Short Title:

Statistical Analysis Plan
CLY935-E002 /
NCT03034928

Full Title:

Statistical Analysis Plan
CLY935-E002

Protocol Title: Clinical Biocompatibility Evaluation of Contact Lens Coatings

Project Number: CLY935-E002

Protocol TDOC Number: TDOC - 0053056

Author: [redacted]

[redacted]

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:

The primary objective is to evaluate corneal staining observed after 2 hours of wear with coated monthly lenses against PureVision™ lenses, all pre-cycled with OPTI-FREE® RepleniSH® multi-purpose disinfection solution.

Decision Criteria for Study Success:

A test coating will be considered successful if $X_{Ti} < (X_C+3)$ where X_{Ti} and X_C are the observed average percent area of corneal staining for Test i (i=1, 2) and Control, respectively.

Table of Contents

List of Tables

List of Figures

No table of figures entries found.

1 Study Objectives and Design

1.1 Study Objectives

The primary objective is to evaluate corneal staining observed after 2 hours of wear with coated monthly lenses against PureVision lenses, all pre-cycled with OPTI-FREE RepleniSH multi-purpose disinfection solution.

1.2 Study Description

This will be a double-masked, randomized, contralateral, crossover, active controlled study evaluating 2 surface coating candidates in subjects at least 18 years of age who are experienced wearers of spherical soft contact lenses and qualified according to all inclusion and exclusion criteria. Approximately 35 subjects will be enrolled and qualifying subjects will be randomized to wear 2 pair of study lenses and will attend 4 visits occurring on 2 different study days (2 visits per day, approximately 2 hours of wear time per lens pair). Visits 1 and 2 (Pair 1 dispense and follow-up) occur on the same study day and 2 to 8 days later Visits 3 and 4 (Pair 2 dispense and follow-up) occur. Subjects must not wear contact lenses for a washout period that includes the day of and day prior to study visits.

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. Randomization will be implemented in Medidata Balance. Qualifying subjects will be randomized in a 1:1:1:1 manner to one of the following lens sequences, where each pair consists of a test and a control lens:

- Test 1 (OD)/ Control (OS) → Control (OD)/ Test 2 (OS)
- Test 2 (OD)/ Control (OS) → Control (OD)/ Test 1 (OS)
- Control (OD)/ Test 1 (OS) → Test 2 (OD)/ Control (OS)
- Control (OD)/ Test 2 (OS) → Test 1 (OD)/ Control (OS)

Where Test 1 is Monthly contact lens with Coating 1 [redacted] pre-cycled with OPTI-FREE RepleniSH multi-purpose disinfection solution, Test 2 is Monthly contact lens with Coating 2 [redacted] pre-cycled with OPTI-FREE RepleniSH multi-purpose disinfection solution, and control is PureVision contact lenses (balafilcon A; Bausch & Lomb, Inc., USA) pre-cycled with OPTI-FREE RepleniSH multi-purpose disinfection solution.

1.4 Masking

This study is double-masked, with subjects randomized to use Test 1, Test 2, and Control in the assigned eyes and lens sequence. The Investigators, Investigators' staff (other than unmasked study coordinators), subjects, and Sponsor personnel (other than the Lead Clinical Site Manager, site monitors and unmasked data managers) involved in reporting, obtaining, and/or reviewing the clinical evaluations will not be aware of the specific treatment (lens and lens sequence) being administered. This level of masking will be maintained throughout the conduct of the study. Subjects will be assigned lens sequence in numerical order; the randomization schedule will be blocked to ensure a balance of study lens sequence allocations within investigational sites. The randomization scheme will be generated and maintained by the Sponsor. Individual subjects may be unmasked only once all study data have been verified and validated and the database has been locked. In the event of a medical emergency where the knowledge of subject treatment is required, an individual Investigator will have the ability to unmask the lens sequence assignment for a specific subject.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

2.1 Safety Analysis Set

The Safety Analysis Set will include all subjects/eyes exposed to any study lens. Safety analysis will be conducted using the safety analysis set on a treatment-emergent basis. For treatment-emergent safety analysis, subjects/eyes will be categorized under the actual lens exposed.

