Clinical Evaluation of Overall Lens Fit of Delefilcon A Contact Lenses of Different Diameters and Base Curves

STUDY ID

CLU484-P007

STATISTICAL ANALYSIS PLAN VERSION 2.0

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Alcon

Statistical Analysis Plan for CLU484-P007

Title: Clinical Evaluation of Overall Lens Fit of Delefilcon A Contact Lenses of Different Diameters and Base Curves

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This version of the Statistical Analysis Plan is based on Version 4.0 of the study protocol.

Executive Summary:

Key Objective:

The primary objective of this study is to demonstrate noninferiority (NI) of LID023681 to LID006961, at Dispense and at 6 Hour Follow-up, in the proportions of optimal/acceptable lenses for lens fit assessments.

[redacted]

Decision Criteria for Study Success:

Success of this study will be based on demonstration of NI of LID023681 to LID006961, at Dispense and at 6 Hour Follow-up, using a margin of 0.05 for the proportions of optimal/acceptable lenses in all 3 lens fit assessments: lens movement at primary gaze, lens movement at peripheral gazes, and lens position.

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1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate NI of LID023681 to LID006961, at Dispense and at 6 Hour Follow-up, in the proportions of optimal/acceptable lenses for lens fit assessments.

[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.

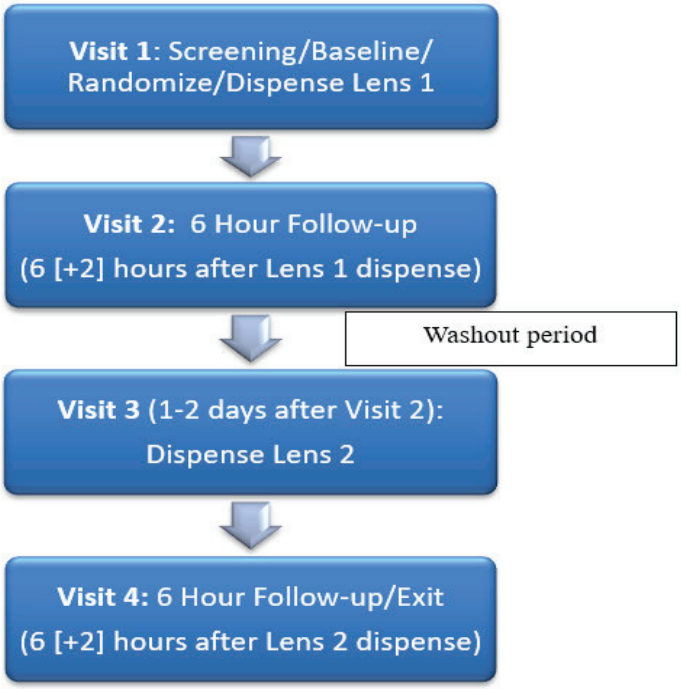
Table 1-1 Study Description Summary

Study Design	Prospective, randomized [redacted] bilateral, crossover, double-masked
Study Population	Volunteer subjects aged 18 or over who are habitual spherical soft contact lens wearers (including DAILIES TOTAL1® [DT1] habitual wearers), wear contact lenses a minimum of 6 hours a day, and with a manifest refraction between -2.00 and -4.00 D. [redacted] Target to complete: 175* Planned to enroll: ~270 [redacted]

Number of Sites	~16 US
Test Product(s)	Delefilcon A soft contact lens (delefilcon A; LID023681; base curve 8.8 mm; diameter 14.4 mm)
Comparator Product(s)	DAILIES TOTAL1® (DT1; delefilcon A; LID006961; base curve 8.5 mm; diameter 14.1 mm)
Planned Duration of Exposure	~2 days total duration (test and comparator) Test Product: 6 (+2) hours Comparator Product: 6 (+2) hours
Visits	Visit 1: Screening/Baseline/Dispense Lens 1 Visit 2: Follow-up Lens 1 (6 [+2] hours after Lens 1 dispense at Visit 1) Visit 3: Dispense Lens 2 (1-2 days after Visit 2) Visit 4: Follow-up Lens 2/Exit (6 [+2] hours after Lens 2 dispense at Visit 3) **Washout period (1-2 days) with habitual spectacles only between Visit 2 and Visit 3*

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.

