Short Title:

Statistical Analysis Plan CLD523-C001

Full Title:

Statistical Analysis Plan CLD523-C001 / NCT03567005

Protocol Title:	Clinical Validation of DACP Digital Design
Project Number:	A03261
Protocol TDOC Number:	TDOC-0055077
Author:	[redacted]
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Approvals:	See last page for electronic approvals.
Job Notes:	

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.

Executive Summary:

Key Objectives:

The primary objective is to demonstrate noninferiority in distance visual acuity (VA) with DAILIES AquaComfort Plus® Digital Soft contact lenses (DACP Digital) when compared to DAILIES® AquaComfort Plus® Sphere Soft contact lenses (DACP) at the 1-Week Follow-up visit.

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in distance VA with DACP Digital when compared to DACP, 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 noninferiority in distance VA with DACP Digital when compared to DACP at the 1-Week Follow-up visit.

SECONDARY OBJECTIVE

The secondary objective is to demonstrate noninferiority in subjective overall vision with DACP Digital when compared to DACP at the 1-Week Follow-up visit.

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, bilateral crossover, double-masked, controlled
Study Population	Volunteer subjects aged 18 to 35 with normal eyes (other than correction for refractive error), currently wearing DACP soft contact lenses on a daily wear, daily disposable basis. Subjects should have at least 2 months of DACP wearing experience, wear these lenses at least 5 days per week and at least 8 hours per day, use digital devices at least 4 hours per day at least 5 days per week, experience symptoms of eye strain, and require distance contact lenses in a power range from -1.50 D to -3.75 D. Target to complete: 48 Planned to enroll: ~60
Number of Sites	~4 (US)
Test Product	DAILIES® AquaComfort Plus® Digital Soft Contact Lenses (DACP Digital) (LID014466)
Control Product	DAILIES® AquaComfort Plus® Sphere Soft Contact Lenses (DACP) (LID007861)

Duration of Treatment	Up to 18 days total duration • Test Product: 7 days (± 2 days) • Control Product: 7 days (± 2 days)
Visits	Visit 1 – Baseline/Fitting* Visit 2 – Dispense Study Product 1 [0 - 7 days from Visit 1] Visit 3 – 1-Week Follow-up Study Product 1 [7 ± 2 days from Visit 2] / Dispense Study Product 2 Visit 4 – 1-Week Follow-up Study Product 2 [7 ± 2 days from Visit 3] / Exit *Randomization will occur at Visit 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 study lens sequence assignment. [redacted]

Qualifying subjects will be randomized in a 1:1 manner to one of 2 lens sequences consisting of the test lens and control lens as described below. For each sequence, subjects wear 1st lens then crossover to 2nd lens.

Sequence 1 = DACP Digital/DACP
Sequence 2 = DACP/DACP Digital

1.4 Masking

This study is double-masked.

[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

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

Demographic characteristics and subject accounting tables will be summarized by lens sequence and overall on the safety, full, and per protocol analysis datasets. Baseline characteristics will be summarized by lens sequence and overall 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 one primary, one secondary, [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 and secondary effectiveness analyses.
[redacted]

