Short Title:

Statistical Analysis Plan
CLL949-C010

Full Title:

Statistical Analysis Plan - US
CLL949-C010 / NCT04085328

Protocol Title:	Clinical Safety and Effectiveness Assessment of an Investigational Frequent Replacement Silicone Hydrogel Lens
[redacted]	[redacted]
Reference Number:	
Protocol TDOC Number:	TDOC-0055758
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
Approvals:	See last page for electronic approvals.
Job Notes:	

This is the fourth revision (Version 5.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 5.0 of the study protocol.

Executive Summary:

Key Objectives:

The objective of this study is to demonstrate safety and effectiveness of [redacted] soft contact lenses as compared to BIOFINITY® (Biofinity) soft contact lenses, when both study lenses are worn for extended wear (6 nights/7 days of continuous wear followed by 1 night of no lens wear) and replaced on a weekly basis.

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in proportion of ocular serious and significant non-serious adverse device effects (ADEs) with [redacted] soft contact lenses when compared to Biofinity soft contact lenses, using a margin of 0.05.

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List of Tables

1 Study Objectives and Design

[redacted].

[redacted] this statistical analysis plan describes the analytical strategy to be undertaken to evaluate the Primary cohort [redacted]

1.1 Study Objectives

PRIMARY OBJECTIVE

The objective of this study is to demonstrate safety and effectiveness of [redacted] soft contact lenses as compared to Biofinity soft contact lenses, when both study lenses are worn for extended wear (6 nights/7 days of continuous wear followed by 1 night of no lens wear) and replaced on a weekly basis.

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 or extended wear frequent replacement soft contact lens wearers, have at least 3 months of soft contact lens wearing experience, and who wear their habitual lenses at least 5 days per week. Subjects must have regularly worn their habitual lenses for at least **10 hours** per day. Additionally, extended wear lens wearers must have regularly worn their habitual lenses for at least 1 night per week. Subjects must require contact lens correction in the power range available for this study as specified in the inclusion criteria. [redacted]Pregnant and breastfeeding women are excluded from this study.

	Primary Cohort [redacted] o Completed: minimum 213 completed each in test and control o Planned: ~632 enrolled, and ~568 randomized (~284 each in test and control) [redacted]
Number of Sites	~45 (US) [redacted]
Test Product	[redacted] soft contact lenses [redacted]
Control Product	CooperVision® BIOFINITY® (comfilcon A) soft contact lenses (Biofinity)
Duration of Treatment	Approximately 12 months
Visits	Visit 1: Baseline/Dispense Visit 2: 24-Hour Follow-Up (24 ± 4 hours) Visit 3: 1-Week Follow-Up (7 ± 2 days) Visit 4: 1-Month Follow-Up (30 ± 4 days) Visit 5: 2-Month Follow-Up (60 ± 7 days) Visit 6: 3-Month Follow-Up (90 ± 7 days) Visit 7: 6-Month Follow-Up (189 -7/+14 days) Visit 8: 9-Month Follow-Up (270 ± 14 days) Visit 9: 12-Month Follow-Up/Exit (365 ± 14 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. Randomization will be implemented in the Electronic Data Capture (EDC)/Interactive Response Technology (IRT) integration system.

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

[redacted]

[redacted]

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

1.4 Masking

This study is double-masked.

[redacted].

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. [redacted]

2.3 Enrolled Not Dispensed

Enrolled Not Dispensed is a subset of All Enrolled subjects/eyes that have not been exposed to study lenses. [redacted]

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 visual acuity (VA) with study lenses, collected in Snellen, for each eye. Conversion will be made to the logMAR scale.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [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, 24 hours, 1 week, 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 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]

[redacted]

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

Primary Endpoint

The primary safety endpoint is the proportion of ocular serious and significant non-serious ADEs, calculated as the number of eyes reporting at least one treatment-emergent device-related ocular serious adverse event (AE) or treatment-emergent device-related ocular significant non-serious AE. A binary variable will be defined for each eye as present/absent with the event of interest.

Other Endpoints

Other safety endpoints include the following:

- AEs (non-serious, non-significant)
- 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

Primary Safety

The null and alternative hypotheses for the primary analysis are formulated in terms of the predefined margin of 0.05 for noninferiority:

H_0: $P_T - P_C \geq 0.05$
H_a: $P_T - P_C < 0.05$

where P_T and P_C denote the proportion of eyes reporting ocular serious and significant non-serious ADEs with Mercury and Biofinity contact lenses, respectively.