A [redacted] randomization will be implemented for this study. [redacted]

[redacted]

Subjects will be randomized in a 1:1 ratio to receive treatment (lens) in 1 of the following crossover sequences:

Sequence 1: LID023681/LID006961

Sequence 2: LID006961/LID023681

1.4 Masking

This study is double-masked.

The following individuals associated with the study will be considered unmasked: unmasked study site coordinator(s), clinical operations lead, clinical site manager, clinical supplies coordinator, unmasked data manager(s), and randomization specialist.

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 Sets

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

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

Adverse events (AE) 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) will include all randomized subjects exposed to any study lens.

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

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 by Lens Sequence
- Baseline Characteristics by Lens Sequence (lens brand; lens power; lens solution; manifest refraction: sphere, cylinder, axis; Best Corrected Visual Acuity (BCVA); keratometry readings; [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 six primary effectiveness endpoints, [redacted]. All effectiveness evaluations will use the FAS as the primary analysis set. Supportive analyses of the primary effectiveness endpoints [redacted] will be conducted using the PP Analysis Set only if the number of subjects excluded from the PP Analysis Set exceeds 5% of the FAS.

All effectiveness analyses will be carried out based on the randomization assignment.

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 counts 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 effectiveness endpoints are:

- Proportion of lenses graded as Acceptably Tight, Optimal Fit, or Acceptably Loose at Dispense, in lens movement (overall lens fit) at primary gaze
- Proportion of lenses graded as Acceptably Tight, Optimal Fit, or Acceptably Loose at Dispense, in lens movement (overall lens fit) at peripheral gazes
- Proportion of lenses graded as Optimal Lens Centration or Acceptable Decentration at Dispense, in lens position (centration)

- Proportion of lenses graded as Acceptably Tight, Optimal Fit, or Acceptably Loose at 6 Hour Follow-up, in lens movement (overall fit) at primary gaze
- Proportion of lenses graded as Acceptably Tight, Optimal Fit, or Acceptably Loose at 6 Hour Follow-up, in lens movement (overall fit) at peripheral gazes
- Proportion of lenses graded as Optimal Lens Centration or Acceptable Decentration at 6 Hour Follow-up, in lens position (centration)

Table 4-1 Definition for the Primary Effectiveness Endpoints

i	Lens Fit Assessment	Graded as
1	Lens movement (overall fit) at primary gaze	Acceptably tight Optimal fit Acceptably loose
2	Lens movement (overall fit) at peripheral gazes	Acceptably tight Optimal fit Acceptably loose
3	Lens position (centration)	Optimal lens centration Acceptable decentration

- Back surface deposits (5-point scale)

4.2 Effectiveness Hypotheses

Primary Effectiveness

At each visit, proportion of lenses graded as indicated in Table 4-1 for each of the lens fit assessments (i) will be tested with the null and alternative hypotheses formulated in terms of the predefined margin of 0.05 for NI.

H_0: $P_i(T) - P_i(C) \leq -0.05$
H_a: $P_i(T) - P_i(C) > -0.05$

where i = 1, 2, 3, and Pi(T) and Pi(C) denote the proportion of lenses defined for LID023681 and LID006961, respectively.

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

For each eye, a binary variable will be defined to indicate 'success' if overall lens fit at primary gaze is graded as -1 (Acceptably Tight), 0 (Optimal), or 1 (Acceptably Loose), and 'failure' if graded as -2 (Unacceptably Tight) or 2 (Unacceptably Loose). Proportions of success will be analyzed using a generalized linear model with a logit link function, with terms for lens, period, sequence, visit, [redacted]

[redacted]

At each visit (Dispense, 6 Hour), a one-sided 95% lower confidence limit (LCL) will be calculated for the difference in proportions between the lenses (LID023681 minus LID006961). The null hypothesis will be rejected if the LCL > -0.05.

