Alcon

Statistical Analysis Plan for CLY935-C019 / NCT04980456
Title: Clinical Assessment of Two Daily Wear Monthly Replacement Soft Silicone Hydrogel Contact Lenses

[redacted]

This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

Executive Summary:

Key Objectives:

The primary objective of this study is to demonstrate noninferiority (NI) in visual acuity (VA) at distance when wearing [redacted] contact lenses [redacted] compared to CooperVision® Biofinity® soft contact lenses (Biofinity).

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in distance VA with [redacted] when compared to Biofinity, using a margin of 0.05.

Table of Contents

[redacted]

[redacted]

List of Tables

List of Figures

[redacted]

1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate noninferiority in visual acuity at distance when wearing [redacted] contact lenses compared to Biofinity contact lenses.

[redacted]

1.2 Study Description

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

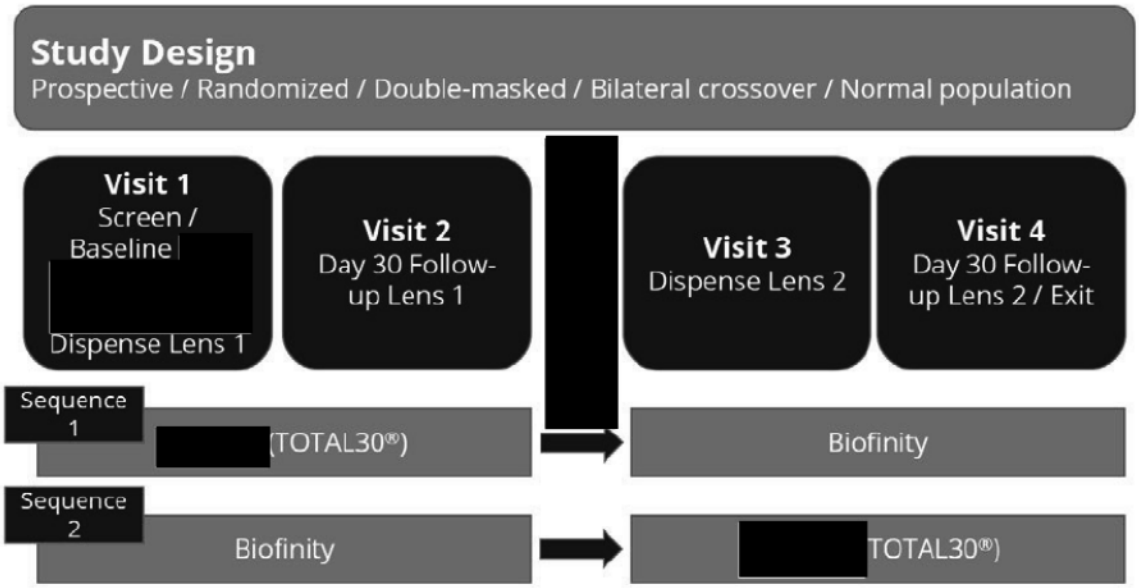
Table 1-1 Study Description Summary

Study Design	Prospective, randomized, controlled, double-masked, bilateral crossover
Study Population	Volunteer subjects aged 18 or older who are habitual weekly/monthly spherical soft contact lens wearers (with the exception of habitual Biofinity wearers), have at least 3 months of contact lens wearing experience, who wear their habitual lenses at least 5 days per week and at least 10 hours per day, [redacted] Target to complete: 232 Planned to enroll: ~260
Number of Sites	12-16 US
Test Product	[redacted] soft contact lenses [redacted]
Comparator Product	CooperVision® Biofinity® soft contact lenses (Biofinity)
Planned Duration of Exposure	~60 days total duration (test and comparator): Test Product: 30 days (± 2 days) Comparator Product: 30 days (± 2 days)

Visits	Pre-Screening Visit 1: Screen/Baseline/[redacted]Dispense Lens 1 (Day 1) Visit 2: Day 30 Follow-up Lens 1 (Day 30 ± 2 days) Visit 3: Dispense Lens 2 (Day 1 after Washout¥) Visit 4: Day 30 Follow-up Lens 2/Exit (Day 30 ± 2 days) [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 as follows:

Sequence	EDC/randomization integration system	Lens Name

Sequence 1	[redacted]/Biofinity	[redacted]/Biofinity
Sequence 2	Biofinity/[redacted]	Biofinity/[redacted]

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]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

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] effectiveness endpoint [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] analyses.