Other Safety

No inferences are to be made on other safety endpoints; therefore, no hypotheses are formulated.

5.3 Statistical Methods for Safety Analyses

5.3.1 Primary Safety Analysis

Proportion of events will be analyzed using a generalized linear model, with a logit link function, accounting for within-subject correlation. Site and Site-by-Treatment interaction terms will also be included to assess potential effect of sites on treatment difference. A one-sided 95% upper confidence limit (UCL) will be calculated for the difference in proportions between treatments (Mercury minus Biofinity), and the null hypothesis will be rejected if UCL < 0.05.

[redacted]

[redacted]

[redacted]

5.3.2 Other Safety Analysis

5.3.2.1 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 [redacted] 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). 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.

5.3.3 Biomicroscopy Findings/Slit Lamp Examination

Biomicroscopy assessment will be performed at all study visits, including Visit 1 to 9 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.

5.3.4 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]

7 Sample Size and Power Calculations

Sample size calculation was based on extended wear clinical studies from three previous PMA submissions [redacted] and one 52-week extended wear study [redacted] that evaluated 5 currently marketed silicone hydrogel contact lenses. The weighted average, based on sample size, on the proportion of ocular serious or significant non-serious ADEs obtained from these five contact lenses was 0.045. Therefore, assuming that the expected difference between test and control is 0 and that the control proportion is 0.045, a sample size of 213 per group will provide 80% power to reject the null hypothesis of inferiority in test compared to control, with a noninferiority margin of 0.05 (5%).

[redacted]

Taking into consideration the exposure duration of 12 months, approximately 568 subjects will be randomized (284 test and 284 control) to compensate for approximately 25% drop-out rate.

[redacted]

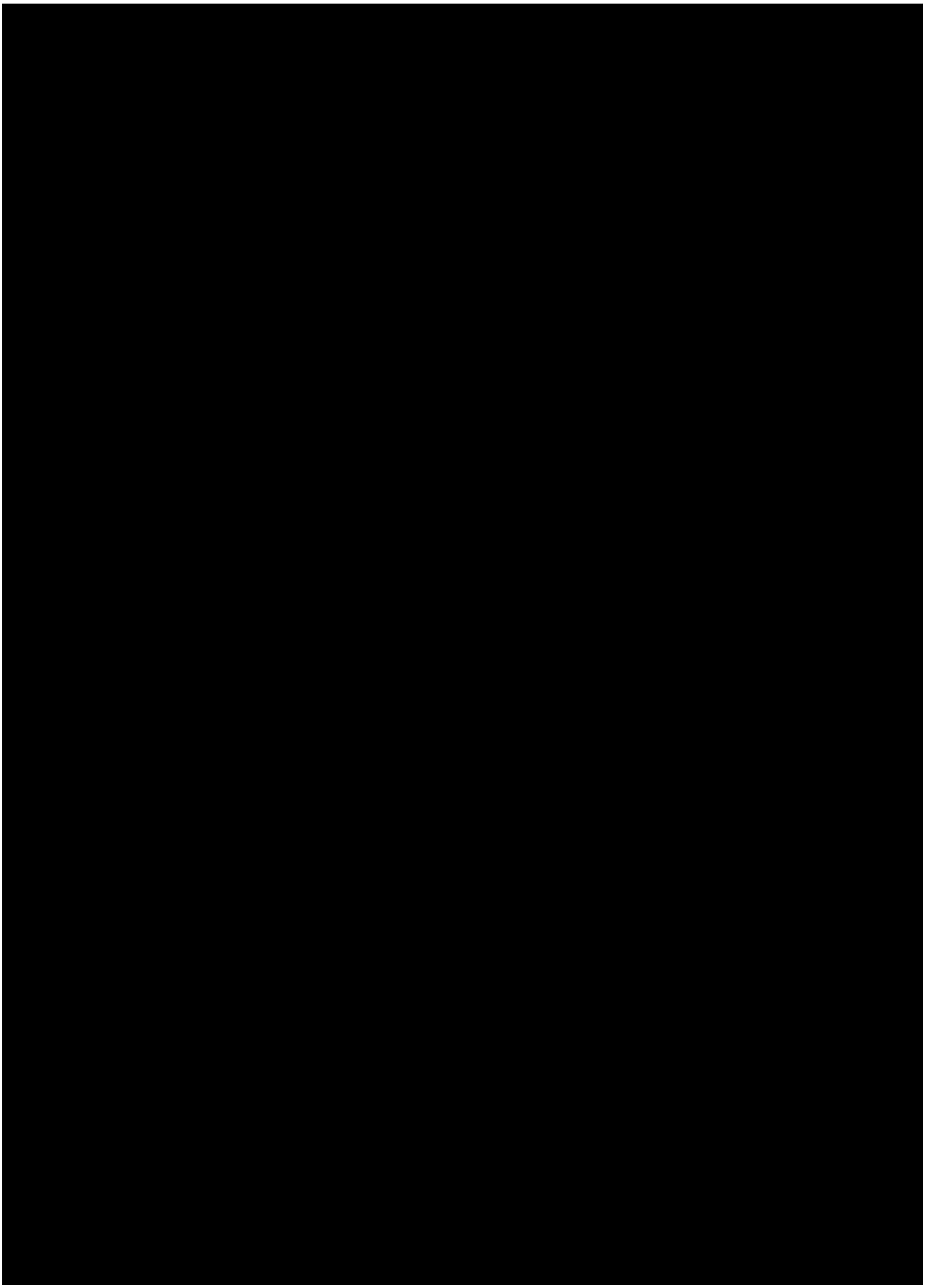
[redacted]

