Short Title:

Statistical Analysis Plan CLC127-C001 / NCT03392532

Full Title:

Statistical Analysis Plan CLC127-C001

Protocol Title:	Axis Orientation Comparison of Two Silicone Hydrogel Toric Contact Lenses
Project Number:	A02946
Protocol TDOC Number:	TDOC-0054499
Author:	[redacted], MS
	[redacted]
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:

To evaluate the percentage of AIR OPTIX plus HydraGlyde for Astigmatism soft contact lenses (AOHG toric) that orient within ± 30 degrees from the 90° axis (ideal location), 10 min after lens insertion.

Decision Criteria:

A threshold value of 90% (as a minimum) for the percentage of lenses orienting within ±30 degrees of the 90° axis has been established for AOHG toric, based on historical data.

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

To evaluate the percentage of AOHG toric lenses that orient within ± 30 degrees from the 90° axis (ideal location), 10 min after lens insertion.

[redacted]

1.2 Study Description

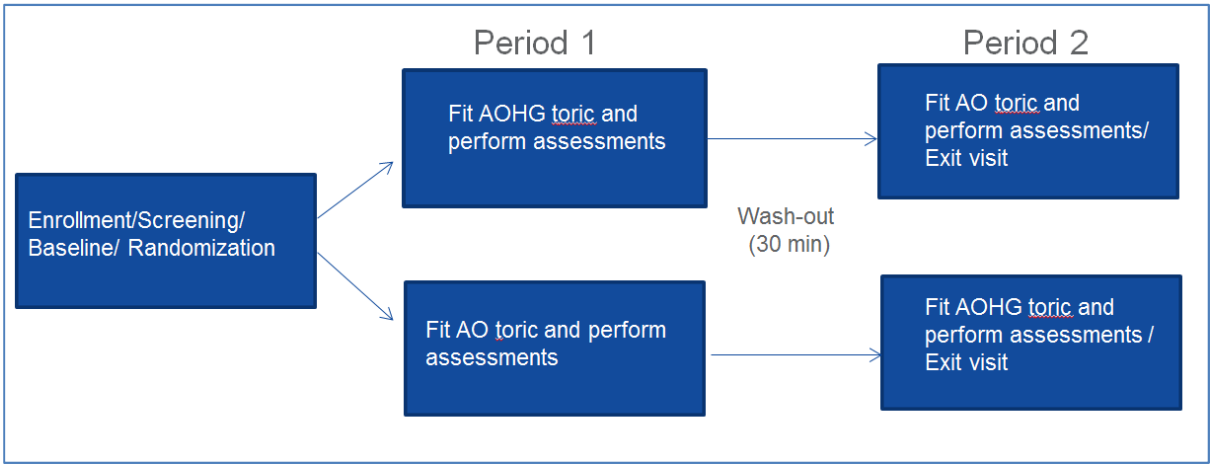
Key components of the study are summarized in Table 1-1.

Table 1-1 Study Description Summary

Study Design	Prospective, randomized, two-period crossover , double-masked, active controlled
Study Population	Volunteer subjects aged 18 or over who are adapted soft contact lens wearers, have at least 3 months of soft contact lens wearing experience, and who wear their habitual lenses at least 3 days per week and at least 8 hours per day. Target to complete: 30; Planned to enroll: ~35
Number of Sites	1-2, US
Test Product	AIR OPTIX plus HydraGlyde for Astigmatism soft contact lenses (LID009941)
Control Product	AIR OPTIX® for Astigmatism soft contact lenses
Duration of Treatment	Test Product: ~30 min.; Control Product: ~30 min. Washout: 30 (+15) min.
Visits	Subjects will attend one office visit consisting of • Baseline/Screening • Exposure Pair 1 – Period 1 • Exposure Pair 2 – Period 2 • Exit

A study design schematic is depicted in Figure 1–1.

Figure 1–1 Study Design



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 for each subject (ie, 1 = AOHG toric → AO toric; 2 = AO toric → AOHG toric). Randomization will be implemented in iMedidata Balance.

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 lenses evaluated in this study. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study lens exposed in the corresponding lens sequence.

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) is the set of all randomized subjects who are exposed to any study lenses evaluated in this study.

2.3 Per Protocol Analysis Set

The per protocol (PP) analysis set is a subset of FAS and excludes all data/subjects which have met any of the critical deviation or evaluability criteria identified in the Deviation and Evaluability Plan.

3 Subject Characteristics and Study Conduct Summaries

The following tables will be presented:

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

Demographics and subject accounting tables will be summarized on the safety, full, and PP analysis datasets. Baseline characteristics will be summarized on the full and PP analysis datasets.

