Short Title:

Statistical Analysis Plan CLL541-P001

Full Title:

Statistical Analysis Plan CLL541-P001 / NCT03169153

Protocol Title:	One-month clinical comparison of silicone hydrogel monthly lenses in high lipid depositors
Project Number:	CLL541-P001/ NCT03169153
Reference Number:	
Protocol TDOC Number:	TDOC-0053541
Author:	[redacted]
	[redacted]
Template Version:	Version 4.0, approved 16MAR2015
Approvals:	See last page for electronic approvals.
Job Notes:	

This is the second revision (Version 3.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 and Version 3.0 of the study protocol.

Executive Summary:

Key Objective:

To demonstrate superiority of AIR OPTIX® plus HydraGlyde (AOHG) compared with ACUVUE® VITA® (VITA) in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.

Decision Criteria for Study Success:

Success of this study will be based on demonstration of superiority of AOHG compared with VITA in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.

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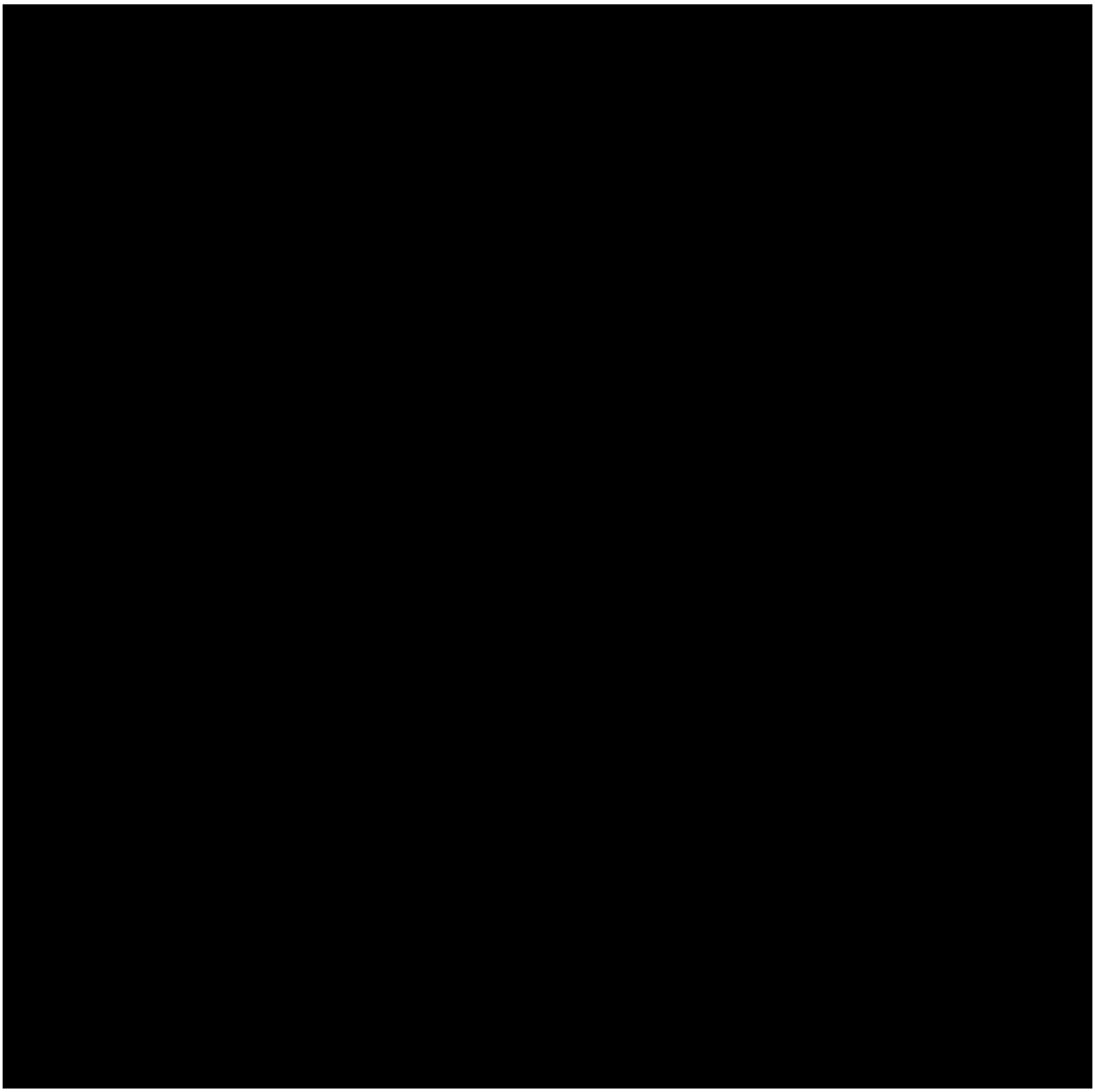
1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary aim of the study is to confirm that a silicone hydrogel contact lens that attracts lower levels of total lipids *in vitro* (AOHG) also attracts lower levels of total lipids *in vivo* compared with a silicone hydrogel contact lens with high *in vitr*o lipid attraction (VITA) in habitual high lipid depositor lens wearers. Therefore, the primary objective is to demonstrate superiority of AOHG compared with VITA in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.



