[redacted] **Short Title:**

Statistical Analysis Plan
CLS312-P001 /
NCT03628599

Full Title:

Statistical Analysis Plan
CLS312-P001

Protocol Title:	Two Daily Disposable Contact Lenses in Symptomatic Patients
Project Number:	A03292
Protocol TDOC Number:	TDOC-0055359
Author:	[redacted]
	Statistician
Template Version:	Version 1.0
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 Objective:

The primary effectiveness objective of this study is to evaluate visual acuity after approximately 4 weeks of lens wear.

Decision Criteria for Study Success:

Decision criteria for study success are not applicable for this study.

Table of Contents

Statistical Analysis Plan CLS312-P001 1
Table of Contents 3
List of Tables 4
List of Figures 4
No table of figures entries found. 4
1 Study Objectives and Design 5
1.1 Study Objectives 5
1.2 Study Description 5
1.3 Randomization 6
1.4 Masking 6
1.5 Interim Analysis 6
2 Analysis Set 6
2.1 Safety Analysis Set 6
3 Subject Characteristics and Study Conduct Summaries 6
4 Effectiveness Analysis Strategy 7
4.1 Effectiveness Endpoints 7
4.2 Effectiveness Hypotheses 8
4.3 Statistical Methods for Effectiveness Analyses 8
4.3.1 Primary Effectiveness Analyses 8
[redacted] [redacted] 8
4.4 Multiplicity Strategy 8
4.5 Subgroup Analyses and Effect of Baseline Factors 8
4.6 Interim Analysis for Efficacy 8
5 Safety Analysis Strategy 8
5.1 Safety Endpoints 8
5.2 Safety Hypotheses 9
5.3 Statistical Methods for Safety Analyses 9
5.3.1 Adverse Events 9
5.3.2 Biomicroscopy Findings 10
5.3.3 Device Deficiencies 10

6 Analysis Strategy for Other Endpoints 10
7 Sample Size and Power Calculations 10
8 References 11
9 Revision History 11
10 Appendix 12

List of Tables

Table 11–1 Overview of Study Plan 12

List of Figures

No table of figures entries found.

1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of the study is to evaluate visual acuity after approximately 4 weeks of lens wear.

[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, parallel group, open-label, bilateral
Study Population	Planned to enroll: ~36; Target to complete: 30
Number of Sites	~4 US
Test Product	DAILIES TOTAL1® Water Gradient silicon hydrogel daily disposable contact lenses (DAILIES TOTAL1)
Control Product	ACUVUE OASYS® 1-DAY with HydraLuxe™ Technology (Acuvue Oasys 1-Day)
Duration of Treatment	Test Product: 28 days (±2 days) Control Product: 28 days (±2 days)
Visits	Visit 1 (Day 1): Baseline/Fitting/Dispense Visit 2 (Day 7 ±2 days): 1-Week Follow-up Visit 3 (Day 28 ±2 days): 4-Week Follow-up/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 assignment. Randomization will be implemented in iMedidata Balance.

Subjects will be randomized in a 1:1 manner to receive treatment with DAILIES TOTAL1 and Acuvue Oasys1-Day, respectively.

1.4 Masking

This study is open-label.

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 Set

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.

Adverse events occurring from the time of informed consent but prior to first exposure to study lenses will be summarized in subject listings.

3 Subject Characteristics and Study Conduct Summaries

The following tables will be presented:

- Subject Disposition
- Analysis Set by Lens
- Subject Accounting by Lens
- Demographics Characteristics by Lens
- Baseline Characteristics [redacted]

In addition, the following subject listings will be provided:

- Listing of Subjects Excluded from Protocol Defined Analysis Set

- Listing of Lens Assignment by Investigator
- Listing of Subjects Discontinued from Study

4 Effectiveness Analysis Strategy

This study defines one primary endpoint [redacted].
The safety analysis set will serve as the primary set for all effectiveness analyses.

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. 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.

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is distance visual acuity with study lenses, collected in Snellen at the 4 week follow-up visit, for each eye. Conversion will be made to the logMAR scale.

[redacted]

4.2 Effectiveness Hypotheses

Primary Effectiveness

No inferences are to be made on the primary effectiveness endpoint; therefore, no hypotheses are formulated.

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

Counts and percentage in each Snellen visual acuity category will be provided, and descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum) for the logMAR converted values will be presented.

[redacted]

4.4 Multiplicity Strategy

No multiplicity adjustment needs to be considered for the effectiveness endpoints since no formal hypothesis testing will be conducted.

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 Efficacy

No interim analysis is planned for effectiveness endpoints.

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 1). 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 All Nonocular 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
- Listing of Subjects With Increased Severity by 2 or More Grades in Biomicroscopy Findings
- 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

For visual acuity with a sample size of 15 in each group, a two-sided 95% confidence interval for the difference of two means will extend 0.05 from the observed difference in means with an assumed common standard deviation of 0.07.

[redacted]

8 References

Not Applicable.

9 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.

10 Appendix

Table 10–1 Overview of Study Plan

Procedure/ Assessment	Pre-screening	Visit 1 (Day 1)	Visit 2 (Day 7 ± 2 days)	Visit 3 (Day 28 ± 2 days)	Unscheduled Visit	Early Exit
		Baseline / Fitting / Dispense	1-week Follow-up	4-week Follow-up / Exit		
[redacted]						
Informed Consent	-	✓	-	-	-	-
Demographics	-	✓	-	-	-	-
Medical History	-	✓	✓	✓	✓	✓
Concomitant Medications	-	✓	(✓)	(✓)	(✓)	(✓)
Inclusion/Exclusion	-	✓	-	-	-	-
VA w/ habitual correction (OD, OS, Snellen distance)*	-	✓[a]	-	-	-	-
[redacted]						
Manifest refraction*	-	✓	(✓)	(✓)	(✓)	(✓)
BCVA (OD, OS, Snellen distance with manifest refraction)*	-	✓	(✓)	(✓)	(✓)	(✓)
Biomicroscopy	-	✓	✓	✓	✓	✓
Dispense study lenses	-	✓	-	-	-	-
VA w/ study lenses (OD, OS, Snellen distance)	-	✓	✓	✓	(✓)	✓
[redacted]						

Procedure/ Assessment	**Pre-screening**	**Visit 1 (Day 1)**	**Visit 2 (Day 7 ± 2 days)**	**Visit 3 (Day 28 ± 2 days)**	**Unscheduled Visit**	**Early Exit**
		Baseline / Fitting / Dispense	**1-week Follow-up**	**4-week Follow-up / Exit**		
[redacted]						
AEs	-	✓	✓	✓	✓	✓
Device deficiencies	-	✓	✓	✓	✓	✓
Exit Form	-	(✓)	(✓)	(✓)	(✓)	✓

[a] Performed based on habitual lenses

(✓) 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:
08/10/2018 18:17:24	[redacted]	Global Device Medical Safety
08/10/2018 18:51:42	[redacted]	biostatistics
08/13/2018 07:06:25	[redacted]	Clinical Project Lead
08/13/2018 23:12:22	[redacted]	Biostatistics