Short Title:

Statistical Analysis Plan LCO115-P001

Full Title:

Statistical Analysis Plan LCO115-P001 / NCT02965820

Protocol Title:	Clinical Study of Opti-Free® PureMoist® for Presbyopic Contact Lens Wearers
Project Number:	LCO115-P001
Protocol TDOC Number:	TDOC - 0052944
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 Objectives:

The primary objective is to demonstrate superiority of Opti-Free PureMoist (OFPM) when compared to the subject's habitual multipurpose solution (HMPS) in reducing symptoms of contact lens induced dryness after 30 days of use, based on responses to the CLDEQ-8 (abbreviated Contact Lens Dry Eye Questionnaire).

Decision Criteria for Study Success:

Success of this study will be based on demonstration of superiority of OFPM compared to habitual MPS in reducing symptoms of contact lens induced dryness after 30 days of use, based on responses to the CLDEQ-8.

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1 Study Objectives and Design

1.1 Study Objectives

The overall objective of this study is to demonstrate the benefit of OFPM compared to non-HYDRAGLYDE multipurpose contact lens solutions in presbyopes currently wearing soft contact lenses and experiencing symptoms of dryness.

PRIMARY OBJECTIVE

- To demonstrate superiority of OFPM when compared to the subject's HMPS in reducing symptoms of contact lens induced dryness after 30 days of use, based on responses to the CLDEQ-8.

EXPLORATORY OBJECTIVES

[redacted]

