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

STUDY ID:

CLR624-C001

STATISTICAL ANALYSIS PLAN,

JULY 03, 2024

NCT06461455

Alcon

Statistical Analysis Plan (US) for CLR624-C001

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

Executive Summary:

Key Objectives:

The primary objective of this study is to demonstrate noninferiority (NI) in visual acuity (VA) at distance when wearing TOTAL30™ Multifocal for Astigmatism (T30 MFfA) lenses compared to ULTRA® Multifocal for Astigmatism (ULTRA MFfA) lenses, after 30 days of wear (Day 30).

[redacted]

Decision Criteria for Study Success:

Success of this study will be based on demonstration of NI in VA with T30 MFfA contact lenses when compared to ULTRA MFfA contact lenses, at Day 30, using a margin of 0.05 on the logMAR scale [redacted]

Table of Contents

[redacted]

List of Tables

[redacted]

1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate NI in VA at distance when wearing T30 MFfA lenses compared to ULTRA MFfA lenses, after 30 days of wear (Day 30).

[redacted]

SAFETY OBJECTIVE

The safety objective of this study is to describe the safety profile of the study products.

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 lenses)
Study Population	• Age and habitual wear consideration: The subject population consists of volunteer subjects aged ≥ 40 years, who are habitual biweekly/monthly replacement soft multifocal or multifocal toric contact lens wearers for at least the past 3 months and who wear their habitual lenses at least 5 days per week for at least 8 hours per day. [redacted]

	[redacted] Target to complete: 74 Planned to enroll: ~82
Number of Sites	~8 US
Test Product	TOTAL30™ Multifocal for Astigmatism (T30 MFfA; lehfilcon A; LID230451)
Comparator Product	ULTRA® Multifocal for Astigmatism (ULTRA MFfA; samfilcon A)
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/Fit Visit 2: Dispense Lens 1 [2-3* days (at least 48 hours) after the end of Visit 1] Visit 3: Day 30 Follow-up Lens 1 [Day 30 (-2/+1 days)] Visit 4: Dispense Lens 2 [2-3* days (at least 48 hours) after the end of Visit 3] Visit 5: Day 30 Follow-up Lens 2/Exit [Day 30 (-2/+1 days)] **Washout period with habitual spectacles only after Visit 1 and after Visit 3*

A study design schematic is depicted in Figure 1-1.

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 lens sequence assignment. Randomization will be implemented in the Electronic Data Capture (EDC)/randomization integration system.

1.4 Masking

This study is double-masked (study lenses).

[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 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 pretreatment.

For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study lenses exposed in the corresponding study 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, except for lenses used at Visit 1 for lens fitting.

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 Data Evaluability Plan (DEP).

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

[redacted]

The following tables will be presented:

- Subject Disposition by Lens Sequence
- Subject Disposition by Study Lens Sequence
- Analysis Sets by Study Lens
- Analysis Sets by Study Lens Sequence
- Subject Accounting by Lens
- Subject Accounting by Study Lens Sequence
- Demographics by Lens Sequence
- Demographics by Study Lens Sequence
- Baseline Characteristics by Study Lens Sequence [redacted]

Subject accounting and demographics 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 effectiveness endpoint, [redacted] effectiveness evaluations will use the FAS as the primary analysis set. [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum, as well as confidence intervals (CIs) or confidence limits (CLs) where 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 effectiveness analyses.

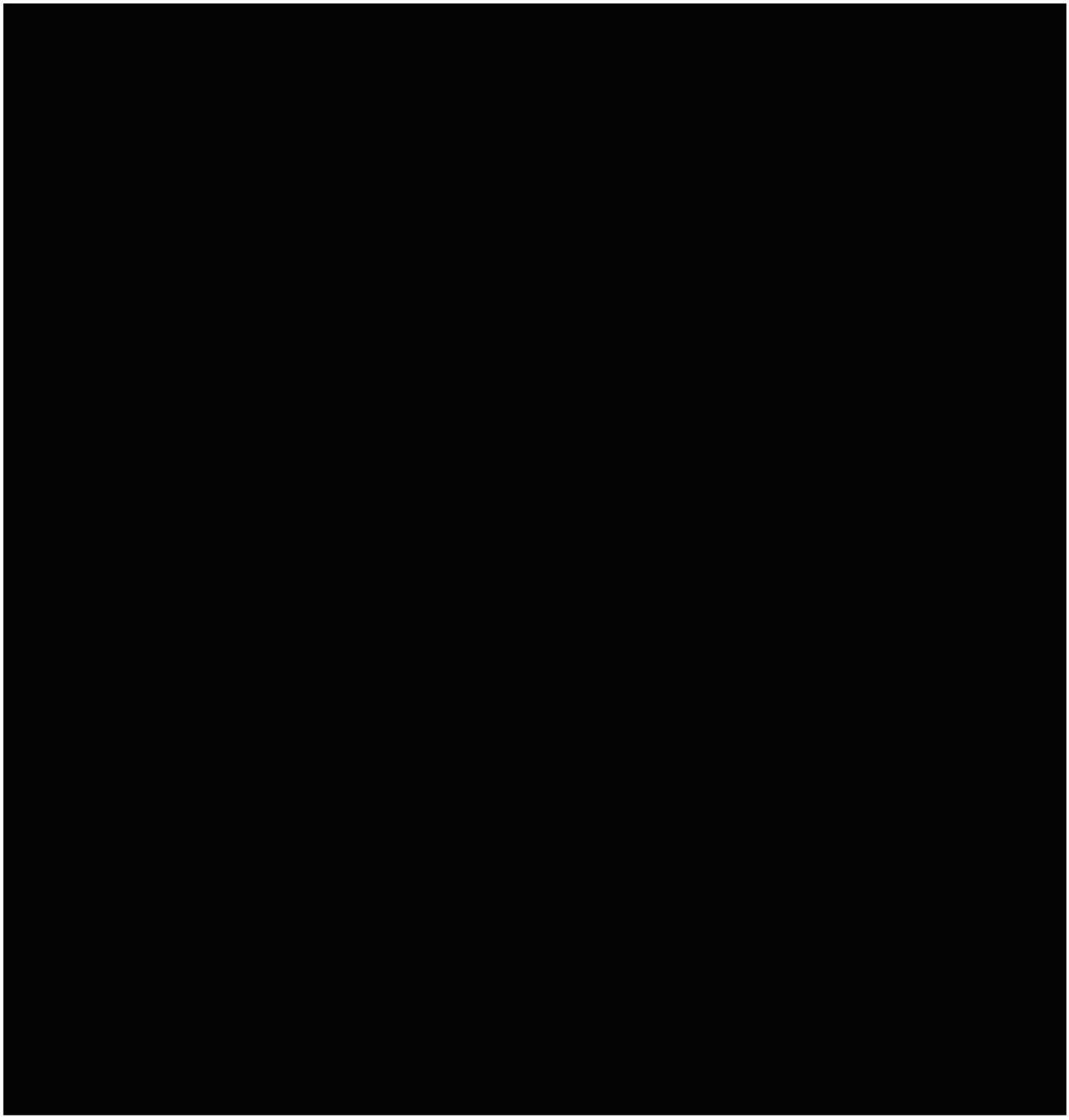
[redacted]

