Short Title:

Statistical Analysis Plan
CLY935-C010 / NCT04178720

Full Title:

Statistical Analysis Plan - US
CLY935-C010

Protocol Title:	Clinical Evaluation of a Daily Wear Monthly Replacement Silicone Hydrogel Lens
Project Number:	[redacted]
Reference Number:	
Protocol TDOC Number:	TDOC-0056910
Author:	[redacted]
	[redacted]
Template Version:	Version 4.0, approved 16MAR2015
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 evaluate visual acuity of the investigational [redacted] soft contact lens compared to the commercially available BIOFINITY® (Biofinity) soft contact lens.

Decision Criteria for Study Success:

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

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective is to evaluate visual acuity of the investigational [redacted] soft contact lens compared to the commercially available Biofinity soft contact lens.

1.2 Study Description

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

Table 1-1 Study Description Summary

Study Design	Prospective, multi-center, randomized, [redacted] controlled, double-masked, parallel-group
Study Population	Volunteer subjects aged 18 or over who are adapted daily wear frequent replacement soft contact lens wearers, excluding Biofinity habitual wearers, have at least 3 months of soft contact lens wearing experience, and who wear their habitual lenses at least 5 days per week and at least 8 hours per day. Subjects must require contact lens correction in a sphere power range from -1.00 to -6.00 D. [redacted] Target to complete: 90 subjects (60:30; Test:Control) Planned to enroll: ~120 subjects
Number of Sites	~8 (US)
Test Product	[redacted] soft contact lenses [redacted]
Control Product	CooperVision® BIOFINITY® (comfilcon A) soft contact lenses (Biofinity)
Duration of Treatment	Approximately 3 months
Visits	Visit 1: Screening/Baseline/Dispense (Day 1) Visit 2: Week 1 Follow-up (Day 8 -2/+2 days) Visit 3: Week 2 Follow-up (Day 15 -3/+3 days) Visit 4: Month 1 Follow-up (Day 30 -3/+5 days) Visit 5: Month 2 Follow-up (Day 60 -3/+5 days) Visit 6: Month 3 Follow-up/Exit (Day 95 -3/+5 days)

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.

Subjects will be randomized in a 2:1 ratio to receive either or Biofinity contact lenses, respectively.

Randomization schedule will be blocked to ensure a balance (2:1) in lens allocation within sites.

1.4 Masking

This study is double-masked.

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 All Enrolled

All subjects who have signed the informed consent for the study will be included in the All Enrolled analysis set.

2.2 Enrolled Dispensed

Enrolled Dispensed is a subset of All Enrolled subjects/eyes that have been exposed to study lenses. Lenses from the trial fitting set used only for fit, power, and/or visual acuity (VA) determination are not considered study lenses in this context.

2.3 Enrolled Not Dispensed

Enrolled Not Dispensed is a subset of All Enrolled subjects/eyes that have not been exposed to study lenses. Lenses from the trial fitting set used only for fit, power, and/or VA determination are not considered study lenses in this context.

2.4 Completed

The Completed analysis set consists of Enrolled Dispensed subjects/eyes completing the study.

2.5 Discontinued

The Discontinued analysis set consists of Enrolled Dispensed subjects/eyes not completing the study.

3 Subject Characteristics and Study Conduct Summaries

Demographic information (age, sex, ethnicity, and race), recent lens wearing experience (wear modality, wear success), and habitual lens information will be presented by lens group and overall for the All Enrolled analysis set.

Baseline data will be summarized by lens group, for Completed and Discontinued analysis sets separately, as applicable.

The following tables and listings for study conduct summaries will be presented:

- Accountability by Eyes Enrolled in the Study and Distribution by Status
- Listing of Lens Assignment by Investigator
- Discontinued Subjects Tabulated by Completed Visits and Reason for Discontinuation with Incidence Rates
- Listing of Subjects Discontinued from Study
- Listing of Out-of-Window Visits

4 Effectiveness Analysis Strategy

This study defines one primary effectiveness endpoint [redacted] Unless otherwise specified, separate summary tables will be presented for the Completed and the Discontinued analysis sets with the following distinction:

- Completed Control (eyes/subjects)
- Completed Test (eyes/subjects)

- Discontinued Control (eyes/subjects)
- Discontinued Test (eyes/subjects)

No inferential testing will be performed on the effectiveness endpoints, and format of the reporting tables will reference FDA's 510(k) guidance document (Clinical Appendix C, Summary of Reporting Tables; Clinical Appendix D, Trend Analysis Profile) as well as ISO 11980:2012 (Appendix A.3, Reporting of Results).

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is distance VA with study lenses, collected in Snellen, 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]

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

Summary statistics will be provided at each visit (Dispense, Week 1, Week 2, Month 1, Month 2, Month 3, and all unscheduled visits combined). Counts and percentages on the Snellen categories will be displayed, and descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) for the converted logMAR values will be provided.

[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 Effectiveness

No interim analysis is planned for effectiveness endpoints.

5 Safety Analysis Strategy

Unless otherwise specified, separate summary tables will be presented for the Completed and the Discontinued analysis sets with the following distinction:

- Completed Control (eyes/subjects)
- Completed Test (eyes/subjects)
- Discontinued Control (eyes/subjects)
- Discontinued Test (eyes/subjects)

Subjects/eyes will be categorized under the actual lens exposed.