In addition, the following subject listings will be provided:

- Listing of Subjects Excluded from Protocol Defined Analysis Sets
- Listing of Lens Sequence Assignment by Investigator
- Listing of Subjects Discontinued from Study

4 Effectiveness Analysis Strategy

This study defines 1 primary, [redacted] endpoints. All effectiveness evaluations will use the FAS as the primary analysis set. Supportive analyses of the primary [redacted] effectiveness endpoints will be conducted using the PP Analysis Set only if the number of subjects excluded from the PP Analysis Set exceeds 5% of the FAS.

For all planned inferential analyses, alternative models/methods may be considered if convergence cannot be achieved. Furthermore, if significant carryover effects are noted (confounded with sequence effect), results will be examined by period, ie, exposure time point, to ensure the overall conclusion is valid.

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.

A listing of selected effectiveness data will also be provided.

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is the percent of AOHG toric lenses with axis orientation within ±30 degrees from the 90° axis (ideal location), 10 min. after lens insertion. This percentage is calculated for the binary variable derived based on axis location of each lens as defined below:

Yes – if the absolute difference between the axis location and 90 is less than or equal to 30 (ie, lens located between the 60° and 120° axis inclusive); or

No – otherwise.

4.2 Effectiveness Hypotheses

Primary Effectiveness

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

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

Frequency and percentage of lenses classified as 'Yes' will be provided for AOHG toric and AO toric, and two-sided 95% confidence intervals (CI) based on the exact binomial distribution will be calculated. The following SAS pseudocode will be used to obtain the confidence interval.

```
proc freq data=effdata order=data;
 by trtpn;
 tables response_outcome/binomial (exact);
run;
```

A threshold of 90% (as a minimum) has been established for this endpoint based on historical data. Therefore, percent of 'Yes' for AOHG toric lenses will be compared numerically to 90%.

4.4 Multiplicity Strategy

Since only one endpoint will be tested inferentially, there is no concern for multiplicity.

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 the 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) – ocular and nonocular
- 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 safety hypotheses planned in this study.

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 study lenses, ie, the Baseline/Screening assessment time point during 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.

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, up until the start of the next lens in the crossover sequence.

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

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 from Baseline/Screening to any subsequent time point will be presented. A supportive listing will be generated which will include all biomicroscopy data from all assessment time points for these eyes experiencing the increase.

The following tables and supportive listings will be provided:

- Frequency and Percentage for Biomicroscopy Findings by Visit (Baseline, Exit)
- 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 table and supportive listings will be provided:

- Frequency of Treatment-Emergent Device Deficiencies
- Listing of Treatment-Emergent Device Deficiencies
- Listing of Device Deficiencies Prior to Exposure of Study Lenses

6 Analysis Strategy for Other Endpoints

Not Applicable.

7 Sample Size and Power Calculations

Although inferential testing is not planned for the primary effectiveness endpoint, expected precision of the observed results is provided. A two-sided 95% confidence interval for a single proportion will extend approximately 0.10 from the observed value when the expected proportion is 0.90, with a sample size of 30.

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 Schedule of Study Procedures and Assessments

Procedure/ Assessment	Baseline/ Screening	Exposure Pair 1 – Period 1	Exposure Pair 2 – Period 2	Exit
Informed Consent	✓	-	-	-
Demographics	✓	-	-	-
Medical History	✓	-	-	-
Concomitant Medications	✓	-	-	(✓)
Inclusion/Exclusion	✓	-	-	-
Habitual lens information (brand, power, axis)*	✓	-	-	-
VA w/ habitual correction (Snellen distance)*	✓	-	-	✓
Manifest refraction*	✓	-	-	-
BCVA (Snellen distance with manifest refraction)*	✓	-	-	-
[redacted]				
Biomicroscopy[#]	✓	-	-	✓
Fit study lenses	-	✓	✓	-
Axis orientation 10 (+2) min after insertion[1]	-	✓	✓	-
[redacted]				

Procedure/ Assessment	Baseline/ Screening	Exposure Pair 1 – Period 1	Exposure Pair 2 – Period 2	Exit
[redacted]				
Adverse Events	✓	✓	✓	✓
Device deficiencies	✓	✓	✓	✓
Exit Form	(✓)	(✓)	(✓)	✓

(✓) if applicable;
* Source only
[redacted]
[1] Data will be used for deriving primary effectiveness endpoint.
[redacted]
[#] PI may choose to take photograph or video of slit lamp observations

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
12/11/2017 17:18:39	[redacted]	[redacted]
12/11/2017 18:33:00	[redacted]	[redacted]
12/11/2017 19:52:21	[redacted]	[redacted]
12/11/2017 20:00:37	[redacted]	[redacted]