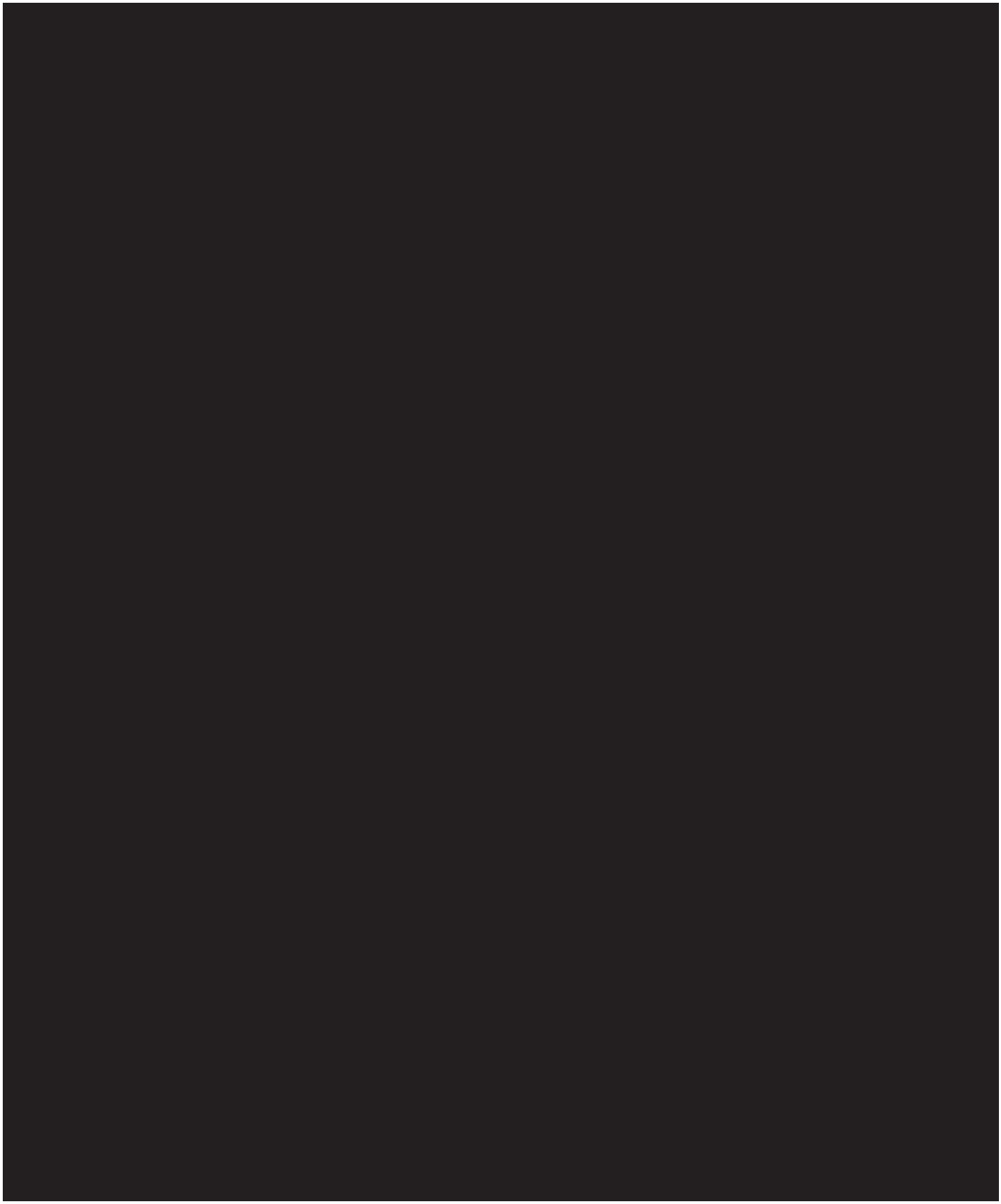
[redacted]

