Alcon

Statistical Analysis Plan for CLY935-E007 / NCT04789382

Title: Clinical Biocompatibility of Three Daily Wear Monthly Replacement Silicone Hydrogel Contact Lenses with Two Multi-purpose Disinfecting Solution Combinations

[redacted] [redacted]

This version of the Statistical Analysis Plan is based on Version 3.0 of the study protocol.

Executive Summary:

Key Objectives:

The primary objective of this study is to evaluate corneal staining observed after 2 hours of wear with LID018869[redacted] against both PureVision® (PV), pre-cycled with Biotrue® multi-purpose solution (Biotrue), and Biofinity® (Biofinity) lenses, pre-cycled with OPTI-FREE® RepleniSH® multi-purpose disinfecting solution (MPDS, RepleniSH).

Decision Criteria for Study Success:

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

Table of Contents

List of Tables

List of Figures

No table of figures entries found.

1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective of this study is to evaluate corneal staining observed after 2 hours of wear with LID018869 [redacted] against both PV, pre-cycled with Biotrue, and Biofinity lenses, pre-cycled with RepleniSH.

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, crossover (MPDS) and contralateral (lenses), double-masked
Study Population	Volunteer subjects aged 18 or over who are habitual spherical soft contact lens 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. Target to complete: 32; Planned to enroll: ~36
Number of Sites	~2 US
Test Product(s)	Test Product 1 (Test1): LID018869 pre-cycled with OPTI-FREE® RepleniSH® multi-purpose disinfecting solution (RepleniSH) Test Product 2 (Test2): LID018869 pre-cycled with Biotrue® multi-purpose solution (Biotrue)
Control Product(s)	Control Product 1 (Control1): Biofinity® pre-cycled with RepleniSH Control Product 2 (Control2): PureVision® (PV) pre-cycled with Biotrue
Planned Duration of Exposure	~ 4 hrs total (test and control, excluding washout): Test1: 2 hrs [redacted] Test2: 2 hrs [redacted] Control1: 2 hrs [redacted] Control2: 2 hrs [redacted]
Visits	Pre-Screening

	Visit 1 (Day 1) – Screen/Baseline/Pair 1 Exposure Visit 2 (Day 1, 2 hours [redacted] – Pair 1 Follow-up Visit 3[redacted] – Baseline/Pair 2 Exposure Visit 4 (same day as Visit 3, 2 hours [redacted] – Pair 2 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 regimen (lens and MPDS) sequence assignment. Randomization will be implemented in the Electronic Data Capture (EDC)/randomization integration system.

Subjects will be randomized in a 1:1:1:1 manner to receive one of 4 regimen sequences:

Sequence 1: LID018869+RepleniSH (OD)/Biofinity+RepleniSH (OS)//PV+Biotrue (OD)/LID018869+Biotrue (OS)

Sequence 2: Biofinity+RepleniSH (OD)/LID018869+RepleniSH (OS)//LID018869+Biotrue (OD)/PV+Biotrue (OS)

Sequence 3: LID018869+Biotrue (OD)/PV+Biotrue (OS)//Biofinity+RepleniSH (OD)/LID018869+RepleniSH (OS)

Sequence 4: PV+Biotrue (OD)/LID018869+Biotrue (OS)//LID018869+RepleniSH (OD)/Biofinity+RepleniSH (OS)

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 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 lens, whether or not pre-cycled in the study MPDS. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study lenses/regimen exposed in the corresponding regimen sequence.

Adverse events occurring from the time of informed consent but prior to first exposure to study lenses, whether or not pre-cycled in the study MPDS, will be summarized in subject listings.