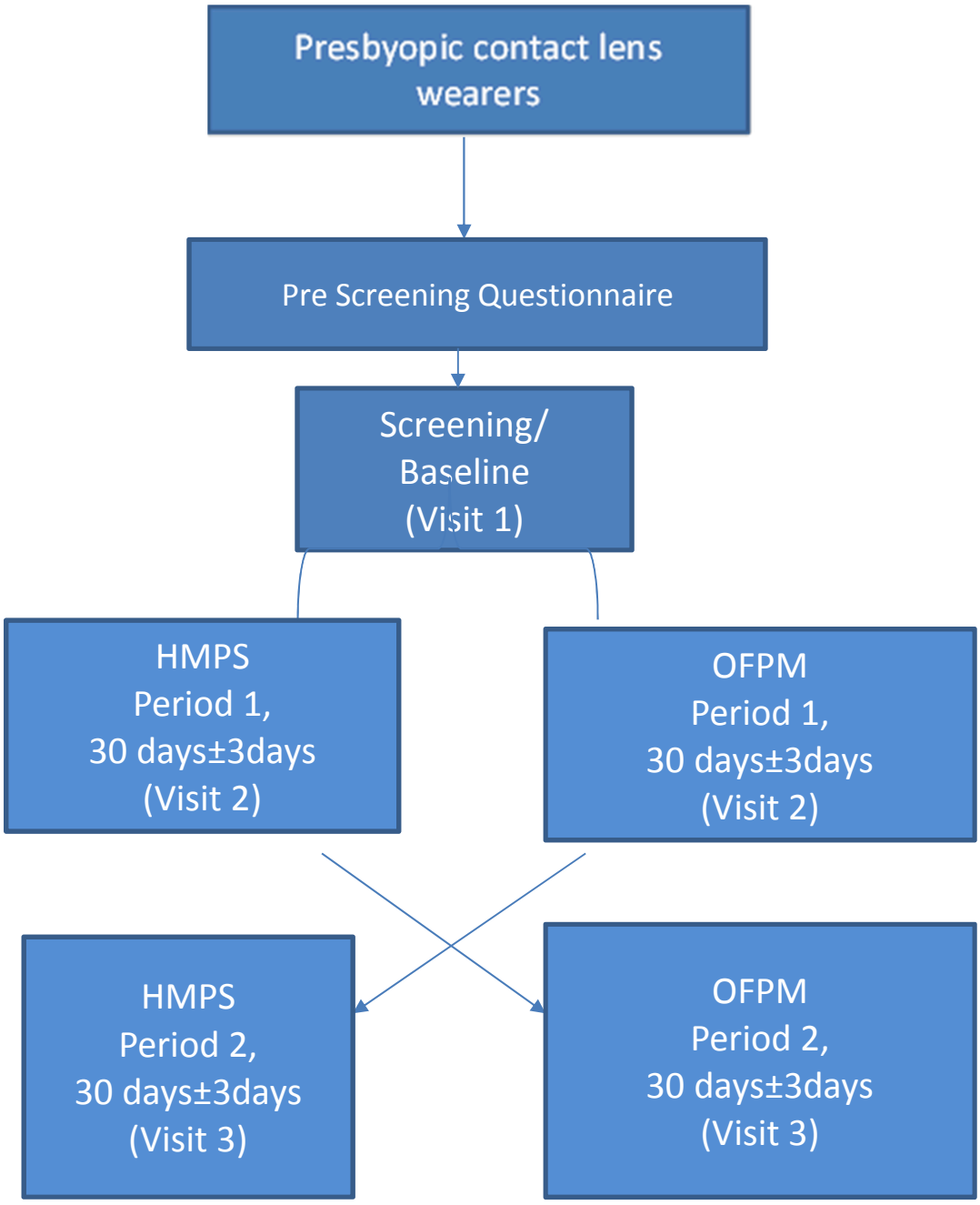
1.2 Study Description

This is a prospective, randomized, crossover (2-treatment, 2-period), observer-masked, and quasi-subject-masked study. The study population will consist of approximately 120 subjects (approximately 8 to 20 subjects per site) to be randomized at approximately 8 United States sites to achieve approximately 110 subjects completed. The enrollment for the study is planned for 6 weeks. The expected duration of subject participation in the study (3 scheduled visits) is 30±3 days per study period (up to 66 days total). Upon completing Pre-screening Questionnaire and satisfying the relevant pre-screening criteria, subjects will sign informed consent and then be considered enrolled into the study. Subjects will be randomized at Visit1, after inclusion and exclusion criteria are confirmed.

Each subject will wear their habitual lens brand (following manufacture recommended replacement) on a daily wear basis for 30 ± 3 days using either OFPM or their habitual solution daily to care for their lenses.

The planned visit schedule is depicted in Figure 1.2.-1.

Figure 1.2-1 Flow Diagram of Study



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 contact lens solution assignment. Subjects eligible after screening at Visit 1 will be randomized (1:1) to receive either OFPM or HMPS to care for their lenses in Period 1 of the study. For Period 2, the contact lens solution that was not allocated for use in Period 1 will be dispensed. Randomization will be blocked to ensure a balance of study treatment (lens care sequence) allocation within investigational sites. Randomization will be implemented in an Electronic Data Capture (EDC) system.

1.4 Masking

This study is investigator-masked and subject quasi-masked (masked to test solution brand only), with subjects randomized to the order in which they will use OFPM and their HMPS for 30±3 days each. The Investigator will not be aware of the specific treatment being administered and the subject will not be aware of the brand of the test solution. Excluding the study monitor, Lead CSM, and person responsible for generating the randomization schedule, all Alcon study personnel will also be masked. This level of masking will be maintained throughout the conduct of the study. 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 treatment 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 the newly dispensed habitual lenses for the study disinfected with at least one study lens product evaluated in this study. 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 care products exposed.

2.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who are exposed to at least one of the study lens care products as defined for the Safety Analysis Set. Each subject will be classified according to the respective lens care products in the randomized lens sequence, irrespective of the exposure. FAS will serve as the primary analysis dataset for all efficacy evaluations.

2.3 Per Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of all randomized subjects and excludes all data/subjects which have met any of the critical deviation or evaluability criteria identified in the Deviations and Evaluability Plan. Each subject will be classified according to the respective lens care products in the randomized lens sequence, irrespective of the exposure.

3 Subject Characteristics and Study Conduct Summaries

Demographic information (age, sex, ethnicity, race) will be summarized on the safety, full, and PP analysis sets. Baseline characteristics on habitual lens and lens care information as well as activities, CLDEQ-8, [redacted], [redacted] will be summarized on the full and PP analysis sets. Due to the crossover design, demographic and baseline data will be presented by lens care sequence group and overall.

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.