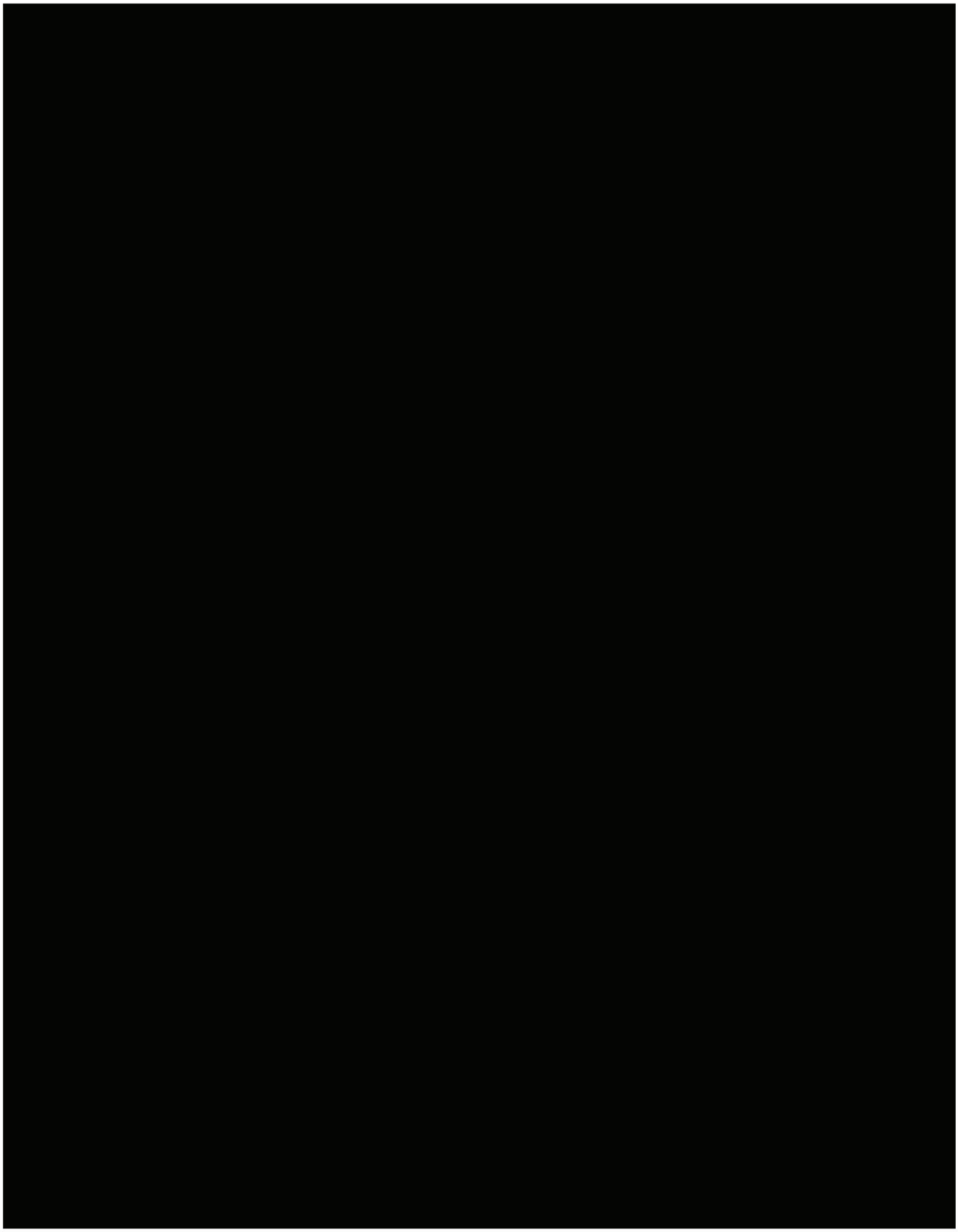
A listing of select effectiveness data will also be provided.