1.2 Study Description

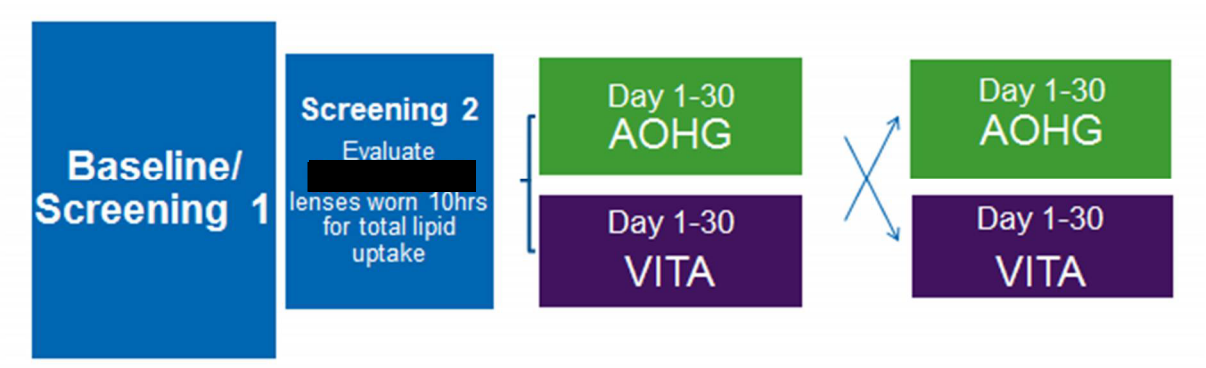
Key components of the study are summarized in Table 1-1.

Table 1-1 Study Description Summary

Study Design	Single-site, prospective, randomized, double-masked, crossover study
Study Population	Volunteer subjects at least 18 years of age who wear monthly replacement silicone hydrogel lens and are classified as high lipid depositors. Required: 70 completed (35/sequence) Planned: Approximately 78 randomized and approximately 140 screened/enrolled
Number of Sites	1 (United Kingdom)
Test Product	AIR OPTIX® plus HydraGlyde (AOHG)
Control Product	ACUVUE® VITA® (VITA)
Duration of Treatment	Test Product:30 (+3) days per period; Control Product: 30 (+3) days per period
Visits	Visit 1 (Screening 1/Baseline) Visit 2 (Screening 2) Visit 3 (Day 1 - Insertion Period 1)* Visit 4 (Day 30 + 3 Period 1) Visit 5 (Day 1 - Insertion Period 2) Visit 6 (Day 30 + 3 Period 2/Study Exit) *Randomization will occur at Visit 3 (Day 1)

A study design schematic is depicted in **Error! Reference source not found.**.

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. Randomization will be implemented in iMedidata Balance.

1.4 Masking

This study is double-masked.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

2.1 Safety Analysis Set

Safety analyses will be conducted using the Safety Analysis Set on a treatment-emergent basis. The Safety Analysis Set will include all subjects/eyes exposed to any study lenses (AOHG or VITA) evaluated in this study. Subjects who are lost to follow-up and their exposure to dispensed study lenses is unknown will be included in the safety data set. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual lens exposed in the corresponding lens sequence.

Adverse events occurring from the time of informed consent but prior to first exposure to study lenses (AOHG or VITA) will be summarized in subject listings.