4 Efficacy Analysis Strategy

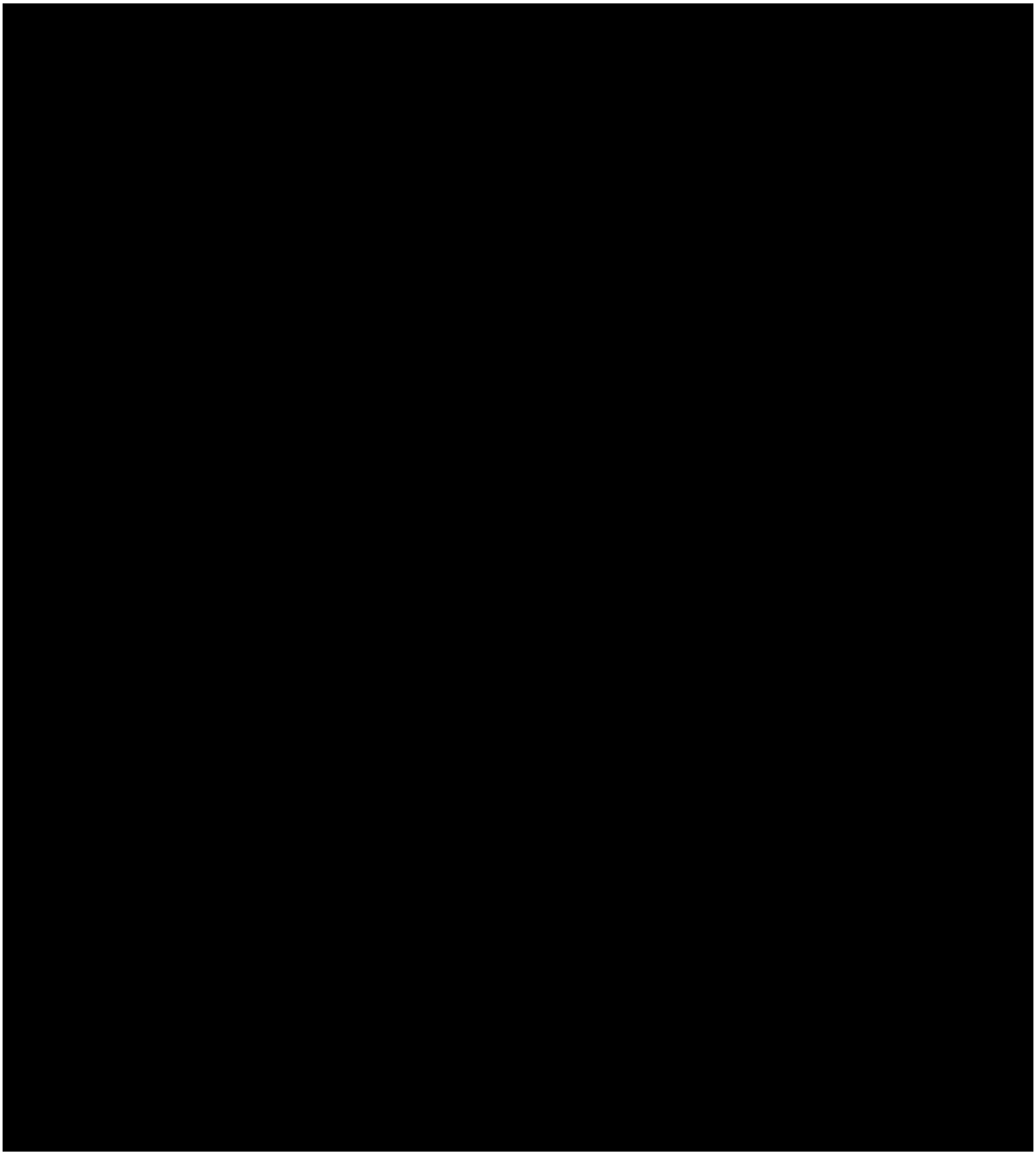
This study defines one primary endpoint [redacted]. The Full Analysis Set will serve as the primary set for all efficacy analyses. [redacted]

4.1 Efficacy Endpoints

Primary Endpoint

The primary endpoint is the score (range 0 to 37) from CLDEQ-8, obtained by adding the numerical responses to each of the 8 items, collected at the Day 30 follow up, for each product (Visit 2 and Visit 3).