4.1 Effectiveness Endpoints

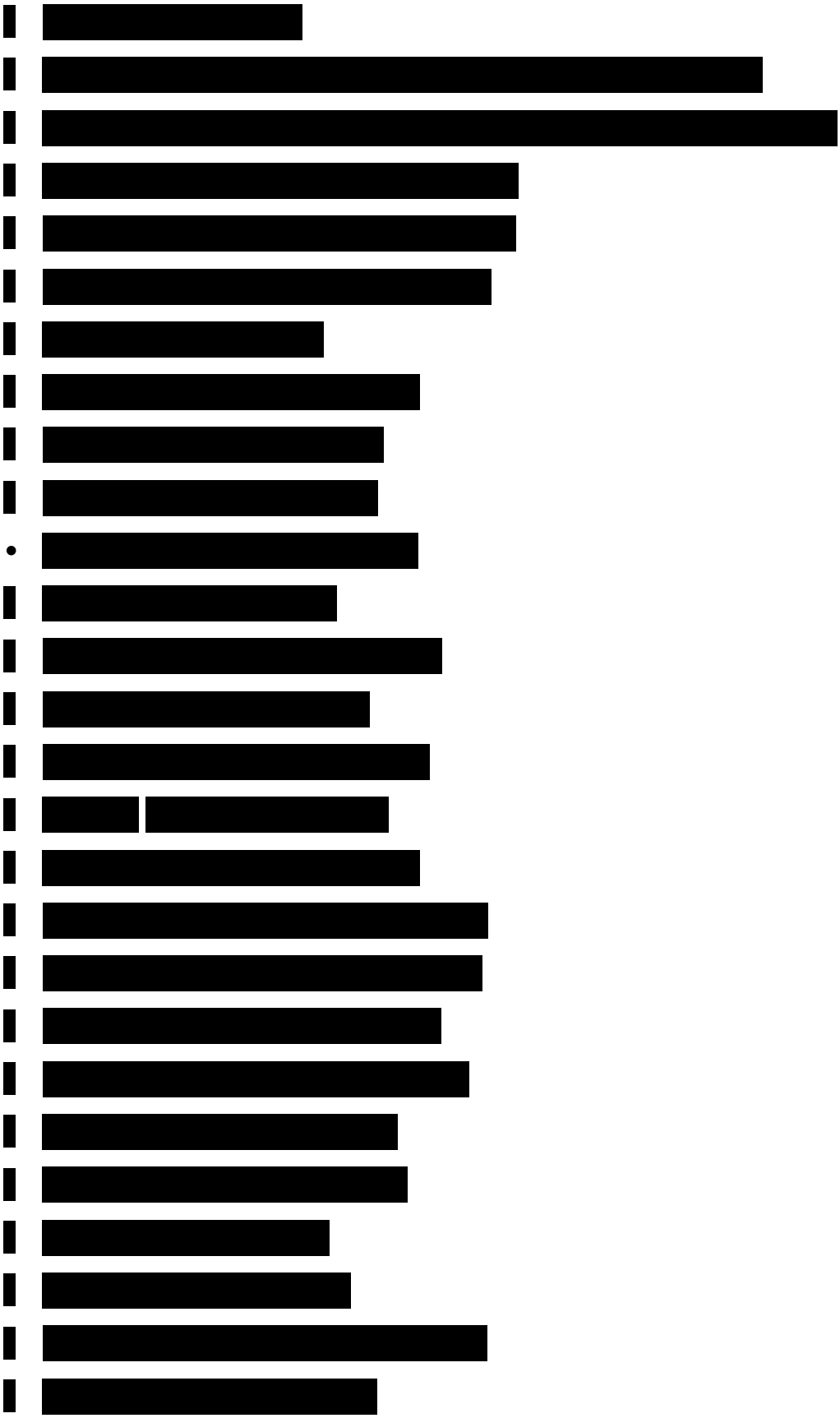
Primary Endpoint

The primary endpoint is distance VA with study lenses, collected bilaterally (OU), in logMAR.

Secondary Endpoint

The secondary endpoint is the subjective rating of overall vision, collected binocularly on a scale of 1 (Poor) to 10 (excellent) at the 1-Week Follow-up visits.

[redacted]



4.2 Effectiveness Hypotheses

Primary Effectiveness

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

H_0: $\mu_{(DACP\ D)} - \mu_{(DACP)} \geq 0.05$
H_a: $\mu_{(DACP\ D)} - \mu_{(DACP)} < 0.05$

where $\mu_{(DACP\ D)}$ and $\mu_{(DACP)}$ denote the mean distance VA (in logMAR) for DACP Digital and DACP, respectively.

Secondary Effectiveness

The null and alternative hypotheses for the secondary analysis are formulated in terms of the predefined margin of 1.0 for noninferiority:

H_0: $\mu_{(DACP\ D)} - \mu_{(DACP)} \leq -1.0$
H_a: $\mu_{(DACP\ D)} - \mu_{(DACP)} > -1.0$

where $\mu_{(DACP\ D)}$ and $\mu_{(DACP)}$ denote the mean overall vision rating for DACP Digital and DACP, respectively.

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

A mixed effect 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 Digital minus DACP) and the corresponding one-sided 95% upper confidence limit will be computed at 1-Week follow-up. Noninferiority in distance VA will be declared if upper confidence limit is less than 0.05.