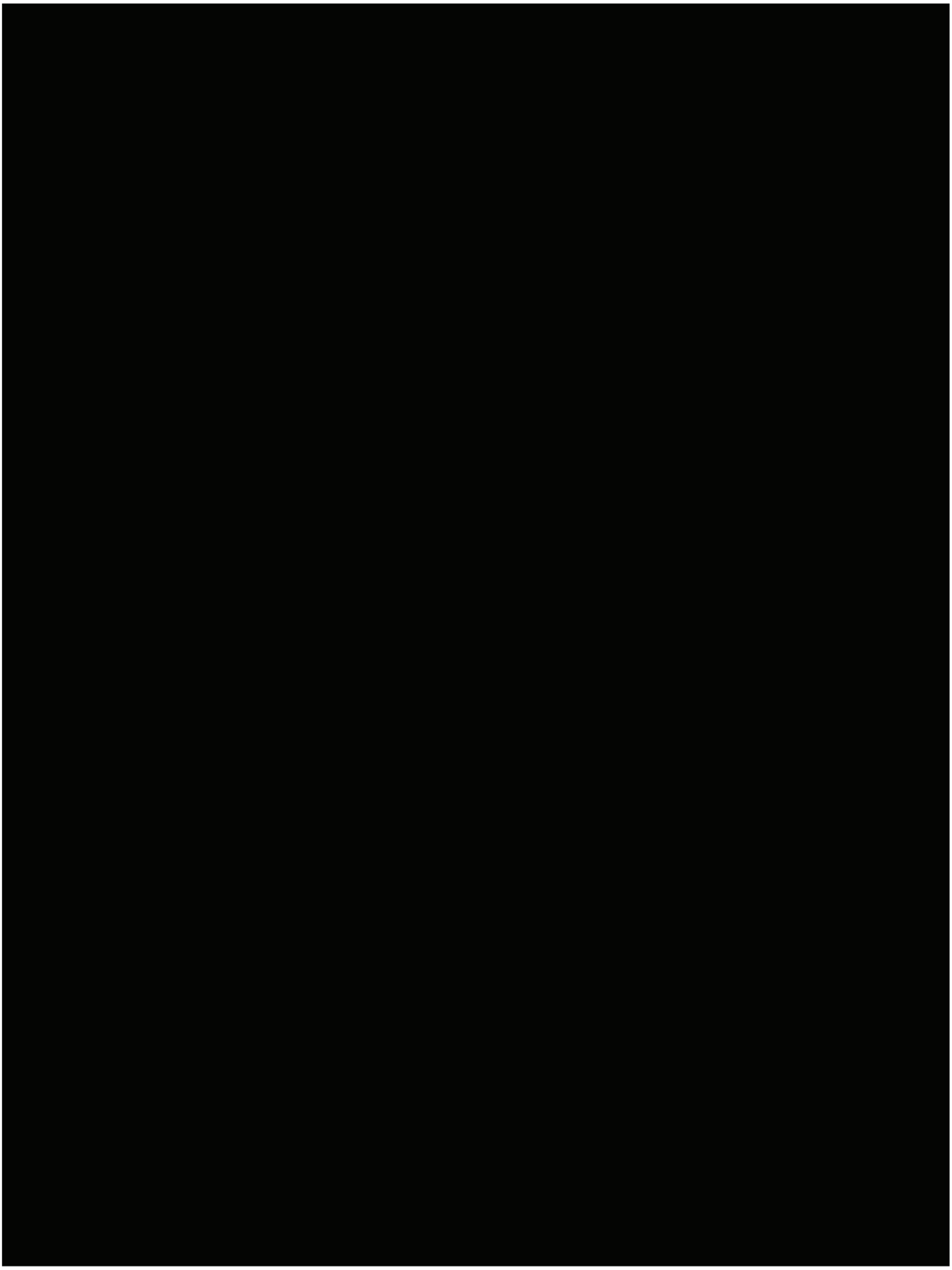
4.1 Effectiveness Endpoints

Primary Effectiveness Endpoint

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







[redacted]