[redacted]



4.2 Efficacy Hypotheses

4.2.1 Hypothesis for the Primary Endpoint

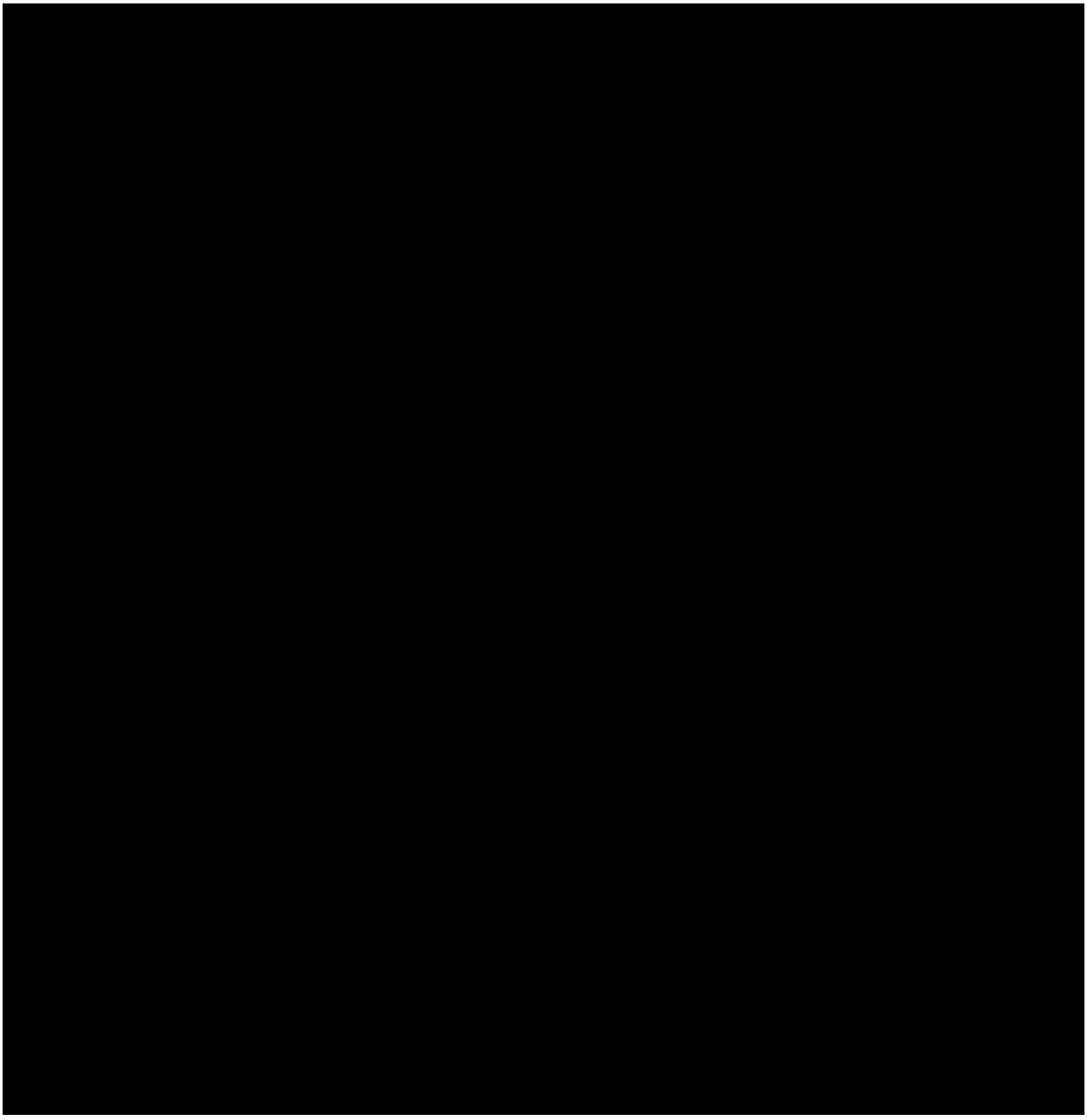
The primary hypothesis to be tested is that OFPM is superior to HMPS in in reducing dryness symptomatology as measured by CLDEQ-8.

The null and alternative hypotheses for the primary efficacy endpoint are formulated as follows:

$$H_0: \mu_{(OFPM)} - \mu_{(HMPS)} \geq 0$$

$$H_a: \mu_{(OFPM)} - \mu_{(HMPS)} < 0$$

where $\mu_{(OFPM)}$ and $\mu_{(HMPS)}$ denote the mean CLDEQ-8 score for OFPM and HMPS, respectively, at the Day 30 follow-up.