2.2 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who satisfy the following criteria:

- Exposed to any study lens
- No biomicroscopy findings at screening as described in exclusion criterion # 5 or no corneal staining at Visit 3 as described in exclusion criterion # 5. If return visit is required for reassessment of corneal staining, only final value will be recorded in EDC and considered for this criterion.
- No current or history of pathological dry eye in either eye (exclusion criterion #6)
- No current or history of herpetic keratitis in either eye (exclusion criterion #7)
- No eye injury in either eye within twelve weeks immediately prior to enrollment for this trial (exclusion criterion #8)
- No history of intolerance or hypersensitivity to any component of the study lenses or solutions (exclusion criterion #9)

These critical deviation criteria will be identified in the Deviations and Evaluability Plan. Each subject will be classified according to the respective lens in the randomized lens, irrespective of the exposure. FAS will serve as the primary analysis dataset for all efficacy evaluations.

3 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition,demographics (age, gender, race, ethnicity) and subject accounting by lens and/or lens sequence, listings of lens sequence assignment by investigator, discontinuation and subjects excluded from key analysis set with reason. All descriptive summary statistics will be displayed with n and % for categorical data, and with mean, standard deviation, median, minimum, and maximum for continuous data.

Demographic information will be summarized based on the safety and full analysis sets by lens sequence group.

4 Efficacy Analysis Strategy

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

Descriptive summaries will be provided by Test 1, Test 2, and Control. Data for the control lens will be separated into those collected with Test 1 worn on the contralateral eye and those collected with Test 2 worn on the contralateral eye.

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

4.1 Efficacy Endpoints

Primary Endpoint

- Average of corneal staining areas observed (expressed as a percent) taken over the 5 regions: central, superior, nasal, inferior, and temporal, after 2 hours of lens wear.

[redacted]

4.2 Efficacy Hypotheses

No inferences are to be made on the primary [redacted] endpoin [redacted] therefore, no hypotheses are formulated.

4.3 Statistical Methods for Efficacy Analyses

4.3.1 Primary Efficacy Analyses

The average of corneal staining areas observed (%) taken over the 5 regions: central, superior, nasal, inferior, and temporal will be calculated for each test lens and the corresponding control. Corneal staining for each of the region will also be summarized.

Only descriptive summary statistics with mean, standard deviation, median, minimum, and maximum will be provided.

[redacted]

[redacted]

4.4 Multiplicity Strategy

No multiplicity adjustment needs to be considered for the efficacy variables as no inferences will be made.

4.5 Subgroup Analyses and Effect of Baseline Factors

Not applicable.

4.6 Interim Analysis for Efficacy

Not applicable.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events
- Biomicroscopy findings
  - Limbal hyperemia
  - Bulbar hyperemia
  - Conjunctival staining
  - Corneal vascularization
  - Corneal epithelial edema
  - Corneal stromal edema
  - Conjunctival compression/indention
  - Chemosis
  - Palpebral conjunctival observations

- Corneal infiltrates
- Other findings

- Device deficiencies

[redacted]

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. The safety variables will be summarized descriptively. Baseline will be defined as the last measurement prior to exposure to the study lens on Visit 1 for Period 1 and Visit 3 for Period 2.

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.

Pre-treatment and between-treatment-period AEs will be presented, with subject listings, separated from treatment-emergent AEs. A pre-treatment AE is an event that occurs after signing informed consent but prior to exposure to a study lens. A between-treatment-period AE is an event that occurs after last exposure to Period 1 study lens but prior to exposure to Period 2 study lens.