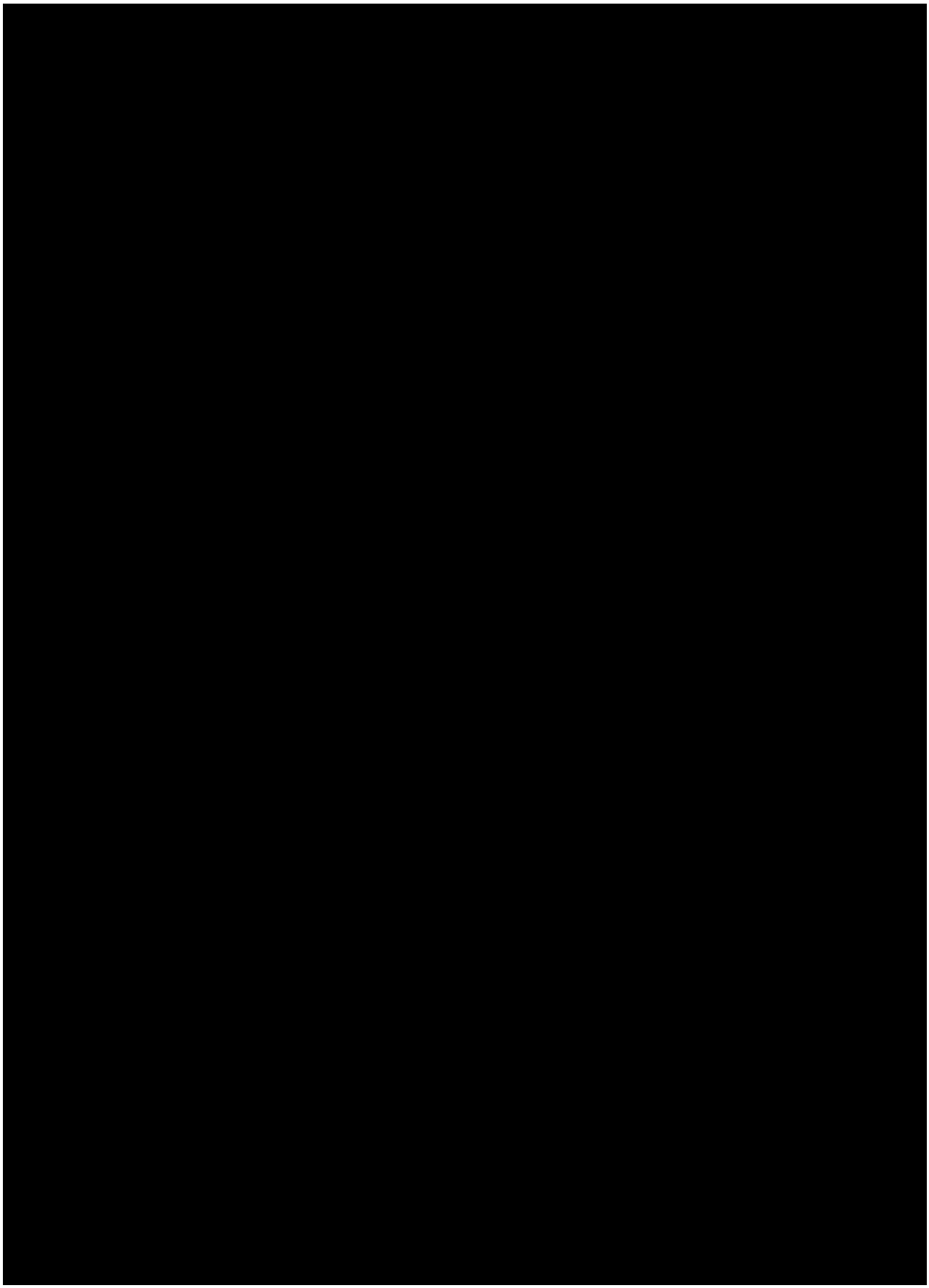
10 Revision History

Revision 4

This is the fourth revision (Version 5.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 