5.1 Safety Endpoints

The safety endpoints include the following:

- Adverse events (AE)
- Biomicroscopy Findings/Slit Lamp Examination
    - 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

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 the study lens (not including trial fitting lenses). The period for treatment-emergent AE analysis starts from exposure to study lens until the subject completes or is discontinued from the study.

Descriptive summaries (counts and percentages) for ocular and nonocular AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT). Serious AEs and significant non-serious ocular AEs will be noted. Additionally, relationship to lens will be identified in all AE tables. Unit of presentation for ocular AEs will be eye and nonocular AEs will be subject.

Individual subject listings will be provided for both pre-treatment and treatment-emergent AEs, where any AE leading to study discontinuation will be indicated.

5.3.2 Biomicroscopy Findings/Slit Lamp Examination

Biomicroscopy assessment will be performed at all study visits, including Visit 1 to 6 and unscheduled visits. The reporting unit for each biomicroscopy finding will be *eye*.

A summary of grade category counts and percentages will be presented for each parameter at each scheduled visit and all unscheduled visits combined. A listing of "Other" slit lamp findings will also be provided.

Additionally, for each biomicroscopy parameter, counts and percentages of eyes that experience an increase of ≥ 2 grades from baseline (Visit 1) to any subsequent visit will be presented, together with a supportive listing.

5.3.3 Device Deficiencies

A frequency table showing counts for each treatment-emergent Device Deficiency category will be presented. In addition, listings for treatment-emergent and pre-treatment device deficiencies will be provided.

[redacted]

8 Sample Size and Power Calculations

Sample size is based upon the following:

- Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses – at least 50 evaluable subjects to be followed for at least 3 months, for claim of substantial equivalence for a lens with different repeating monomer Units (new Parent USAN). In addition, a 2:1 ratio in Test vs Control evaluable subject allocation should be adopted.
- ISO 11980:2012 – 50 completed subjects in Test, for 3 months. Either 2:1 or 1:1 ratio of Test to Control can be accepted.

9 References

1. Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses
2. ISO 11980:2012 Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations

10 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.

SAP Section	Information Changed
[redacted]	[redacted]
Title page (page 1)	Administrative: to update author's name and credential

11 Appendix

Table 11-1 Schedule of Study Procedures and Assessments

Procedure/ Assessment	Visit 1 Screening/ Baseline/ Dispense	Visit 2 Week 1 Follow-up[5]	Visit 3 Week 2 Follow-up[5]	Visit 4 Month 1 Follow-up[5]	Visit 5 Month 2 Follow-up[5]	Visit 6 Month 3 Follow-up/Exit[5]	Early Exit	USV
	Day 1	Day 8 (-2/+2 days)	Day 15 (-3/+3 days)	Day 30 (-3/+5 days)	Day 60 (-3/+5 days)	Day 95 (-3/+5 days)		
Informed Consent	X							
Demographics	X							
Medical History	X	X	X	X	X	X	X	(X)
Concomitant Medications	X	X	X	X	X	X	X	(X)
Inclusion/Exclusion	X							
Habitual lens information (brand/manufacturer, power, modality/wear success, habitual lens care brand)	X							
VA w/ habitual correction (OD,OS Snellen distance)	X					X	X	(X)
Manifest refraction[4]	X	(X)	(X)	(X)	(X)	X	X	(X)
BCVA[4] (OD,OS Snellen distance with manifest refraction)	X	(X)	(X)	(X)	(X)	X	X	(X)
[redacted]	[redacted]					[redacted]	[redacted]	[redacted]
Biomicroscopy	X	X	X	X	X	X	X	(X)
[redacted]	[redacted]							

Procedure/ Assessment	Visit 1 Screening/ Baseline/ Dispense	Visit 2 Week 1 Follow-up[5]	Visit 3 Week 2 Follow-up[5]	Visit 4 Month 1 Follow-up[5]	Visit 5 Month 2 Follow-up[5]	Visit 6 Month 3 Follow-up/Exit[5]	Early Exit	USV
	Day 1	Day 8 (-2/+2 days)	Day 15 (-3/+3 days)	Day 30 (-3/+5 days)	Day 60 (-3/+5 days)	Day 95 (-3/+5 days)		
Randomize and record lens power	X							
[redacted]	[redacted]							
Order study lenses*	X							
IP Dispense*	X	X	(X)	(X)	(X)			(X)
VA w/ study lenses (OD, OS Snellen distance)[1]	X	X	X	X	X	X	X	(X)
[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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Printed By:

Print Date:

Procedure/ Assessment	Visit 1 Screening/ Baseline/ Dispense	Visit 2 Week 1 Follow-up[5]	Visit 3 Week 2 Follow-up[5]	Visit 4 Month 1 Follow-up[5]	Visit 5 Month 2 Follow-up[5]	Visit 6 Month 3 Follow-up/Exit[5]	Early Exit	USV
	Day 1	Day 8 (-2/+2 days)	Day 15 (-3/+3 days)	Day 30 (-3/+5 days)	Day 60 (-3/+5 days)	Day 95 (-3/+5 days)		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	X	X	X	X	X	X	X	(X)
Device deficiencies	X	X	X	X	X	X	X	(X)
Exit Form	(X)	(X)	(X)	(X)	(X)	X	X	(X)

[redacted].

USV = Unscheduled Visit

*source only

[redacted]

[5]All follow-up visits should be scheduled at least 4 hours after lens insertion.

[redacted].

[redacted]