[redacted]

4.3 Statistical Methods for Efficacy Analyses

4.3.1 Primary Efficacy Analyses

A mixed effect repeated measures model will be fit to test these hypotheses, including terms for lens care solution, period, sequence group, and baseline CLDEQ-8 as fixed effects and subject as a random effect. Lens care difference (OFPM minus HMPS) and the corresponding one-sided 95% upper confidence limit will be provided. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5 Interim Analysis for Efficacy

No interim analysis is planned for the study.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events
- Biomicroscopy Findings
  - Limbal hyperemia
  - Bulbar hyperemia

- Corneal infiltrates
- Other Findings
- Conjunctival staining
- Lid Papillae
- Corneal staining

- 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. The 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 the study lens care for period 1 and period 2. The period for treatment-emergent AE analysis starts from exposure to the study lens care for period 1 and period 2 until the subject completes or is discontinued from the study.

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 special classes of AEs such as treatment-related AEs and serious AEs. AEs leading to study discontinuation will be identified. Presentation of ocular AEs will be by eye.

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

5.3.2 Biomicroscopy Findings

Baseline is defined to be Visit 1. Each biomicroscopy parameter will be tabulated by its grade, at Baseline and Day 30. A shift table showing grade at baseline relative to Day 30 will also be presented for each parameter. For each biomicroscopy parameter, counts and percentages of eyes that experience an increase of ≥ 2 grades from baseline to any subsequent visit will be presented. A supportive listing will be generated which will include all biomicroscopy data from the affected visit for these eyes experiencing the increase of ≥ 2 grades, with the following variables: lens care solution, 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 of investigational products, and treatment-emergent) will be provided.

6 Analysis Strategy for Other Endpoints

Not Applicable

7 Sample Size and Power Calculations

Sample size calculation for each of the relevant efficacy endpoints is described below.

Primary Efficacy:

Sample size calculation for the primary efficacy hypothesis on decrease in symptomatology is based on published data (Chalmers 2012). With an assumed standard deviation for paired differences of 10, a sample size of 36/sequence will provide 80% power to detect a difference of 3 at one-sided α=0.05.

[redacted]

8 References

Chalmers RL, Begley CG, Moody K, Hickson-Curran SB. Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and Opinion of Contact Lens Performance. Optom Vis Sci. 2012; 89 (10):1415-1442.

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

	Visit 1	Visit 2	Visit 3	USV
Procedure/Assessment	**Screening & Baseline Period 1/ Day 1**	**Period 1 Day 30±3 Follow-Up Period 2/Day 1**	**Period 2 Day 30±3 Follow-Up /Exit**	**Unscheduled Visit**
Pre-Screening questionnaire (Symptomatology, Digital Device use, and HMPS identification)[a]	X (before consent)			
Informed consent	X			
Collect demographics and activities	X			
Medical and lens/lens care history	X			
Concomitant medications/ changes in concomitant medications	X	X	X	X
Subjective (manifest) refraction[a]	X	(X)	(X)	(X)
BCVA[a]	X	(X)	(X)	(X)
Inclusion/exclusion	X			
Randomization	X			
Dispense a new pair of habitual lenses and assign/dispense the study lens care solution per randomization. Educate on instructions for use.	X	X		(X)
Snellen VA with lenses	X[b]	X[b,d]	X[d]	(X)
[redacted]				
Biomicroscopy	X	X	X	X
CLDEQ-8 Questionnaire	X[c]	X	X	

[redacted]				
Assess AEs	X[e]	X	X	
Assess device deficiencies	X	X	X	X
Document wear time compliance (days, hours) and lens care compliance[a]		X	X	(X)
Exit form	(X)	(X)	X	(X)

[a]Source only
[b]With new lenses being dispensed at the visit
[c]Based on habitual regimen
[d]With lenses worn for the study period.
[e]AEs are collected from the time of informed consent.
(X)= as needed.

AEs=adverse events, BCVA=best corrected visual acuity, CLDEQ-8=Contact Lens Dry Eye Questionnaire-8, HMPS= Habitual multi-purpose solution, IRB= Institutional review board, USV=unscheduled visit, VA=visual acuity