4.2 Effectiveness Hypotheses

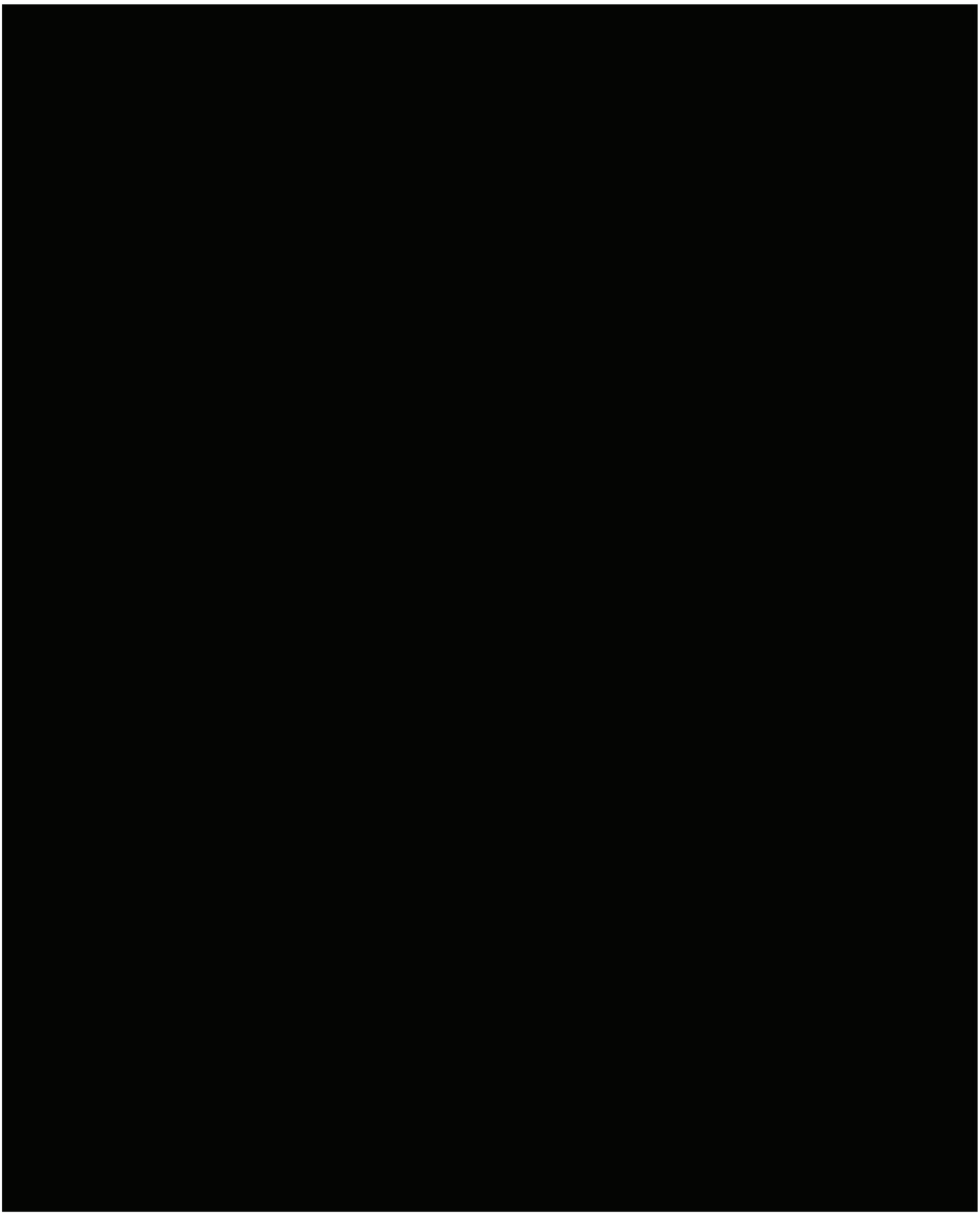
Primary Effectiveness

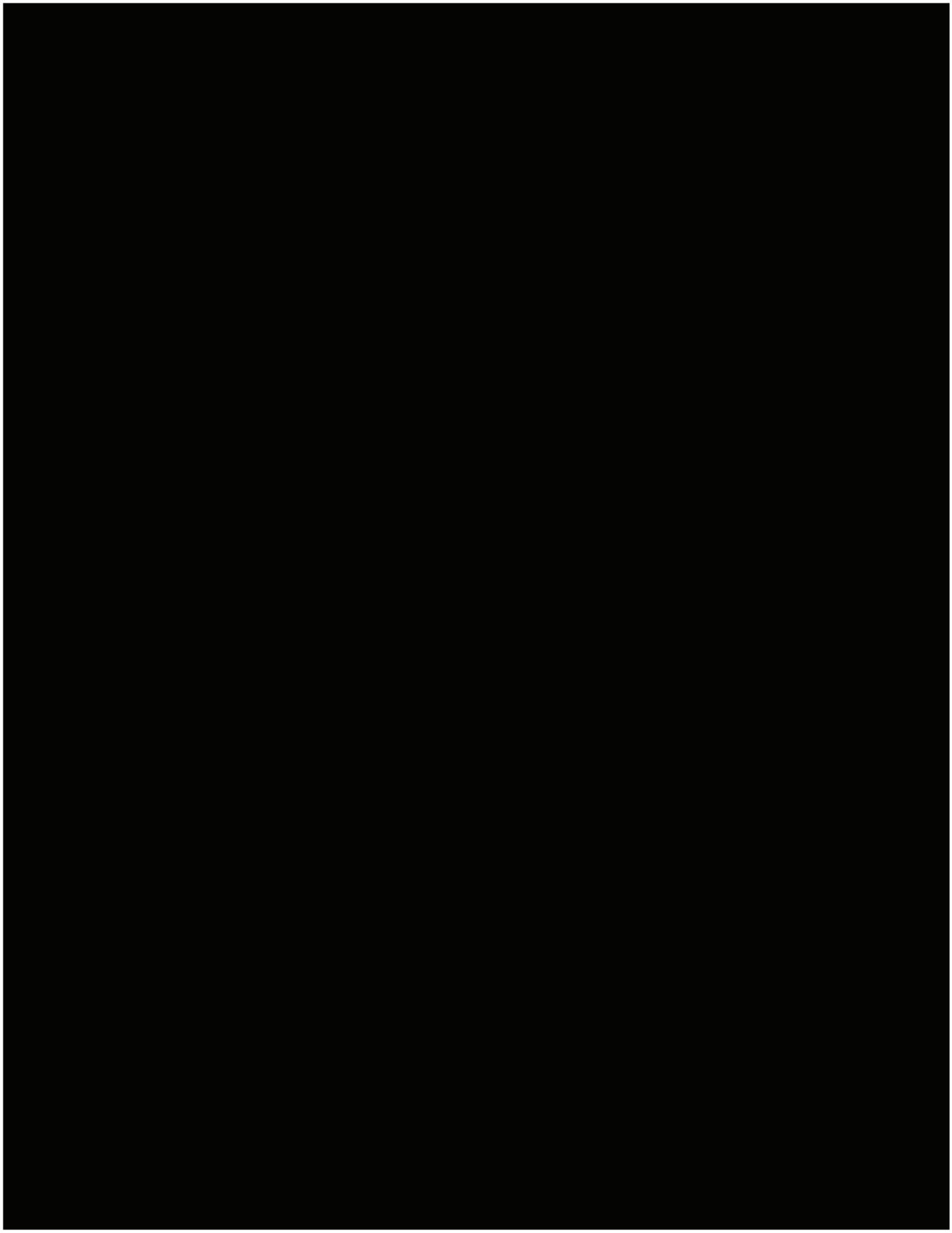
The null and alternative hypotheses are formulated in terms of the predefined margin of 0.05 for NI:

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 T30 MFfA and ULTRA MFfA, respectively, in logMAR scale.

[redacted]





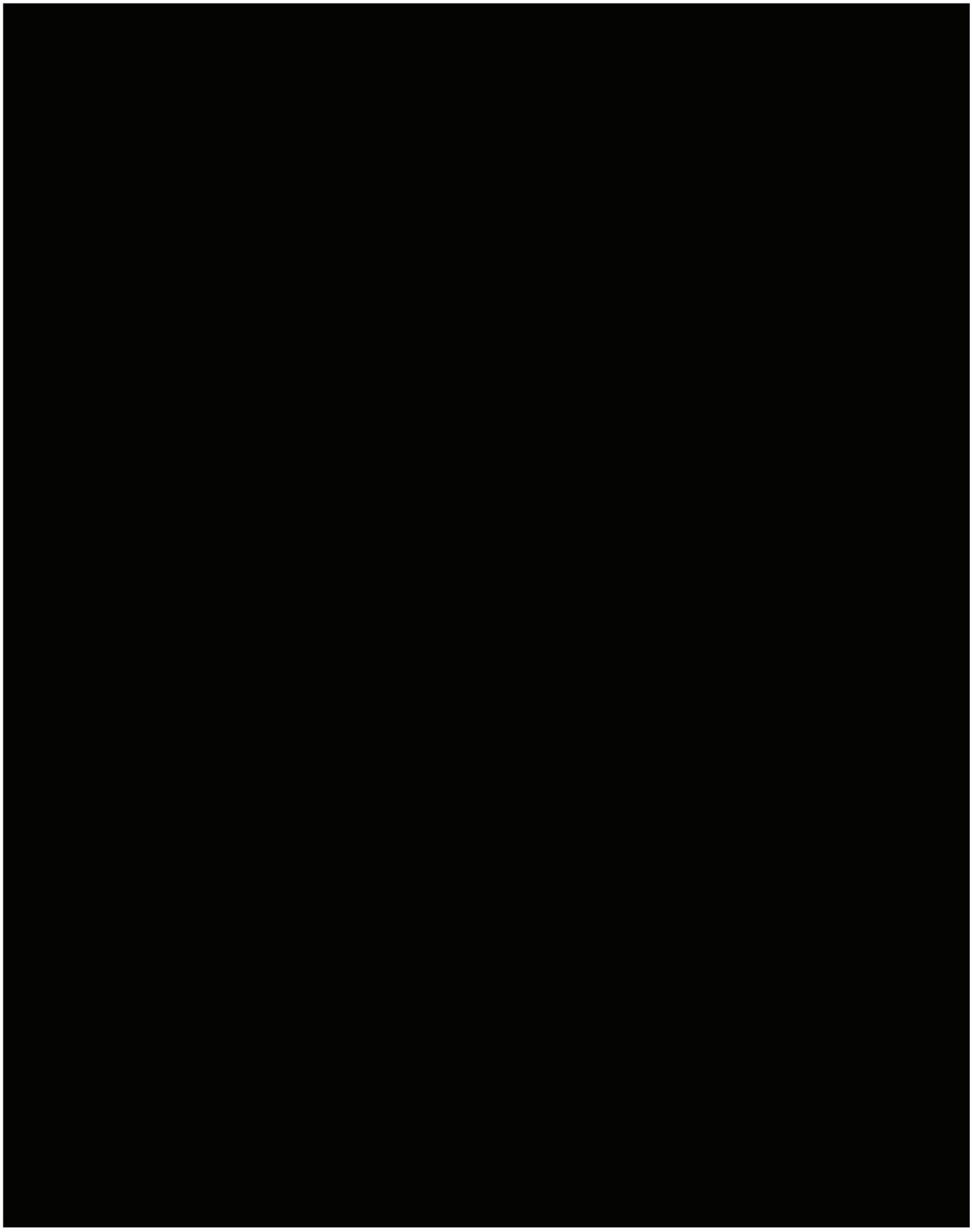
[redacted]

