Short Title:

Statistical Analysis Plan
CLD523-P001

Full Title:

Statistical Analysis Plan
CLD523-P001/NCT04013789

Protocol Title:	Comparison of Two Daily Disposable Lenses
Project Number:	A03392
Protocol TDOC Number:	TDOC-0056324
Author:	[redacted]
	Statistician
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Approvals:	See last page for electronic approvals
Job Notes:	

This is the first version (Version 2.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 of the study protocol.

Executive Summary:

Key Objective:

The primary objective of this study is to demonstrate noninferiority in mean distance visual acuity (VA) of DAILIES® AquaComfort PLUS® (DACP) FreshTech compared to DACP at the Week 1 Follow-up visit.

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in mean distance visual acuity of DACP FreshTech compared to DACP at the Week 1 Follow-up visit, using a margin of 0.05.

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of the study is to demonstrate noninferiority in mean distance visual acuity of DACP FreshTech compared to DACP at the Week 1 Follow-up visit.

[redacted]

[redacted]

[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	Habitual soft contact lens wearers aged 18 to 35 years with normal eyes and a spherical distance contact lens prescription between -1.00 and -6.00D (inclusive). The subjects must be symptomatic, which means they have self-reported eye fatigue, use their digital devices for ≥ 4 hours/5 days a week, and score ≥ 6 on the Computer Vision Syndrome Questionnaire (CVS-Q). Planned to enroll: ~72; Target to complete: 66
Number of Sites	1 US
Test Product	DAILIES® AquaComfort PLUS® (nelfilcon A) FreshTech (DACP FreshTech)
Control Product	DAILIES® AquaComfort PLUS® (nelfilcon A) (DACP)
Duration of Treatment	Test Product: 7±2 days Control Product: 7±2 days

Visits	Visit 1 (Day 1): Screening/Fitting/Dispense Optimized Habitual Visit 2: Week 1 Follow-up and Baseline with Optimized Habitual/ Dispense Study Product 1 [7±2 days from V1] Visit 3: Week 1 Follow-up Study Product 1/Dispense Study Product 2 [7±2 days from V2] Visit 4: Week 1 Follow-up Study Product 2/Exit [7±2 days from V3]

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 treatment assignment. Randomization will be implemented in Medidata Rave RTSM.

Subjects will be randomized in a 1:1 manner to receive treatment (lens) in crossover sequence DACP FreshTech then DACP or DACP then DACP FreshTech, respectively.

1.4 Masking

This is a double-masked study.

1.5 Interim Analysis

[redacted]

[redacted]

[redacted]

[redacted]

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 (DACP FreshTech or DACP) evaluated in this study. The optimized habitual lenses and trial-fit lenses are not considered study lenses for the purpose of safety evaluation. 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) will include all randomized subjects who are exposed to any study lenses evaluated in this study, not including the optimized habitual and trial-fit lenses.

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 Deviations 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 Sequence
- Analysis Sets by Lens
- Subject Accounting by Lens Sequence
- Demographics Characteristics by Lens Sequence
- Baseline Characteristics by Lens Sequence

Demographic characteristics and subject accounting tables will be summarized by lens sequence and overall on the safety, full, and PP analysis datasets. Baseline characteristics will be summarized by lens sequence and overall on the full and PP 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 one primary endpoint, [redacted] 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 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 those effectiveness endpoints planned for inferential testing.

For all planned inferential analyses, alternative models/methods may be considered 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

Primary Endpoint

The primary endpoint is the mean distance VA with study lenses. The corresponding assessment is collected bilaterally (OU) in logMAR, at the Dispense and Week 1 Follow-up visits.

[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 logMAR VA for DACP FreshTech and DACP, respectively, at Week 1 Follow-up.

[redacted]

[redacted]

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

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 crossover will also be accounted for in the model. Lens difference (DACP FreshTech minus DACP) and the corresponding one-sided 95% upper confidence limit (UCL) will be computed. Noninferiority in VA will be declared if the UCL is less than 0.05.