[redacted]

4.1 Effectiveness Endpoints

Primary Effectiveness Endpoint

The primary endpoint is distance VA with study lenses, collected for each eye in logMAR.

[redacted]

[redacted]

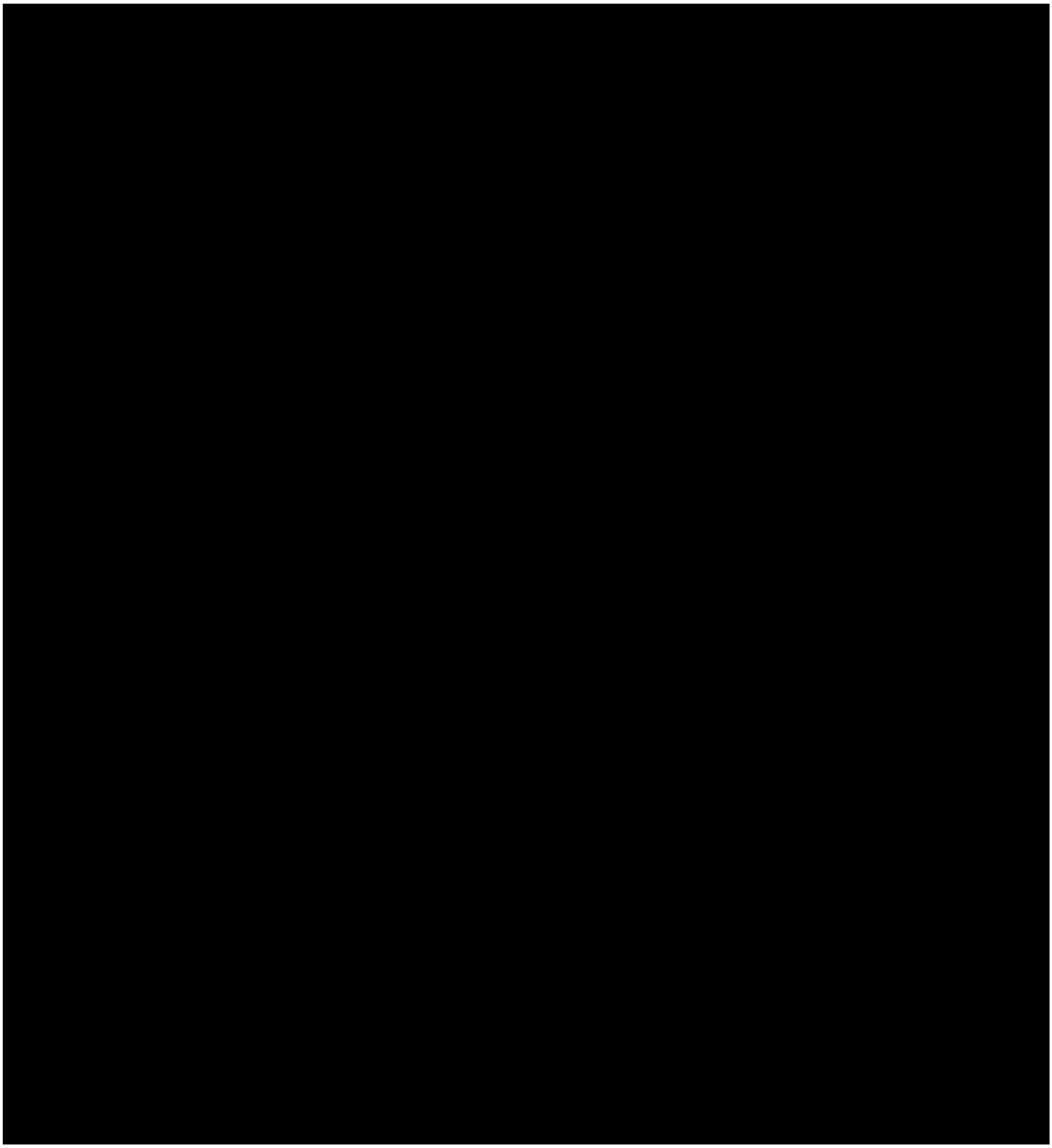
4.2 Effectiveness Hypotheses

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 VA for Phoenix and Biofinity, respectively, on the logMAR scale.