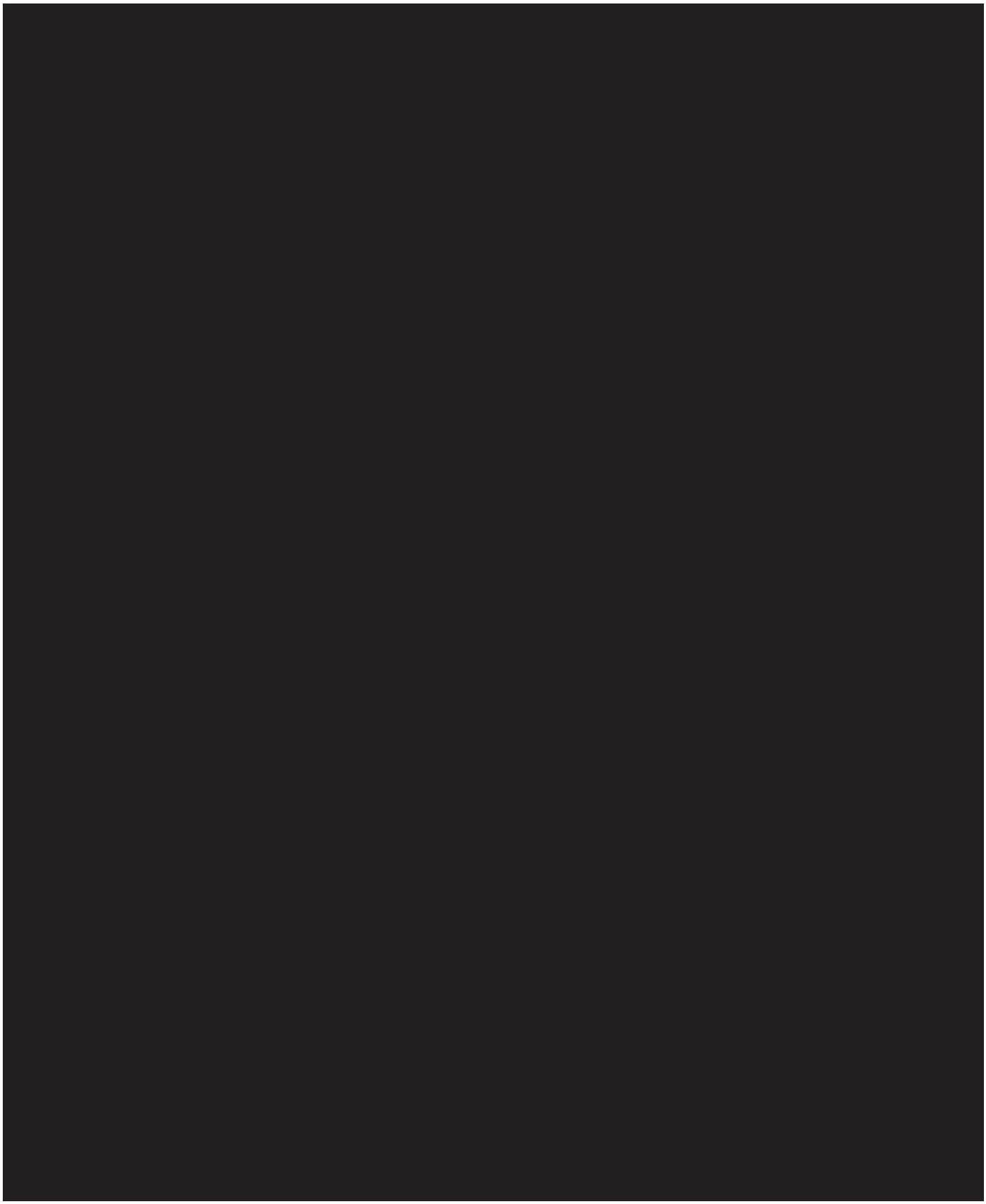
Crosstabulation summarizing overall lens fit of paired data (i.e., LID023681 vs. LID006961) will be displayed at each visit.

[redacted]

A similar statistical model and analysis method will be employed for lens movement at peripheral gazes and for lens position (with ‘success’ including lenses graded as 0 (Optimal Centration) or 1 (Acceptable Decentration)).