5.0 of the study protocol.

[redacted]





[redacted]

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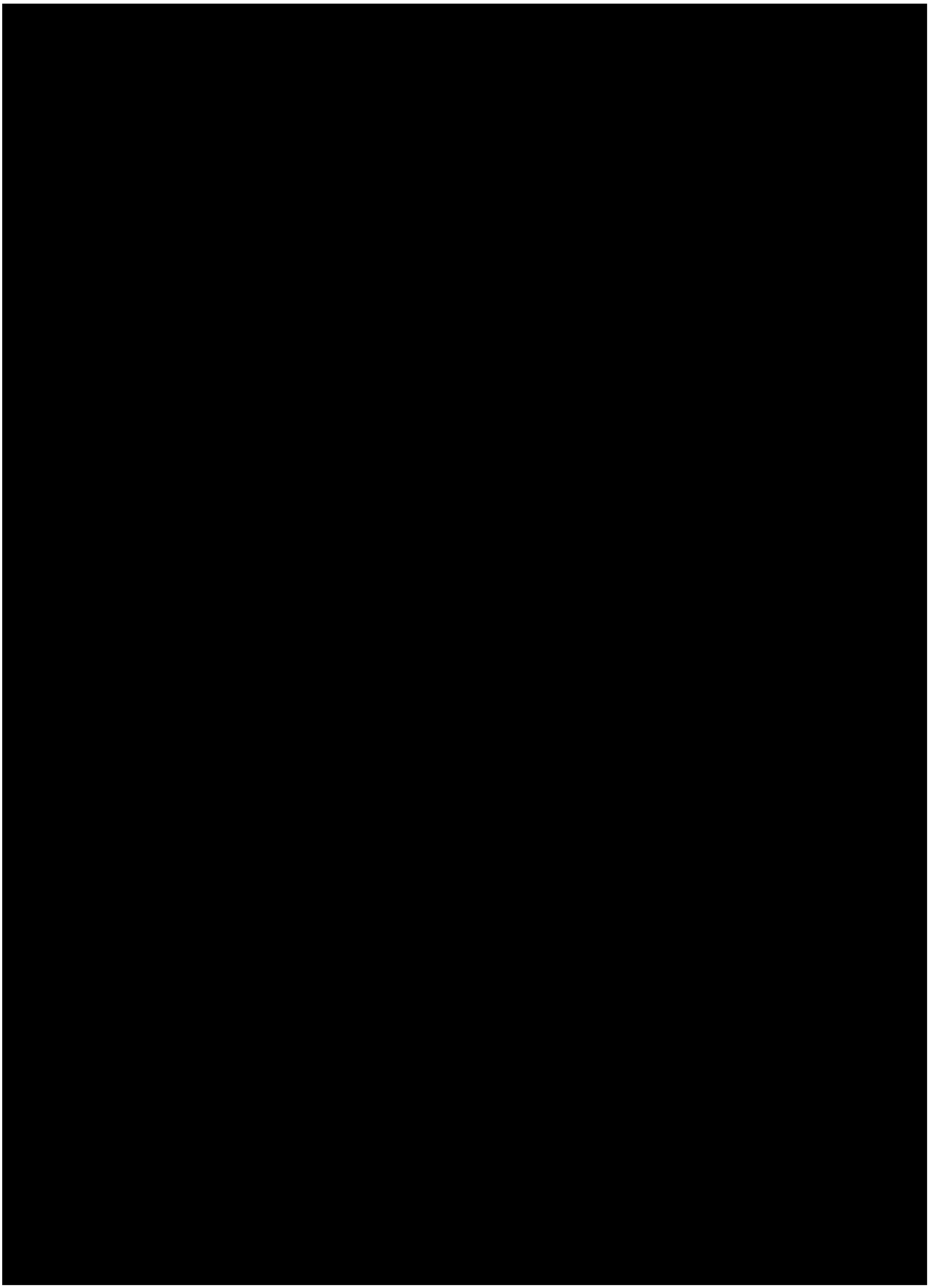