4.3 Statistical Methods for Effectiveness Analyses

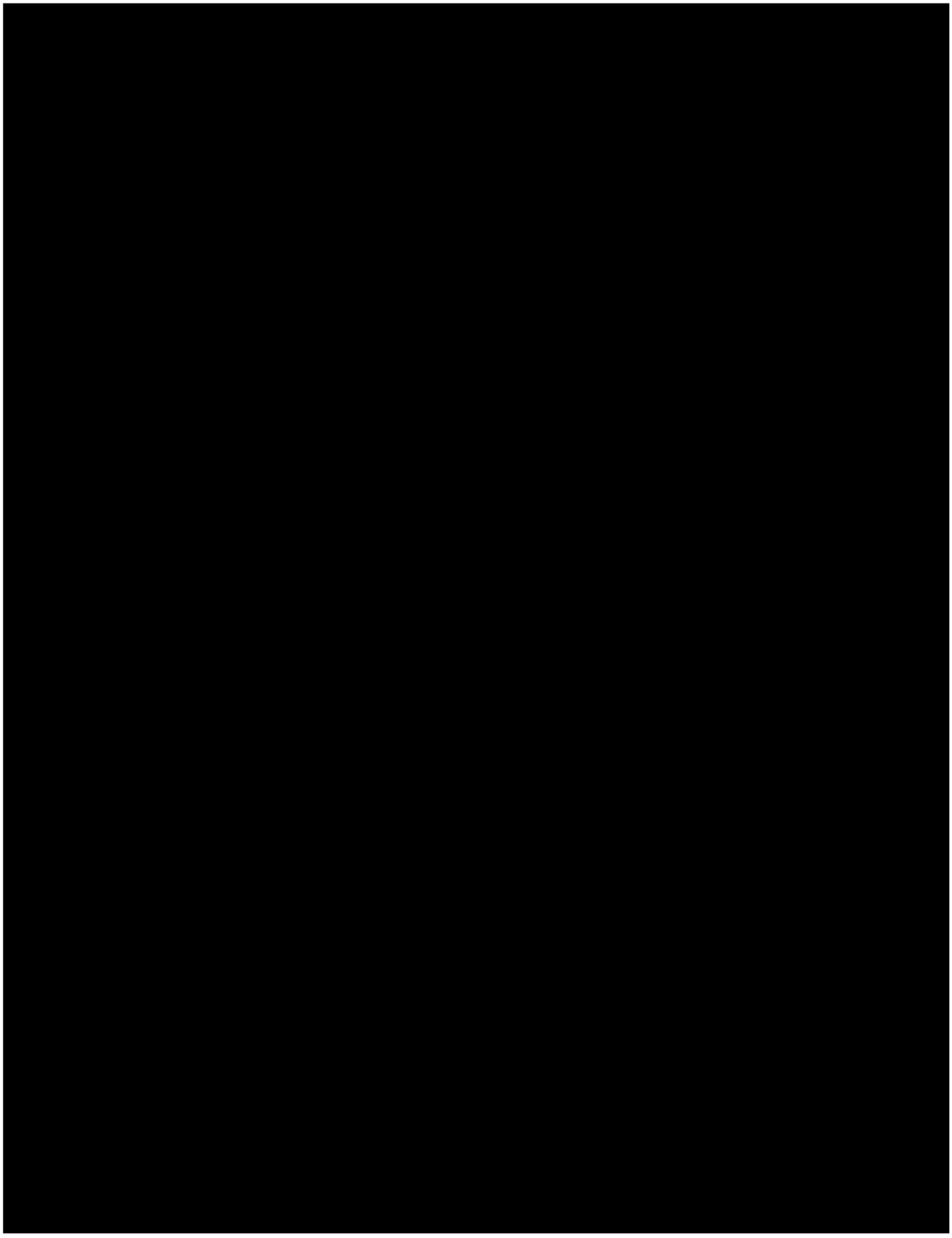
4.3.1 Primary Effectiveness Analysis

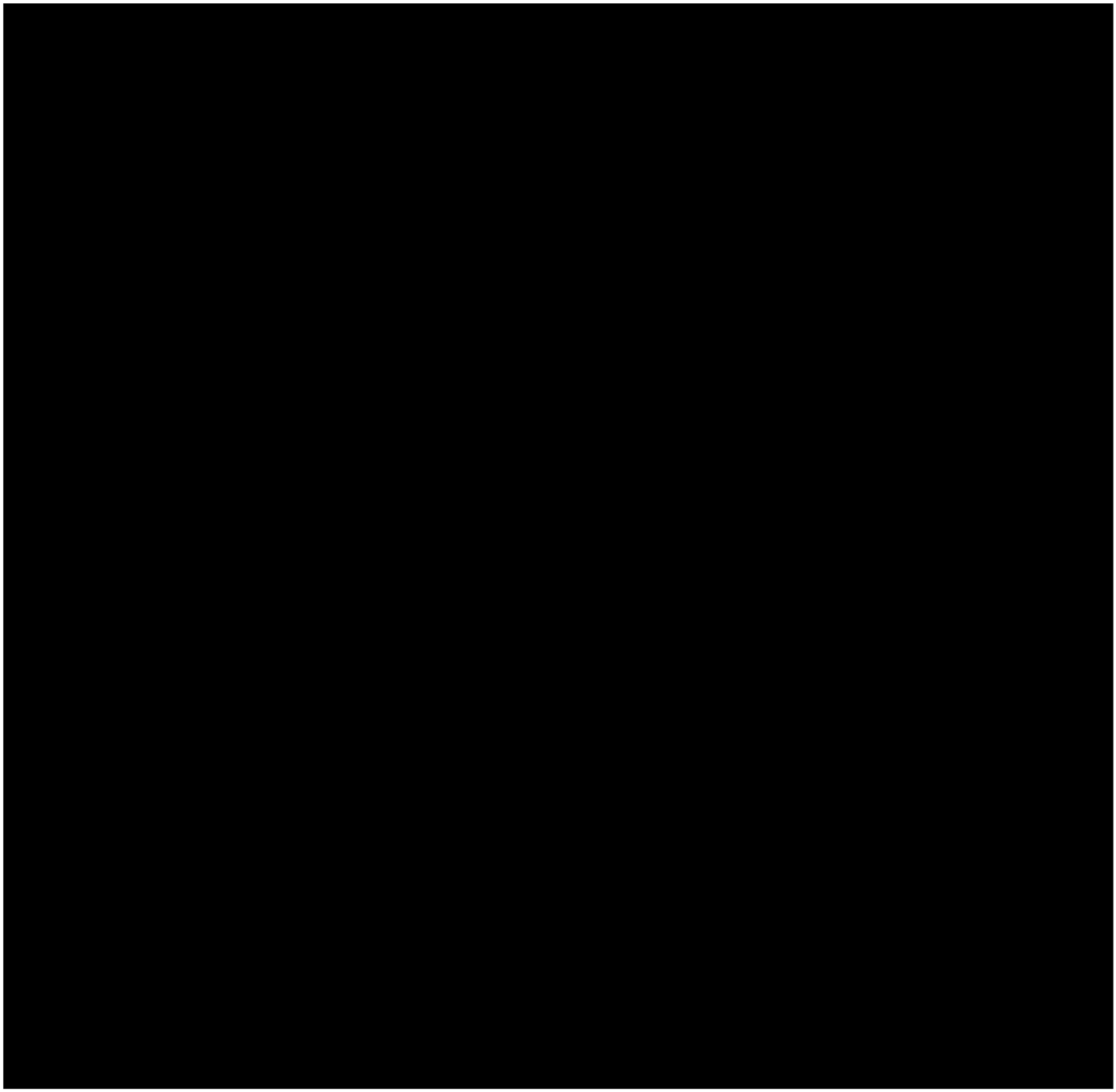
A mixed effects repeated measures model will be utilized to test these hypotheses. The model will include terms for lens, visit, lens by visit interaction, period, and sequence. Within-

subject correlation due to eye and the crossover design will also be accounted for in the model. Lens difference ([redacted] minus Biofinity) and the corresponding one-sided 95% upper confidence limit will be computed. Noninferiority in distance VA will be declared if upper confidence limit is less than 0.05.