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

The following tables will be presented:

- Subject Disposition by Regimen Sequence
- Analysis Set by Regimen
- Analysis Set by Regimen Sequence
- Subject Accounting by Regimen Sequence
- Demographics Characteristics by Regimen Sequence
- Baseline Characteristics by Regimen Sequence [lens brand, lens care brand]

In addition, the following subject listings will be provided:

- Listing of Subjects Excluded from Protocol Defined Analysis Set
- Listing of Regimen Sequence Assignment by Investigator
- Listing of Subjects Discontinued from Study

4 EFFECTIVENESS ANALYSIS STRATEGY

This study defines one primary effectiveness endpoint [redacted] The Safety Analysis Set will be used 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 frequencies 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 effectiveness analyses.

4.1 Effectiveness Endpoints

Primary Effectiveness Endpoint

The primary endpoint is the 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.

4.2 Effectiveness Hypotheses

Primary Effectiveness

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

[redacted]

[redacted]

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

Primary Effectiveness

Descriptive statistics will be presented.

[redacted]

[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

The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters. Therefore, no inferential testing will be done for the safety analysis.

5.1 Safety Endpoints

The safety endpoints are

- Adverse events (AE)
- Biomicroscopy Findings/Slit Lamp Examinations
    - Limbal hyperemia

- 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 (whether or not pre-cycled). For biomicroscopy data, baseline will be defined as Visit 1 for Period 1 and Visit 3 for Period 2. 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.

Pre-treatment AEs and between-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 lens. A between-treatment AE is an event that occurs after last exposure to Pair 1 lenses but prior to exposure to Pair 2 lenses. The period for treatment-emergent AE analysis starts from exposure to study lenses for Period 1 or Period 2 until the subject completes the respective period 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
- Listing of All Ocular Between-Treatment Adverse Events
- Listing of All Nonocular Between-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
- 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
- Listing 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

[redacted]

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

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 3.0 of the study protocol.

10 APPENDIX

Table 10-1 Schedule of Study Procedures and Assessments

Schedule of Study Procedures and Assessments

Procedure/ Assessment	PRESCREENING	Visit 1[µ] Screen/ Baseline/ Pair 1 Exposure	Visit 2 Pair 1 Follow-up 2 hrs [redacted]	Washout[µ] (the day of and day prior to Visit 3)	Visit 3 Baseline/ Pair 2 Exposure [redacted]	Visit 4 Pair 2 Follow-up 2 hrs [redacted] Exit^	Early Exit	USV
Washout Consent*	X							
Informed Consent		X						
Demographics		X						
Medical History*		X	X		X	X	X	X
Concomitant Medications*		X	X		X	X	X	X
Habitual lens (brand, power*, lens care)		X						
Review compliance*			X		X	X	X	(X)
VA w/ habitual spectacles (OD, OS, Snellen distance)*		X	X		X	X	X	(X)
VA w/ habitual spectacles OU*		X						
Manifest refraction*		X	(X)		(X)	(X)	(X)	(X)
[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

Procedure/ Assessment	**PRESCREENING**	**Visit 1[µ] Screen/ Baseline/ Pair 1 Exposure**	**Visit 2 Pair 1 Follow-up 2 hrs** [redacted]	**Washout[µ]** (the day of and day prior to Visit 3)	**Visit 3 Baseline/ Pair 2 Exposure** [redacted]	**Visit 4 Pair 2 Follow-up 2 hrs** [redacted] **Exit^**	**Early Exit**	**USV**
Biomicroscopy [including Corneal Staining, per region (type, area)]		X[∞]	X		X[∞]	X	X	(X)
Inclusion/Exclusion		X						
Randomization		X						
Dispense pre-cycled study lenses		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]

Procedure/ Assessment	PRESCREENING	Visit 1[µ] Screen/ Baseline/ Pair 1 Exposure	Visit 2 Pair 1 Follow-up 2 hrs [redacted]	Washout[µ] (the day of and day prior to Visit 3)	Visit 3 Baseline/ Pair 2 Exposure [redacted]	Visit 4 Pair 2 Follow-up 2 hrs [redacted] Exit^	Early Exit	USV
[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]
AEs		X	X		X	X	X	X
Device deficiencies		X	X		X	X	X	X
Exit Form		(X)	(X)		(X)	X	X	(X)

[redacted]