11 Appendix

Table 11-1 Schedule of Study Procedures and Assessments[α]

Procedure/Assessment	Baseline	Follow-Up Visits							Exit	Early Exit	USV
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9		
	Day 1 Dispense	24 hrs Day 2 ± 4 hrs	1-week Day 7 ± 2 d	1-month Day 30 ± 4 d	2-months Day 60 ± 7 d	3-months Day 90 ± 7 d	6-months Day 189 -7 / + 14 d	9-months Day 270 ± 14 d	12-months Day 365 ± 14 d		
Informed Consent	✓	-	-	-	-	-	-	-	-	-	-
Demographics	✓	-	-	-	-	-	-	-	-	-	-
Medical History including pregnancy[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	(✓)
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	(✓)
Inclusion/Exclusion	✓	-	-	-	-	-	-	-	-	-	-
Habitual lens information (brand / manufacturer, modality, power, wear success, habitual lens care brand)	✓	-	-	-	-	-	-	-	-	-	-
Distance VA w/ habitual correction (Snellen)	✓	-	-	-	-	-	-	-	✓	✓	(✓)
Manifest refraction	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	✓	✓	(✓)
[redacted]											
Keratometry	✓	-	-	-	-	-	✓	-	✓	✓	(✓)
Biomicroscopy[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Determine study lens fit and power for each eye [redacted]	✓	-	-	-	-	-	-	-	-	-	-

Procedure/Assessment	Baseline	Follow-Up Visits							Exit	Early Exit	USV
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9		
	Day 1 Dispense	24 hrs Day 2 ± 4 hrs	1-week Day 7 ± 2 d	1-month Day 30 ± 4 d	2-months Day 60 ± 7 d	3-months Day 90 ± 7 d	6-months Day 189 -7 / + 14 d	9-months Day 270 ± 14 d	12-months Day 365 ± 14 d		
[redacted]O/R as necessary.											
Order study lenses	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	-	-	(✓)
IP Dispense	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	-	-	(✓)
Distance VA w/ study lenses (Snellen)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[redacted]

Procedure/Assessment	Baseline	Follow-Up Visits							Exit	Early Exit	USV
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9		
	Day 1 Dispense	24 hrs Day 2 ± 4 hrs	1-week Day 7 ± 2 d	1-month Day 30 ± 4 d	2-months Day 60 ± 7 d	3-months Day 90 ± 7 d	6-months Day 189 -7 / + 14 d	9-months Day 270 ± 14 d	12-months Day 365 ± 14 d		
[redacted]											
Symptoms, problems & complaints[4]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]											
Study lens and accessories return log	(✓)	✓	✓	✓	✓	✓	✓	✓	✓	✓	(✓)
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	(✓)
Device deficiencies	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	(✓)
Exit Form	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	✓	✓	(✓)
[redacted]											

[α] See Section 26 of the MOP (Manual of Procedures) for a chronological order of procedures per visit

(✓) assessment performed as necessary, eg, decrease of VA by 2 lines or more with IP.

USV=Unscheduled Visit

[1] Pregnancy to be self-reported by subject

[redacted]

[4] Symptoms, problems, and complaints will include burning/stinging, itching, lens awareness, dryness, discomfort, blurred vision, fluctuating/variable vision, halo, lens needs cleaning, redness, excessive tearing, secretions, photophobia, and other (description required). The response will be recorded as “present” or “absent”.

[redacted]