[redacted]

[redacted]





4.6 Interim Analysis for Effectiveness

No interim analysis is planned for the effectiveness endpoints.

5 SAFETY ANALYSIS STRATEGY

The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters. Therefore, no inferential testing will be done for the safety analysis.

5.1 Safety Endpoints

The safety endpoints are

- Adverse events (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 1 for Period 1 and Visit 3 for Period 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 when a subject exits the study will be accounted for in the reporting.

Analysis and presentation of pre-treatment AEs 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 lenses. A between-treatment AE is an event that occurs after exposure to Period 1 lenses but prior to exposure of Period 2 lenses. The period for treatment-emergent AE analysis starts from exposure to study lenses for Period 1 or Period 2 until the subject completes the respective period or is discontinued from the study.

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 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
- Listing of All Ocular Between-Treatment Adverse Events
- Listing of All Nonocular Between-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 Increased Severity by 1 Grade in Biomicroscopy Findings [This listing will include all relevant visits within the crossover period]
- Listing of Subjects With Increased Severity by 2 or More Grades in Biomicroscopy Findings [This listing will include all relevant visits within the crossover period]
- Listing of Subjects with Infiltrates

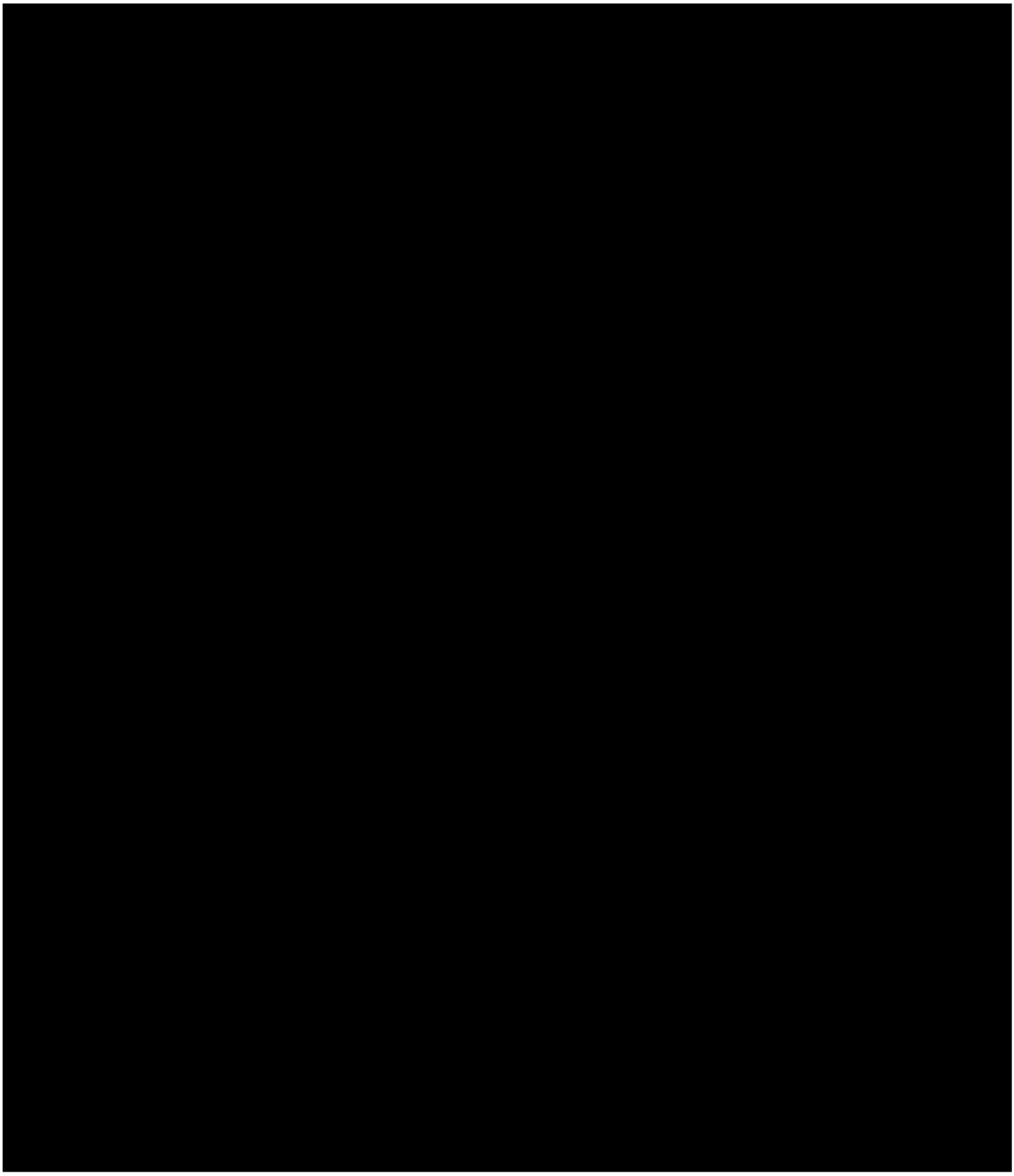
5.3.3 Device Deficiencies

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

6 ANALYSIS STRATEGY FOR OTHER ENDPOINTS

Not Applicable



[redacted]

8 REFERENCES

Not applicable

9 REVISION HISTORY