Descriptive summaries (counts and percentages) for ocular and non-ocular AEs will be presented by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms. In addition to an overall presentation of AEs, reports will be generated for significant non-serious AEs, and serious AEs. AEs leading to study discontinuation will be identified. Presentation of ocular AEs will be by eye. Individual subject listings will be provided, as necessary.

Individual subject's listings will be provided for both pre-treatment and between-treatment-period AEs.

5.3.2 Biomicroscopy Findings

For each biomicroscopy finding, all exposed eyes will be summarized; hence, the unit will be eye. A summary of grade category counts and percentages will be presented for each parameter by visit.

Each biomicroscopy parameter will be tabulated by its grade. For each biomicroscopy parameter, counts and percentages of eyes that experience an increase of ≥ 2 grades between baseline (Visit 1 for Period 1 and Visit 3 for Period 2) and any subsequent visits will be presented. A supportive listing will be generated and will include all biomicroscopy data from the affected period for these eyes experiencing the increase, with the following variables: lens, Investigator, subject, age, sex, visit, eye, parameter, baseline value, and value at the visit.

5.3.3 Device Deficiencies

The applicable definition of a device deficiency is in the study protocol. A frequency table showing counts for each device deficiency category will be presented.

In addition, two listings (prior to exposure to investigational products, and treatment-emergent) of device deficiencies will be provided.

6 Analysis Strategy for Other Endpoints

Not Applicable

7 Sample Size and Power Calculations

No inferential testing is planned for this study; therefore, sample size/power calculation is not relevant. The proposed sample size of 32 is adapted from Andrasko (2008), which recruited

30 successful hydrogel contact lens wearers for each of the lens-solution biocompatibility studies, and allows for a balance allocation of lens sequences.

8 References

Andrasko G, Ryen K. Corneal staining and comfort observed with traditional and silicone hydrogel lenses and multipurpose solution combinations. Optometry. 2008;79(8):444-54.

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 Screening / Baseline / Pair 1 Dispense	Visit 2 Pair 1 Follow-up 2 hrs (-15 min/+1 hr)	Visit 3 Baseline / Pair 2 Dispense (+2 to 8 days)	Visit 4 Pair 2 Follow-up / Exit 2 hrs (-15 min/+1 hr)	Unsched.
Informed Consent	✓	-	-	-	-
Demographics	✓	-	-	-	-
Medical History	✓	✓	✓	✓	✓
Concomitant Medications	✓	✓	✓	✓	✓
Inclusion/Exclusion	✓	-	-	-	-
Randomize subject	✓	-	-	-	-
Reassess corneal health	(✓)	-	✓	-	-
[redacted]					
VA w/ spectacles (OD, OS, OU as needed, Snellen distance)	✓	✓	✓	✓	(✓)
Manifest refraction [1]	✓	(✓)	(✓)	(✓)	(✓)
BCVA[1] (OD, OS, Snellen distance with manifest refraction)	✓	(✓)	(✓)	(✓)	(✓)
Biomicroscopy [including Corneal Staining, per region (type, area)][2]	✓	✓	✓	✓	✓
Dispense study lenses	✓	-	✓	-	-
[redacted]					

Procedure/ Assessment	**Visit 1** **Screening / Baseline / Pair 1 Dispense**	**Visit 2** **Pair 1 Follow-up** 2 hrs (-15 min/+1 hr)	**Visit 3** **Baseline / Pair 2 Dispense** (+2 to 8 days)	**Visit 4** **Pair 2 Follow-up / Exit** 2 hrs (-15 min/+1 hr)	**Unsched.**
AEs	✓	✓	✓	✓	✓
Device deficiencies	✓	✓	✓	✓	✓
[redacted]					
Exit Form	(✓)	(✓)	(✓)	✓	(✓)

[1] Source only
[2] Primary endpoint
[redacted]
(✓) assessment performed as needed

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
01/05/2017 20:22:22	[redacted]	[redacted]
01/05/2017 20:43:05	[redacted]	[redacted]
01/05/2017 20:58:30	[redacted]	[redacted]