[redacted]

4.3.2 Secondary Effectiveness Analyses

Similarly, a mixed effect repeated measures model will be utilized to test the secondary effectiveness hypotheses. The model will include terms for lens, period, and sequence. Within-subject correlation due to crossover will also be accounted for in the model. Lens difference (DACP Digital minus DACP) and the corresponding one-sided 95% lower confidence limit will be computed. Noninferiority in overall vision will be declared if lower confidence limit is greater than -1.0.

[redacted]

[redacted]

4.4 Multiplicity Strategy

A sequential gatekeeping strategy will be implemented to control testing of multiple effectiveness endpoints. [redacted]

[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 on Visit 2 (or Visit 1 if both visits occur on the same date). 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 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 [redacted] 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/Slit Lamp Examination

The following tables and [redacted] 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 [redacted] 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 calculation is based on a prior clinical study (M-14-010) which partly evaluated performance of DACP Multifocal and DACP lenses.

To demonstrate noninferiority (margin = 0.05 logMAR) as a one-tailed hypothesis with α=0.05, and using a standard deviation of 0.098 for paired differences, 80% power can be attained with a sample size of 36 (18 per sequence group).

To demonstrate noninferiority (margin = 1.0) as a one-tailed hypothesis with α=0.05, and using a standard deviation of 2.29 for paired differences, 80% power can be attained with a sample size of 48 (24 per sequence group).

8 References

Not applicable

9 Revision History

Revision 1

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.

The purpose of this revision is to update the Subject Population based on revision of certain Inclusion Criteria.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

	[redacted]

10 Appendix

Table 10–1 Overview of Study Plan

Procedure/ Assessment	Pre-screening	Visit 1	Visit 2	Visit 3	Visit 3	Visit 4	Unscheduled Visit	Early Exit
			0-7 days from V1	7 (±2) days from V2		7 (±2) days from V3		
		Baseline/ Fitting	Dispense Study Product 1	Follow-up Study Product 1	Dispense Study Product 2	Follow-up Study Product 2 / Exit		
Digital Use Time	✓*			✓		✓	✓	✓
Symptomatology	✓*							
Informed consent		✓						
Demographics		✓						
Medical history		✓	✓	✓		✓	✓	✓
Concomitant Medications		✓	(✓)	(✓)		(✓)	(✓)	(✓)
Inclusion/Exclusion		✓						
Distance VA w/habitual lenses (logMAR, OD, OS)*		✓						
Over-refraction w/ habitual lenses (OD, OS)*		✓						
Manifest refraction*		✓	(✓)	(✓)		(✓)	(✓)	(✓)
BCVA (OD, OS, logMAR distance with manifest refraction)*		✓	(✓)	(✓)		(✓)	(✓)	(✓)
Biomicroscopy		✓	✓	✓		✓	✓	✓
Dispense study lenses / Rx			✓		✓			
VA w/ study lenses ([redacted] OU, logMAR distance)			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]		[redacted]			
[redacted]			✓		✓			

Procedure/ Assessment	Pre-screening	Visit 1	Visit 2	Visit 3	Visit 3	Visit 4	Unscheduled Visit	Early Exit
			0-7 days from V1	7 (±2) days from V2		7 (±2) days from V3		
		Baseline/ Fitting	Dispense Study Product 1	Follow-up Study Product 1	Dispense Study Product 2	Follow-up Study Product 2 / Exit		
[redacted]				[redacted]		[redacted]	[redacted]	[redacted]
[redacted]				[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		✓		✓		✓	(✓)	✓
Subjective ratings with study lenses				✓		✓	(✓)	✓
[redacted]						[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]				✓		✓	(✓)	(✓)
AEs		✓	✓	✓		✓	✓	✓
Device deficiencies		✓	✓	✓		✓	✓	✓
Exit form		(✓)	(✓)	(✓)		✓	(✓)	✓

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

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
07/17/2018 17:35:29	[redacted]	Biostatistics
07/17/2018 20:30:47	[redacted]	biostatistics
07/17/2018 23:41:54	[redacted]	Global Device Medical Safety
07/26/2018 17:33:25	[redacted]	Clinical Project Lead & SME