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

10 APPENDIX

Table 10-1 Overview of Study Plan

Procedure/ Assessment	Prescreening	Lens 1 (Period 1)		[redacted]	Lens 2 (Period 2)		Early Exit	USV
		Visit 1 Screen/ Baseline/ [redacted] Dispense Lens 1 [Day 1]	Visit 2 Follow-up Lens 1 [Day 30 ± 2 days]		Visit 3 Dispense Lens 2 [Day 1]	Visit 4 Follow-up Lens 2 / Exit [Day 30 ± 2 days]		
Informed Consent		X						
Demographics		X						
Medical History¥		X	X		X	X	X	X
Concomitant Medications¥		X	X		X	X	X	X
Pregnancy		X	X		X	X	X	X
Inclusion/ Exclusion		X						
Habitual (lens brand, lens power*, lens care)		X						
VA w/ habitual correction* (OD, OS, Snellen distance)		X				X	X	(X)
Manifest Refraction and BCVA with manifest refraction* (OD, OS, Snellen distance)		X	(X)		(X)	(X)	(X)	(X)
Biomicroscopy		X	X		X	X	X	(X)
[redacted]	[redacted]	[redacted]						
[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Randomization and record lens power*		X						
Dispense study lenses		X			X			(X)
VA w/ study lenses (OD, OS, logMAR distance)		X	X		X	X	X	(X)

Procedure/ Assessment	Prescreening	Lens 1 (Period 1)			Lens 2 (Period 2)			
		Visit 1 Screen/ Baseline/ [redacted] Dispense Lens 1	Visit 2 Follow-up Lens 1 [Day 30 ± 2 days]	[redacted]	Visit 3 Dispense Lens 2 [Day 1]	Visit 4 Follow-up Lens 2 / Exit [Day 30 ± 2 days]	Early Exit	USV
[redacted]								

Procedure/ Assessment	Prescreening	Lens 1 (Period 1)		[redacted]	Lens 2 (Period 2)		Early Exit	USV
		Visit 1 Screen/ Baseline/ [redacted] Dispense Lens 1 [Day 1]	Visit 2 Follow-up Lens 1 [Day 30 ± 2 days]		Visit 3 Dispense Lens 2 [Day 1]	Visit 4 Follow-up Lens 2 / Exit [Day 30 ± 2 days]		
[redacted]								
Collect worn lenses*β			X			X	X	(X)
AEs§		X	X		X	X	X	X
Device deficiencies		X	X		X	X	X	X
Exit Form						X	X	

USV = Unscheduled visit; [redacted]

[redacted]

Signature Page for V-CLN-0013475 v1.0