 Follow-up visit]**	**Day 30 (-2/+1) Days**	**N/A**	**N/A**
[redacted]							
[redacted]			[redacted]		[redacted]		[redacted]
[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	
Adverse Events	X	X	X	X	X	X	X
Device deficiencies	X	X	X	X	X	X	X
Exit Form	(X)	(X)	(X)	(X)	X		X

(X) assessment performed as necessary, e.g., decrease of VA by 2 lines or more with investigational product (IP), for example when comparing between V3 and V2 for Distance VA with Lens 1 and between V4 and V3 for Distance VA with Lens 2.

* Source only (source provided to sponsor upon request).

∞ Concomitant medications (past 30 days) and Medical History (past year) must be fully documented and collected in the subject source documents with targeted collection in EDC.