[redacted]

[redacted]

lsmeans lens/ cl diff alpha=0.10;
[redacted]

- [redacted]
- [redacted]

[redacted].

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

4.6 Interim Analysis for Effectiveness

No interim analysis is planned for effectiveness endpoints. [redacted]

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are

- Adverse events (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 (eg, 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 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 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.

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 Non-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

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 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]
- Listings 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.

7 Sample Size and Power Calculations

Sample size calculations are based on prior clinical study (CLD523-C001) [redacted]

Primary Effectiveness

To demonstrate noninferiority (margin = 0.05 in logMAR; ½ line in Snellen) in mean distance VA as a one-tailed hypothesis with α=0.05, and using a standard deviation of 0.075 for paired differences based on CLD523-C001, 80% power can be attained with a sample size of 16 (8 per sequence).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted])

8 References

Not Applicable.

9 Revision History

This is the first revision (Version 2.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 of the study protocol.

[redacted]

Itemized Changes:

[redacted]	[redacted]

10 Appendix

Table.11–2 Overview of Study Plan

Procedure/ Assessment	Pre-screening	VISIT 1	VISIT 2		VISIT 3		VISIT 4	Unscheduled Visit	Early Exit
		Day 1	1 Week (7±2 Days) from V1		1 Week (7±2 Days) from V2		1 Week (7±2 Days) from V3		
		Screening / Fitting / Dispense Optimized Habitual	Week 1 Follow-up and Baseline with Optimized Habitual	Dispense Study Product 1	Week 1 Follow-up Study Product 1	Dispense Study Product 2	Week 1 Follow-up Study Product 2 / Exit		
Digital Use Time	✓	-	✓	-	✓	-	✓	-	-
Symptomatology Question	✓	-	✓	-	-	-	-	-	-
CVS-Q	✓	-	✓	-	✓	-	✓	-	-
Informed Consent	-	✓	-	-	-	-	-	-	-
Demographics	-	✓	-	-	-	-	-	-	-
Habitual Lens (brand and wear schedule), Lens Care, Drops	-	✓	-	-	-	-	-	-	-
Medical History	-	✓	✓	-	✓	-	✓	✓	✓
Concomitant Medications	-	✓	✓	-	✓	-	✓	(✓)	✓
Inclusion/Exclusion	-	✓	✓	-	-	-	-	-	-
VA (OD, OS,OU logMAR distance with habitual contact lenses)	-	✓	-	-	-	-	✓	-	(✓)
Subjective (manifest) refraction*	-	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)
BCVA (OD, OS, OU, logMAR distance with manifest refraction)*	-	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)
Habitual contact lens power optimization (if needed)	-	✓	-	-	-	-	-	-	-
Biomicroscopy	-	✓	✓	-	✓	-	✓	(✓)	✓
Dispense new (optimized) habitual contact lenses	-	✓	-	-	-	-	-	-	-
VA (OD, OS, OU logMAR	-	✓	✓	-	-	-	-	-	-

distance with new (optimized) habitual contact lenses)									
Determine power and fit study lenses	-	✓	-	-	-	-	-	-	-
Randomization (after re-verifying qualifications)	-	-	✓	-	-	-	-	-	-
Dispense study lenses in a masked manner	-	-	-	✓	-	✓	-	-	-
VA (OD, OS, OU logMAR distance with study lenses)	-	-	-	✓	✓	✓	✓	-	-
[redacted]									
[redacted]									
[redacted]									
[redacted]									
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[redacted]									
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[redacted]									
[redacted]									
AEs	-	✓	✓	✓	✓	✓	✓	✓	✓
Device deficiencies	-	✓	✓	✓	✓	✓	✓	✓	✓
Exit form	-	(✓)	(✓)	(✓)	(✓)	(✓)	✓	(✓)	(✓)

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

[redacted]