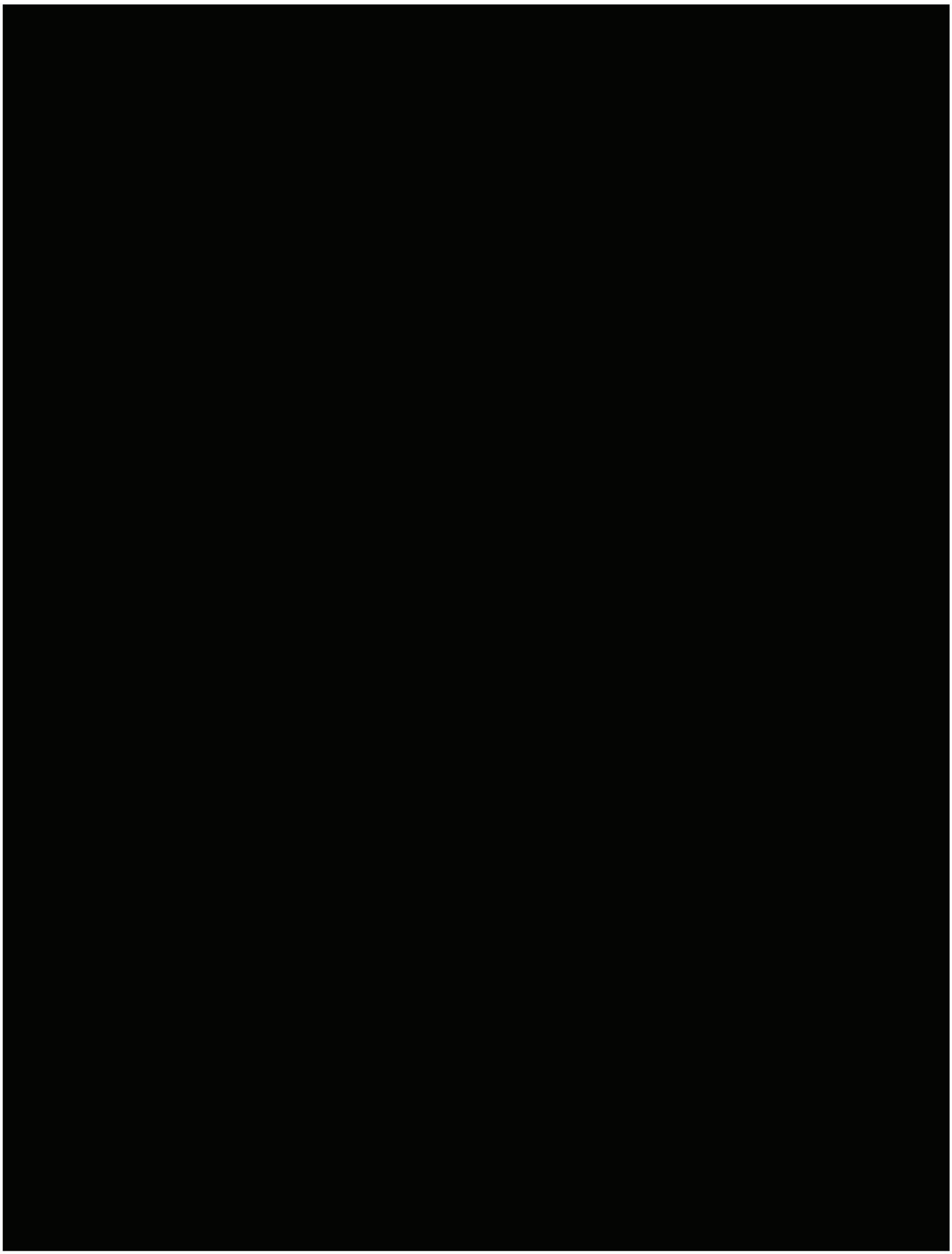
4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analysis

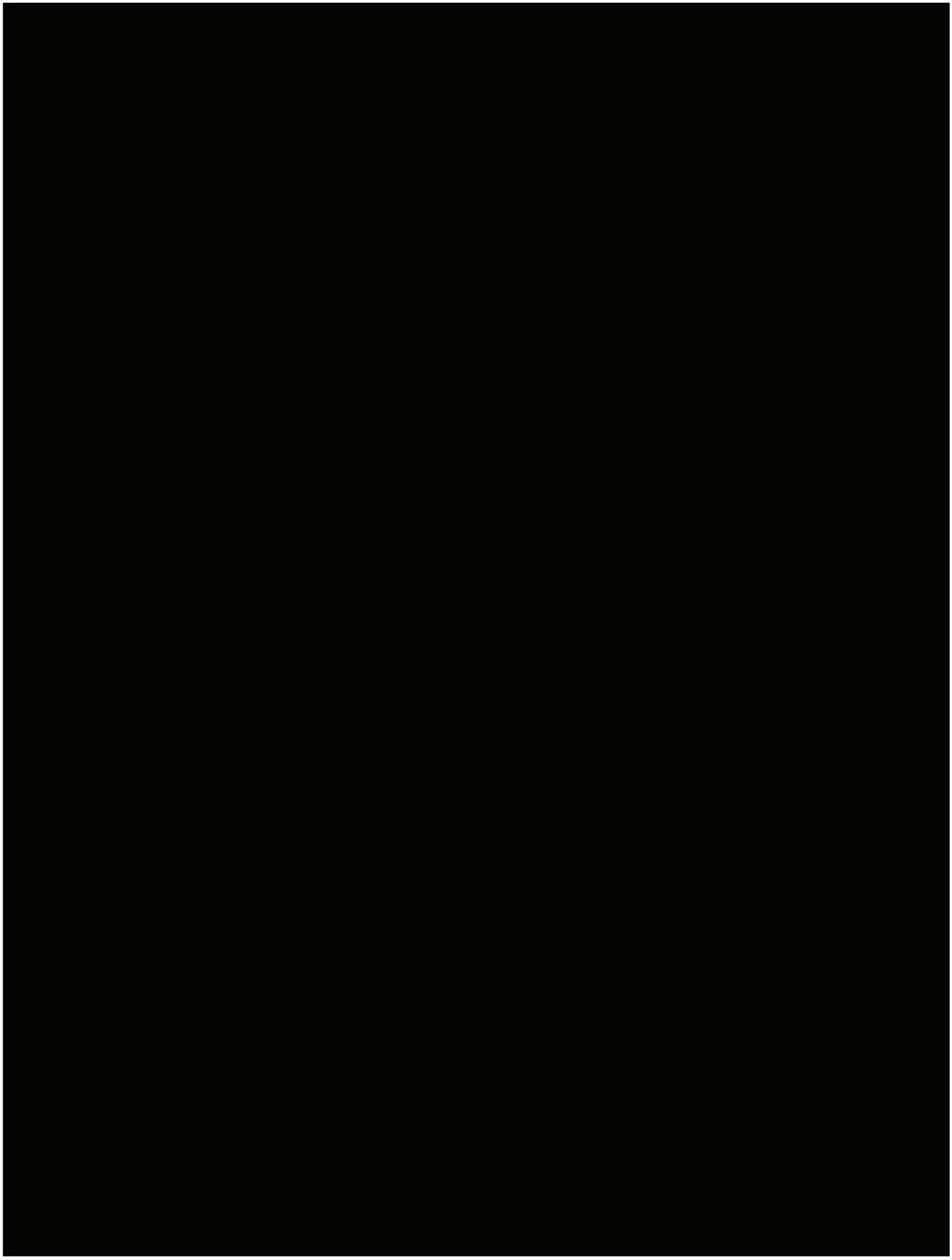
A mixed effects repeated measures model will be utilized to test these hypotheses. The model will include terms for lens, visit, lens-by-visit interaction, period, and study lens sequence. Within-subject correlation due to crossover will also be accounted for in the model. Lens difference (T30 MFfA minus ULTRA MFfA) and the corresponding one-sided 95% upper confidence limit (UCL) at Day 30 will be computed. Noninferiority will be declared if the UCL is less than 0.05.