2.2 Full Analysis Set (FAS)

The FAS is the set of all randomized subjects who are exposed to any study lenses (AOHG or VITA) evaluated in this study.

2.3 Per Protocol (PP) Analysis Set

The PP Analysis Set is a subset of all randomized subjects and excludes all data/subjects that meet any of the critical deviation or non-evaluable criteria identified in the Deviations 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 [habitual lens VA, habitual lens care solution]

In addition, the following subject listings will be provided:

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

4 Effectiveness Analysis Strategy

This study defines 1 primary, endpoints. All effectiveness evaluations will use the FAS as the primary analysis set. Supportive analyses of the primary 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.

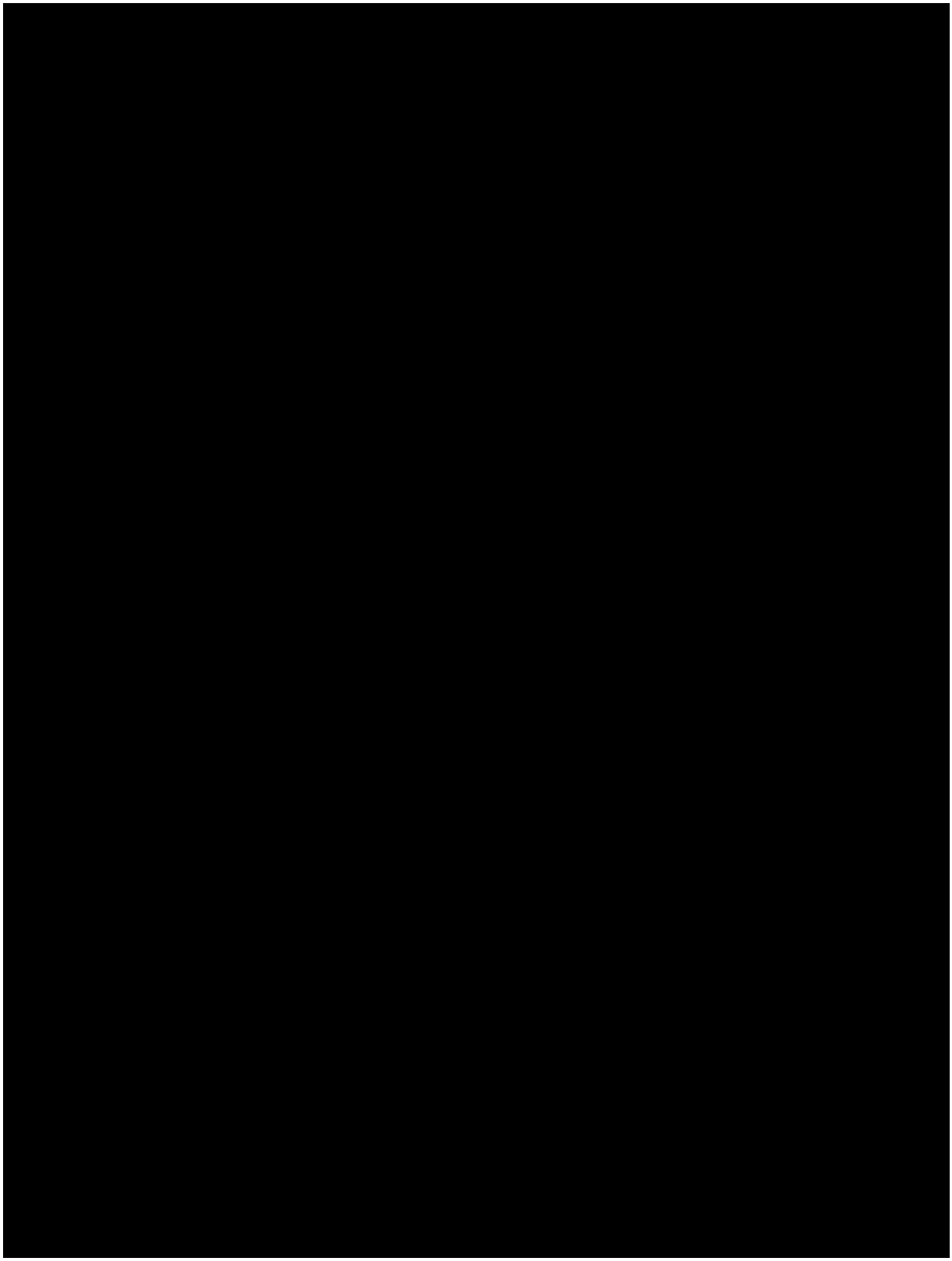
For all planned inferential analyses, alternative models/methods may be considered if convergence cannot be achieved. Furthermore, if significant carryover effects are noted (confounded with sequence effect), results will be examined by period to ensure the overall conclusion is valid.

