Short Title:

Statistical Analysis Plan CLP691-C002

Full Title:

Statistical Analysis Plan CLP691-C002 / NCT03762668

Protocol Title:	Performance Assessment of a Modified Daily Disposable Contact Lens
Project Number:	A01989
Protocol TDOC Number:	TDOC-0055936
Author:	[redacted]
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Approvals:	See last page for electronic approvals.
Job Notes:	

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.

Executive Summary:

Key Objectives:

Demonstrate that visual acuity (VA) with modified delefilcon A contact lens (MDACL) is noninferior to that with the current delefilcon A contact lens (DACL).

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in high contrast distance VA with MDACL when compared to DACL, using a margin of 0.05.

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1 Study Objectives and Design

1.1 Study Objectives

Primary Objective

The primary objective is to demonstrate that VA with MDACL is noninferior to that with the current DACL.

[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, double-masked, bilateral crossover
Study Population	Adapted DAILIES TOTAL1® (DT1) contact lens wearers with normal eyes [redacted] willing and able to be fit with the study lenses and comply with the visit and wearing schedule. Planned to enroll: ~60 Target to complete: 54
Number of Sites	~5 US
Test Product	Modified Delefilcon A Contact Lens (MDACL) (LID016029)
Control Product	Delefilcon A Contact Lens (DACL) (LID006961)
Duration of Treatment	Total exposure: ~14 days Test Product: 7 (±2) days Control Product: 7 (±2) days
Visits	Visit 1: Day 1 Baseline / Dispense Lens 1 Visit 2: Day 7 (±2 days) Follow-up Lens 1 / Dispense Lens 2 Visit 3: Day 7 (±2 days) Follow-up Lens 2 / Exit

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 Medidata Rave RTSM.

Subjects will be randomized in a 1:1 ratio to receive treatment (lens) in crossover sequence for bilateral wear per the specified sequence group:

Sequence 1 = MDACL/DACL

Sequence 2 = DACL/MDACL

1.4 Masking

This is a double-masked study.

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. 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 (MDACL or DACL) 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.

2.3 Per Protocol Analysis Set

The per protocol (PP) analysis set is a subset of FAS and excludes all data/subjects which 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

Demographic characteristics and subject accounting tables will be summarized by lens sequence and overall on the safety, 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, 1[redacted] effectiveness endpoints. All 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 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 the primary[redacted] effectiveness analyses.

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.

4.1 Effectiveness Endpoints

4.1.1 Primary Endpoint

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

[redacted]

4.2 Effectiveness Hypotheses

4.2.1 Primary Effectiveness

The primary effectiveness analysis is to assess whether the high contrast distance VA with Test is noninferior to that with Control.

The null and alternative hypotheses are formulated in terms of the predefined margin of 0.05 in logMAR 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 high contrast distance VA, in logMAR, for Test and Control, respectively.

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analysis

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

Analysis of the mixed effect repeated measures model will be implemented in SAS. The pseudocode is provided below.

```
proc sort data = one; by subject visit; run;
proc mixed data = one;
    class subject lens period sequence visit eye;
    model logMAR = period sequence lens|visit / ddfm = kr;
    random int lens / subject=subject;
   repeated visit / subject = subject*eye  type = cs;
   lsmeans lens * visit / cl diff alpha=0.10;
run;
```

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

4.4 Multiplicity Strategy

A sequential gatekeeping strategy will be implemented to control multiplicity. Thereby controlling the overall type I error at one-sided 0.05.

4.5 Subgroup Analyses and Effect of Baseline Factors

It is not expected that demographic or baseline characteristics will have an impact on the study results in this study. No subgroup analyses are planned.

4.6 Interim Analysis for Effectiveness

No interim analysis is planned for effectiveness endpoints.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events (AEs)
- Biomicroscopy Findings
    - Limbal hyperemia

  - Bulbar hyperemia
  - Corneal staining
  - Conjunctival staining
  - Palpebral conjunctival observations
  - Corneal epithelial edema
  - Corneal stromal edema
  - Corneal vascularization
  - Conjunctival compression/indentation
  - 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 as 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 at Visit 1. No inferential testing will be carried out for safety endpoint. Safety endpoints 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 will be separated from treatment-emergent AEs occurring during the study periods. 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

The following tables and supportive listings will be provided:

- Frequency and Percentage for Biomicroscopy Findings by Visit
- Incidence of Increased Severity of 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
- Listing of Subjects With Increased Severity of 2 or More Grades in Biomicroscopy Findings [This listing will include all biomicroscopy data from all visits within the same affected period]
- Listings of Subjects with Infiltrates

5.3.3 Device Deficiencies

The following tables and supportive listings will be provided:

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

6 Sample Size and Power Calculations

[redacted]

Visual Acuity

To demonstrate noninferiority (margin=0.05 logMAR) as a one-tailed hypothesis with α=0.05, and using a standard deviation of 0.0383 for paired differences, 80% power can be attained with a sample size of 8 (4 per sequence group).

[redacted]

[redacted]

7 References

Not applicable

8 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.

9 Appendix

Table 9-1 Overview of Study Plan

Procedure/ Assessment	Visit 1	Visit 2		Visit 3	Unscheduled Visit	Early Exit
	Day 1 Baseline / Dispense Lens 1	Day 7 (± 2 days) Follow-up Lens 1 / Dispense Lens 2		Day 7 (±2 days) Follow-up Lens 2 / Exit		
Informed Consent	✓	-	-	-	-	-
Demographics	✓	-	-	-	-	-
Medical/Ocular History	✓	-	-	-	-	-
Concomitant Medications	✓	(✓)	-	(✓)	(✓)	(✓)
Inclusion/Exclusion	✓	-	-	-	-	-
VA w/ habitual correction (logMAR distance)*	✓	-	-	-	(✓)	✓
Manifest refraction*	✓	(✓)	(✓)	(✓)	(✓)	(✓)
BCVA (logMAR distance with manifest refraction)*	✓	(✓)	(✓)	(✓)	(✓)	(✓)
AEs (Both reported and observed)	✓	✓		✓	✓	✓
Biomicroscopy	✓	✓		✓	✓	✓
Device deficiencies	✓	✓		✓	✓	✓
Randomize subject	✓	-	-	-	-	-
IP Dispense	✓	-	✓	-	-	-
High contrast VA w/IP (logMAR distance)	✓	✓	✓	✓	(✓)	(✓)
[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]

Procedure/ Assessment	Visit 1	Visit 2		Visit 3	Unscheduled Visit	Early Exit
	Day 1 Baseline / Dispense Lens 1	Day 7 (± 2 days) Follow-up Lens 1 / Dispense Lens 2		Day 7 (± 2 days) Follow-up Lens 2 / Exit		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exit Form	(✓)	(✓)	(✓)	(✓)	(✓)	✓

(✓) assessment performed as necessary, eg, decrease of VA by 2 lines or more with investigational products (IPs)
* Source only

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