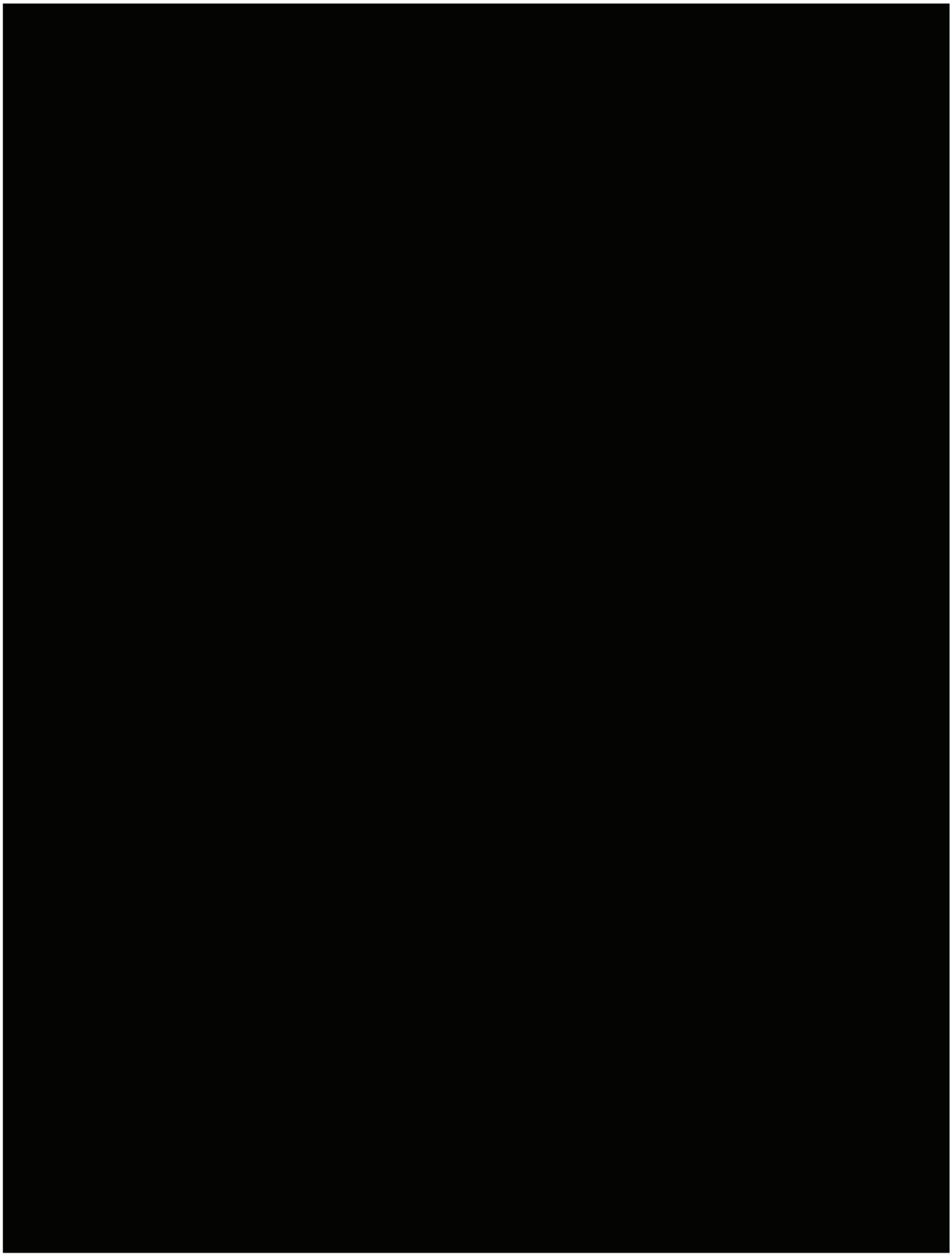
[redacted]





[redacted]





[redacted]

4.6 Interim Analysis for Effectiveness

No interim analysis is planned for 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

- AE
- Biomicroscopy Findings
    - 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 for Period 1 and Visit 4 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 the time of their study exit will be accounted for in the reporting.