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 analysis.

4.1 Efficacy Endpoints

Primary Endpoint

The primary endpoint is the total amount of lipids (µg) absorbed/adsorbed and extracted (total of surface and bulk uptake) from worn test and control lenses at Day 30. Only OD lenses will be used for the *ex vivo* analysis.



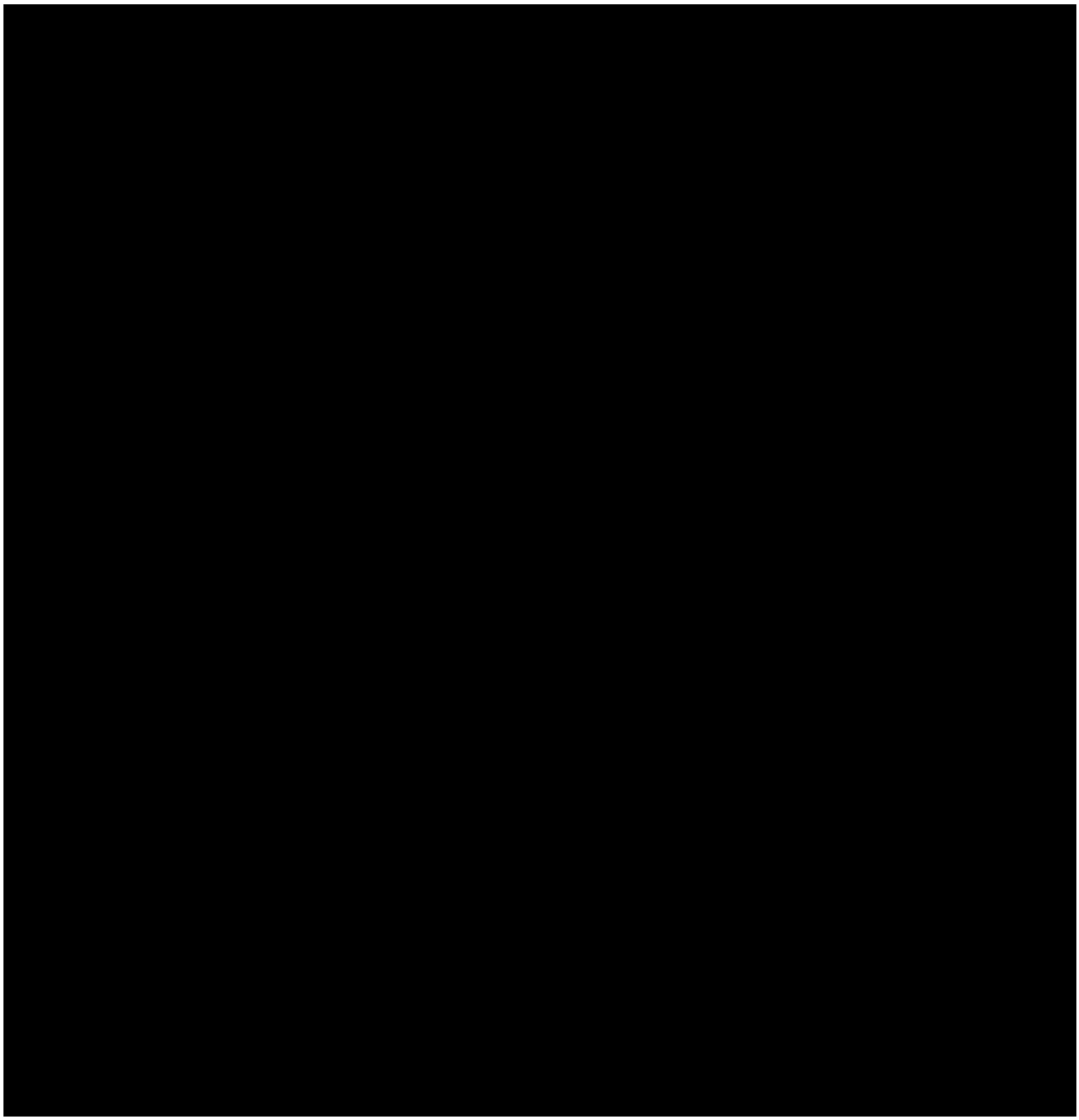
4.2 Effectiveness Hypotheses

Primary Effectiveness

The null and alternative hypotheses are formulated as follows:

H_0: $\mu_T - \mu_C \geq 0$
H_a: $\mu_T - \mu_C < 0$

where μ_T and μ_C represent the mean total lipid uptake (total of surface and bulk uptake) measured from the test and control lenses, respectively.



[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

A mixed effect repeated measures model will be fit to test these hypotheses. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.6 Interim Analysis for Efficacy

There are no plans to conduct an interim analysis and no criteria by which the study would be terminated early based upon statistical determination.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are

- Adverse events
- Biomicroscopy Findings/Slit Lamp Examination
    - Limbal hyperemia
    - Bulbar hyperemia
    - Conjunctival compression/indentation
    - Chemosis
    - Corneal vascularization
    - Palpebral conjunctival observations
    - Corneal infiltrates
    - Anterior Segment Inflammation
    - Other findings
    - Bulbar Conjunctival staining
    - 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. Safety variables will be summarized descriptively. Baseline will be defined as the last

measurement prior to exposure to study lens. For biomicroscopy data, baseline will be defined as Visit 3 for Period 1 and Visit 5 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.

Analysis and presentation of pre-treatment and between-treatment AEs will be separated from treatment-emergent AEs occurring during the study periods. A pre-treatment AE is an event that occurs after signing informed consent but prior to exposure to study lenses (AOHG or VITA). A between-treatment AE is an event that occurs after last exposure to Period 1 lenses but prior to exposure to Period 2 lenses. The period for treatment-emergent AE analysis starts from exposure to the study lenses for Period 1 or Period 2 until the subject completes or isdiscontinued from the study.

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
- Incidence of Serious Ocular Treatment-Emergent Adverse Events
- Incidence of Serious Nonocular Treatmen-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
- Shift Analysis for Biomicroscopy Findings from Baseline by Visit
- Incidence of Increased Severity of 2 or More Grades in Biomicroscopy Findings
- Listing of Subjects With Other Biomicroscopy Findings
- Listing of Subjects With Increase of Severity of 2 or More Grades in Biomicroscopy Findings from Visit 3/Visit 5 to Any Subsequent Visit within Each Period

[This listing will include all visits within the affected period.]

- Listings of Subjects with Infiltrates

5.3.3 Device Deficiencies

The following tables and supportive listings will be provided:

- Frequency of Device Deficiencies
- Listing of Treatment-Emergent Device Deficiencies
- Listing of Device Deficiencies Prior To Treatment Exposure

6 Analysis Strategy for Other Endpoints

Not Applicable.

7 Sample Size and Power Calculations

[redacted]

Sample sizes per sequence group required to attain 80% power at 1-sided, α=0.05 for the primary [redacted] endpoints are shown below:

Endpoint	Assumptions	N/sequence group
Primary		
Ex vivo total lipid uptake	SD paired differences = 13.88 Detectable difference = 10	7 (based on t-test for difference of means in 2x2 crossover design)
[redacted]		

8 References

N/A.

9 Revision History

Revision 2

This is the second revision (Version 3.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 and Version 3.0 of the study protocol.

[redacted]

Itemized Changes:

Section	Information Changed
[redacted]	

Revision 1

This is the first revision (Version 2.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 and Version 3.0 of the study protocol.

Summary of changes:

- To expand the time period between Visit 2 and Visit 3

[redacted]

Itemized Changes:

<table>
<tr><th>Section</th><th>Information Changed</th></tr>
<tr><td>Section 1.1 (Page 5)
Primary Objective</td><td>Changed from

The primary objective is to demonstrate superiority of AOHG compared with VITA in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.