[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 AEs 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:

- AEs
- 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 1 for Period 1 and Visit 3 for Period 2. Safety variables will be summarized descriptively.

5.3.1 Adverse Event

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 pretreatment 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 Period 1 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

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

6 ANALYSIS STRATEGY FOR OTHER ENDPOINTS

A listing for unplanned lens replacement will also be provided.

7 SAMPLE SIZE AND POWER CALCULATIONS

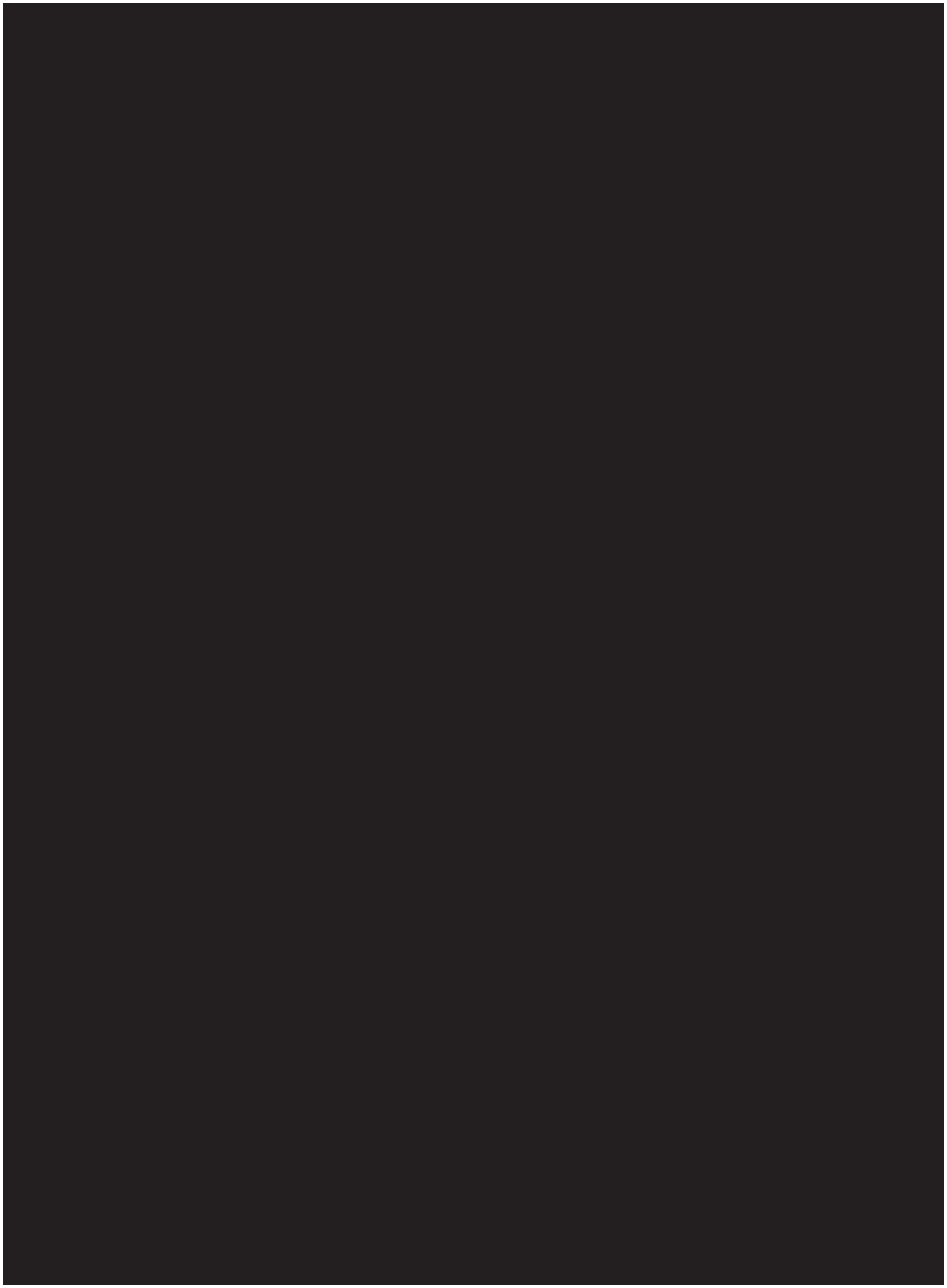
Sample size calculation is based on several base curve optimization studies with Alcon lens materials.