Presentation of AEs will be separated into pre-treatment AEs, between-treatment AEs, and treatment-emergent AEs as defined below:

- Pretreatment: an event that occurs after signing informed consent but prior to exposure to study lenses
- Between-treatment: an event that occurs one day after last exposure to Period 1 study lenses but prior to exposure to Period 2 study lenses
- Treatment-emergent: an event that occurs from exposure to Period 1 study lenses until subject exits from the study, excluding those classified as between-treatment

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 All 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 Pretreatment Adverse Events
- Listing of All Nonocular Pretreatment 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 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
- Listing of Between-Treatment Device Deficiencies

7 SAMPLE SIZE AND POWER CALCULATIONS

Sample size calculation is based on a prior feasibility clinical study [redacted]

[redacted]

8 REFERENCES

Not applicable.

9 REVISION HISTORY

This is the original (Version 1.0) Statistical Analysis Plan for this study [redacted]

10 APPENDIX

Table 10-1 Schedule of Study Procedures and Assessments

	[redacted]	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
	Visit 1 Screening/ Baseline/ Fit	Visit 2 Dispense Lens 1	Visit 3 Day 30 Follow-up Lens 1	Visit 4 Dispense Lens 2	Visit 5 Day 30 Follow-up Lens 2 / Exit		
Procedure		**Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)**	**Day 30 (-2/+1 days)**	**Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)**	**Day 30 (-2/+1 days)**		
Informed consent	X						
Demographics	X						
Medical history∞	X	X	X	X	X	X	X
Concomitant medications∞	X	X	X	X	X	X	X
Habitual lens information (brand, power*, lens care*)	X						
[redacted]	[redacted]						
VA with habitual spectacles correction (OD, OS,	X				X	(X)	X

	[redacted]	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
	Visit 1 Screening/ Baseline/ Fit	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 4 Dispense Lens 2**	**Visit 5 Day 30 Follow-up Lens 2 / Exit**		
Procedure		**Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)**	**Day 30 (-2/+1 days)**	**Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)**	**Day 30 (-2/+1 days)**		
Snellen distance)*							
Keratometry (OD, OS)	X						
Autorefractometry (OD, OS, uncorrected or with study lenses)	X uncorrected		X with study lenses		X with study lenses		X with study lenses
Manifest refraction	X	(X)	(X)	(X)	(X)	(X)	(X)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biomicroscopy	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X						
Randomization	X						

	[redacted]	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
	Visit 1 Screening/ Baseline/ Fit	Visit 2 Dispense Lens 1	Visit 3 Day 30 Follow-up Lens 1	Visit 4 Dispense Lens 2	Visit 5 Day 30 Follow-up Lens 2 / Exit		
Procedure		**Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)**	**Day 30 (-2/+1 days)**	**Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)**	**Day 30 (-2/+1 days)**		
[redacted]	[redacted]						
Determine and record study lens power (T30 MFfA, ULTRA MFfA)	X						
[redacted]	[redacted]						
Dispense study lenses per randomization*		X		X		(X)	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
	Visit 1 Screening/ Baseline/ Fit	Visit 2 Dispense Lens 1	Visit 3 Day 30 Follow-up Lens 1	Visit 4 Dispense Lens 2	Visit 5 Day 30 Follow-up Lens 2 / Exit		
Procedure		**Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)**	**Day 30 (-2/+1 days)**	**Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)**	**Day 30 (-2/+1 days)**		
[redacted]							
HC/HI VA (logMAR) with study lenses: • Distance (4 m; OD, OS, OU) [redacted]		X	X	X	X	(X)	X
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
	Visit 1 Screening/ Baseline/ Fit	Visit 2 Dispense Lens 1	Visit 3 Day 30 Follow-up Lens 1	Visit 4 Dispense Lens 2	Visit 5 Day 30 Follow-up Lens 2 / Exit		
Procedure		**Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)**	**Day 30 (-2/+1 days)**	**Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)**	**Day 30 (-2/+1 days)**		
			review)		review)		
[redacted]		■		■		■	
[redacted]			■		■	■	■
[redacted]		■		■			
[redacted]			■		■		■
[redacted]		■		■		■	

	[redacted]	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
	Visit 1 Screening/ Baseline/ Fit	Visit 2 Dispense Lens 1	Visit 3 Day 30 Follow-up Lens 1	Visit 4 Dispense Lens 2	Visit 5 Day 30 Follow-up Lens 2 / Exit		
Procedure		**Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)**	**Day 30 (-2/+1 days)**	**Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)**	**Day 30 (-2/+1 days)**		
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]	
Unplanned lens replacement with reason		(X)		(X)		(X)	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
	Visit 1 Screening/ Baseline/ Fit	Visit 2 Dispense Lens 1	Visit 3 Day 30 Follow-up Lens 1	Visit 4 Dispense Lens 2	Visit 5 Day 30 Follow-up Lens 2 / Exit		
Procedure		**Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)**	**Day 30 (-2/+1 days)**	**Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)**	**Day 30 (-2/+1 days)**		
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Collect worn lenses*			X		X	(X)	X
[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

[redacted]

∞ Concomitant medications and medical history must be fully documented and collected in the subject source documents with targeted collection in the EDC.

- [redacted]
- [redacted]