Changed to

The primary aim of the study is to confirm that a silicone hydrogel contact lens that attracts lower levels of total lipids in vitro (AOHG) also attracts lower levels of total lipids in vivo compared with a silicone hydrogel contact lens with high in vitro lipid attraction (VITA) in habitual high lipid depositor lens wearers. Therefore, the primary objective is to demonstrate superiority of AOHG compared with VITA in total lipid uptake (total of surface and bulk uptake) after 30 days of wear by high lipid depositors.</td></tr>
<tr><td>Section 10 (Page 17)
Overview of Study Plan</td><td>Changed from

<table><tr><th>Visit 3
(Period 1)/
Visit 5
(Period 2)</th></tr><tr><td>Day 1-Insertion
1 to 14 days from Visit 2 and Visit 4 respectively
No lenses worn</td></tr></table>
Changed to

<table><tr><th>Visit 3
(Period 1)/
Visit 5
(Period 2)</th></tr><tr><td>Day 1-Insertion
Within 80 days from Visit 2 and 1 to 14 days from Visit 4 respectively
No lenses worn</td></tr></table></td></tr>
</table>

	[redacted]

10 Appendix

Table .10–1 Overview of Study Plan

	Visit 1	Visit 2	Visit 3 (Period 1)/ Visit 5 (Period 2)	Visit 4 (Period 1)/ Visit 6 (Period 2, Exit)	USV
Assessment	**Screening 1/ Baseline** *Habitual lenses worn*	**Screening 2** 1 to 7 days from Visit 1 After 10 h (± 30 min) wear of [redacted]	**Day 1-Insertion** Within 80 days from Visit 2 and 1 to 14 days from Visit 4 respectively *No lenses worn*	**Day 30 (+3 days)** After 10 h (± 30 min) wear of study lenses **Early Exit**	
Informed Consent	✓				
Randomization			✓[a]		
Demographics	✓				
Medical History/CL wear history	✓				
Concomitant Medications	✓	✓	✓	✓	✓
Inclusion/Exclusion	✓	✓	✓		
[redacted]					
Conduct a spherical over-refraction and optimize the Rx as required	✓[b]		✓		
LogMAR VA with lenses	✓[b]		✓	✓	(✓)
BCVA with Manifest Refraction[c]	✓	✓	✓	✓	✓
Biomicroscopy	✓	✓	✓	✓	✓
[redacted]					
Assess Lens Fit	✓[c, e]		✓	✓	
[redacted]					

Assessment	Visit 1 **Screening 1/ Baseline** *Habitual lenses worn*	Visit 2 **Screening 2** 1 to 7 days from Visit 1 After 10 h (± 30 min) wear of [redacted]	Visit 3 (Period 1)/ Visit 5 (Period 2) **Day 1-Insertion** Within 80 days from Visit 2 and 1 to 14 days from Visit 4 respectively *No lenses worn*	Visit 4 (Period 1)/ Visit 6 (Period 2, Exit) **Day 30 (+3 days)** After 10 h (± 30 min) wear of study lenses **Early Exit**	USV
[redacted]					
Provide [redacted] lenses for 10 h (± 30 min) of wear on the day of Visit 2	✓				
Collect 10-h worn [redacted] lenses for *ex vivo* total lipid uptake analysis		✓[f]			
Collect study lenses for *ex vivo* total lipid uptake analyses				✓	
Complete Exit Form	(✓)	(✓)	(✓)	✓	(✓)
Assess AEs (observed and reported)	✓[g]	✓	✓	✓	✓
Assess Device Deficiencies	✓	✓	✓	✓	✓

a) Randomization to be performed after the Biomicroscopy examination
b) Visit 1 with habitual lenses [redacted]
c) Source document only [redacted]
e) With [redacted] lenses
f) Confirm scheduling of Visit 3 after [redacted] *ex vivo* lipid analysis is complete and eligibility confirmed
g) AEs will be collected from the time of Informed Consent.
(✓) As needed or if a 2-line change in Contact Lens Corrected logMAR VA is observed
AE = adverse event, BCVA = Best Corrected Visual Acuity, CL = contact lens, [redacted] h = hours, logMAR = logarithmic Minimum Angle of Resolution, min = minutes, [redacted], USV = unscheduled visit, VA = visual acuity

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
06/28/2018 20:47:51	[redacted]	[redacted]
06/29/2018 02:07:41	[redacted]	[redacted]
07/03/2018 01:17:42	[redacted]	[redacted]
07/03/2018 16:46:47	[redacted]	[redacted]