Primary Effectiveness Endpoints

With an assumed difference of 0 in the proportion of optimal or acceptable fits/decentration and 0.051 for proportion of discordant pairs, 90% power can be attained with a sample size of 175 in rejecting the null hypothesis of inferiority (margin = 0.05; one-sided α=0.05). Power increases to 93% and 96% with an increase in sample size of 200 and 250, respectively.

8 REFERENCES

Newcombe RG. Interval estimation for the difference between dependent proportions: comparison of methods. Statistics in Medicine. 1998;17(22):2635–2650.



10 APPENDIX

Table 10-1 Schedule of Study Procedures and Assessments

Visit	Lens 1 (Period 1)		Lens 2 (Period 2)			
	Visit 1 Screening / Baseline/Dispense Lens 1	Visit 2 Follow-up Lens 1	Visit 3 Dispense Lens 2	Visit 4 Follow–up Lens 2/Exit	Early Exit[#]	Unscheduled Visit (USV)
		6 (+2) hours after Lens 1 dispense at Visit 1	1-2 days after Visit 2	6 (+2) hours after Lens 2 dispense at Visit 3	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)
Inclusion/Exclusion	X					
Habitual lens (brand, power), solution (brand if applicable)	X					
VA with habitual spectacle correction (OD, OS, logMAR distance)*	X	X	X	X	X	(X)
Keratometry	X				(X)	(X)
Manifest refraction	X	(X)	(X)	(X)	(X)	(X)

Visit	Lens 1 (Period 1)		Lens 2 (Period 2)			
	Visit 1 Screening / Baseline/Dispense Lens 1	Visit 2 Follow-up Lens 1	Visit 3 Dispense Lens 2	Visit 4 Follow–up Lens 2/Exit	Early Exit[#]	Unscheduled Visit (USV)
		6 (+2) hours after Lens 1 dispense at Visit 1	1-2 days after Visit 2	6 (+2) hours after Lens 2 dispense at Visit 3	N/A	N/A
BCVA (OD, OS, logMAR distance with manifest refraction)	X	(X)	(X)	(X)	(X)	(X)
Biomicroscopy	X	X	X	X	X	X
Randomize	X					
Dispense study lenses*	X		X			(X)
VA with study lenses (OD, OS, logMAR distance)	X[Δ]	X	X	X	X	(X)
Lens fit assessments (OD, OS) (study lenses): • Lens movement (overall fit) at primary gaze • Lens movement (overall fit) at peripheral gazes • Lens position (centration)	X	X	X	X	X	(X)

[redacted]

Visit	Lens 1 (Period 1)		Lens 2 (Period 2)			
	Visit 1 Screening / Baseline/Dispense Lens 1	Visit 2 Follow-up Lens 1	Visit 3 Dispense Lens 2	Visit 4 Follow–up Lens 2/Exit	Early Exit#	Unscheduled Visit (USV)
		6 (+2) hours after Lens 1 dispense at Visit 1	1-2 days after Visit 2	6 (+2) hours after Lens 2 dispense at Visit 3	N/A	N/A
[redacted]						
Unplanned lens replacement	(X)		(X)			
Subject instructions (verbal)*	X	X	X			(X)
Collect worn lenses*		X		X	X	(X)
Adverse events	X	X	X	X	X	X
Device deficiencies	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)

* Source only

Δ Reassess lens power (and dispense different power(s), if applicable) if VA has decreased by 2 lines or more from BCVA with MR. If lens is changed, repeat VA.

If subject exits during a scheduled visit, assessments should be recorded in EDC in the Early Exit form, and the Visit should be updated to "not done due to Early Exit."