Short Title:

Statistical Analysis Plan
CLE383-C003

Full Title:

Statistical Analysis Plan
CLE383-C003 /
NCT03095027

Protocol Title:	Clinical Performance of a Silicone Hydrogel for Daily Disposable Wear
Project Number:	CLE383-C003
Reference Number:	
Protocol TDOC Number:	TDOC-0053428
Author:	[redacted]
	Contract Biostatistician
Template Version:	Version 4.0, approved 16MAR2015
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:

To demonstrate noninferiority in visual acuity of Daily Disposable T2 Soft Contact Lenses (DD T2) when compared to CooperVision® MyDay® (stenfilcon A) Daily Disposable Contact Lenses (MYDAY).

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferior VA with DD T2 against MYDAY, [redacted]

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate noninferiority in visual acuity of DD T2 when compared to MYDAY.

[redacted]

[redacted]

1.2 Study Description

Key components of the study are summarized in Table 1-1 Study Description Summary.

Table 1-1 Study Description Summary

Study Design	Prospective, randomized, crossover, multi-center
Study Population	Volunteer subjects aged 18 or over who are soft contact lens wearers, (excluding MYDAY habitual wearers), have at least 3 months of contact lens wearing experience, and who wear their habitual lenses at least 5 days per week and at least 8 hours per day. To qualify, subjects must require contact lenses in a power range from -1.50 to -4.00DS. Target to complete: 44; Planned to enroll: ~54
Number of Sites	~3 in US
Test Product	Daily Disposable T2 Soft Contact Lenses (DD T2)
Control Product	CooperVision® MyDay® (stenfilcon A) Daily Disposable Contact Lenses (MYDAY)
Duration of Treatment	~12 Days total duration • Test Product: 6 days (±1 day) • Control Product: 6 days (±1 day)
Visits	Visit 1 (Day 1) – Baseline/Dispense Study Lens 1 Visit 2 (6 Days ± 1 Day) – Follow-up Study Lens 1 / Dispense Study Lens 2 Visit 3 (6 Days ± 1 Day) – Follow-up Study Lens 2 / Exit Visit

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 iMedidata Balance.

1.4 Masking

This study is double-masked.

1.5 Interim Analysis

No interim analyses are planned for this study.

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.

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 be the set of all randomized subjects who are exposed to any study lenses evaluated in this study. Each subject/eye in FAS will be analyzed according to the respective randomized lens, irrespective of the exposure.

2.3 Per Protocol Analysis Set

The Per Protocol (PP) analysis set is a subset of FAS and excludes all data which have met any of the critical deviation or evaluability criteria identified in the Deviations and Evaluability Plan (DEP). Each subject/eye in PP analysis set will be analyzed according to the respective randomized lens, irrespective of the exposure.

3 Subject Characteristics and Study Conduct Summaries

The following tables will be presented:

[redacted]

In addition, the following subject listings will be provided:

[redacted]

4 Effectiveness Analysis Strategy

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

All data obtained in evaluable subjects/eyes will be included in the analysis. No imputation for missing values will be carried out for the effectiveness analysis.

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is visual acuity at Dispense and Week 1, in logMAR.

[redacted]

[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:

$$H_0: \mu_{(DDT2)} - \mu_{(MYDAY)} \geq 0.05$$
$$H_a: \mu_{(DDT2)} - \mu_{(MYDAY)} < 0.05$$

where $\mu_{(DDT2)}$ and $\mu_{(MYDAY)}$ denote the mean visual acuity for DD T2 and MYDAY, 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 eye and crossover will also be accounted for in the model. Lens difference (DD T2 minus MYDAY) and the corresponding one-sided 95% upper confidence limit will be computed. [redacted]

```
proc sort data = one; by subject visit; run;
proc mixed data = one;
   class subject lens period sequence visit;
    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]

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

There are no plans to conduct an interim analysis and no criteria by which the study would be terminated early based upon statistical determination.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are

- Adverse events
- Biomicroscopy Findings/Slit Lamp Examinations
    - 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 listed in Section 5.1.

5.3 Statistical Methods for Safety Analyses

The analysis set for all safety analyses is the safety analysis set as defined in Section 2.1. Baseline will be defined as the last measurement prior to exposure to investigational product, Visit 1. Safety variables will be summarized descriptively.

5.3.1 Adverse Events

The applicable definition of an Adverse Event (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 investigational product. The period for treatment-emergent AE analysis starts from exposure to the investigational product until the subject completes or is discontinued from the study.

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/Slit Lamp Examination

The following tables and supportive listings will be provided:

- Frequency and Percentage for Biomicroscopy Findings by Visit
- Increase of Severity by 2 Grades or More in Biomicroscopy Findings Between Baseline and Any Subsequent Visit
- Listing of Subjects With Other Biomicroscopy Findings
- Listing of Subjects With Increase of Severity by 2 Grades or More in Biomicroscopy Findings Between Baseline and Any Subsequent Visit
  [This listing will include all visits within the 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 Device Deficiencies
- Listing of Device Deficiencies Prior To Treatment Exposure

6 Analysis Strategy for Other Endpoints

Not Applicable.

[redacted]

8 References

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	Visit 1, Day 1: Baseline/Dispense Study Lens 1	Visit 2, Week 1: 6 Days (± 1 day) Follow up Study Lens 1 / Dispense Study Lens 2	Visit 3, Week 2: 6 Days (± 1 Day) Follow up Study Lens 2/ Exit
Informed Consent	✓	-	-
Demographics	✓	-	-
Medical History	✓	-	-
Concomitant Medications	✓	✓	✓
Inclusion/Exclusion	✓	-	-
Habitual lens (brand, power)	✓	-	-
VA w/ habitual correction (OD, OS, Snellen distance)	✓	✓	✓
[redacted]			
Biomicroscopy	✓	✓	✓
Dispense study lenses	✓	✓	-
VA w/ study lenses (OD, OS, Snellen distance[1])	✓	✓	✓
[redacted]			

Procedure/ Assessment	Visit 1, Day 1: Baseline/Dispense Study Lens 1	Visit 2, Week 1: 6 Days (± 1 day) Follow up Study Lens 1 / Dispense Study Lens 2	Visit 3, Week 2: 6 Days (± 1 Day) Follow up Study Lens 2/ Exit
[redacted]			
AEs	✓	✓	✓
Device deficiencies	✓	✓	✓
Exit Form	(✓)	(✓)	(✓)

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

[redacted]

[1] Primary effectiveness endpoint

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
03/21/2017 15:15:06	[redacted]	[redacted]
03/21/2017 15:20:54	[redacted]	[redacted]