Short Title:

Statistical Analysis Plan CLT792-P001

Full Title:

Statistical Analysis Plan CLT792-P001/NCT03757039

Protocol Title:	Multifocal Visual Performance Study – Seamless transition with Precision Profile MF lenses
Project Number:	[redacted]
Protocol TDOC Number:	TDOC-0055656
Author:	[redacted]
	[redacted]
Template Version:	Version 4.0, approved 16MAR2015
Approvals:	See last page for electronic approvals.
Job Notes:	

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 of the study protocol.

Executive Summary:

Key Objectives:

The overall objective is to demonstrate noninferiority of multifocal (MF) contact lenses versus progressive addition lens spectacles (PALs) in the transition time [redacted] in presbyopes.

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in transition time between distance and intermediate vision with MF contact lenses when compared to PALs, using a margin of 0.5.

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective is to demonstrate noninferiority in transition time between distance and intermediate vision with MF contact lenses compared to PALs.

[redacted]

1.2 Study Description

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

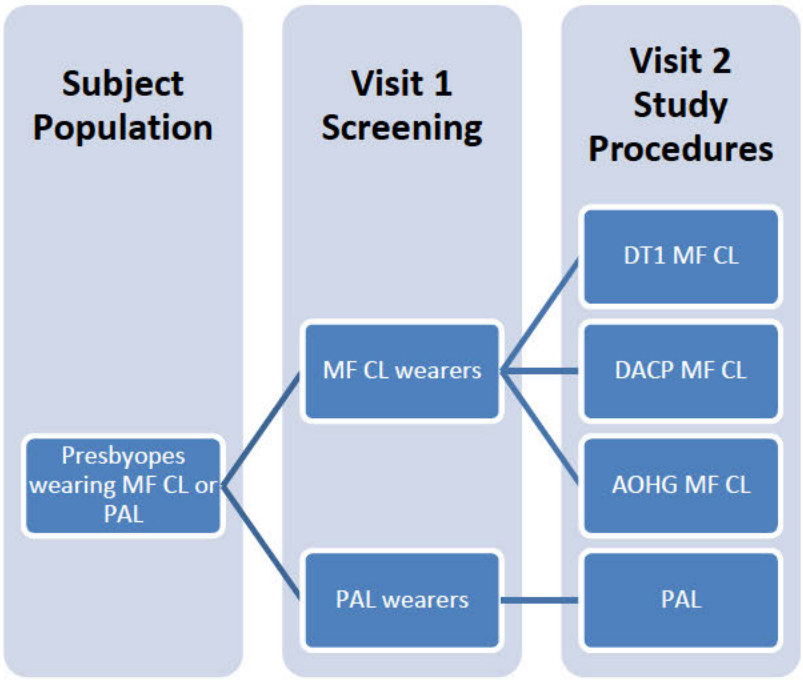
Table 1-1 Study Description Summary

Study Design	Prospective, randomized, parallel group, double-masked for contact lens wearers, single-masked (investigator to type of brand) for PALs wearers
Study Population	Presbyopic subjects aged ≥ 38 and ≤ 58 years with normal eyes (other than correction for refractive error), whose habitual correction is either any MF contact lens (with a preference for Alcon Precision Profile Design wearers) with a LO or MED ADD (or equivalent to an ADD of max +2.00 D) or progressive addition lens spectacles. Wear of habitual correction must be at least 5 days per week and at least 6 hours per day. Target to complete: 48 (12 per group) Planned to enroll: ~60
Number of Sites	2 (1 UK, 1 US)
Test Product(s)	• AIR OPTIX® plus HydraGlyde® (lotrafilcon B) Multifocal contact lens (AOHG MF) • DAILIES TOTAL1® (delefilcon A) Multifocal contact lens

	(DT1 MF) • DAILIES® AquaComfort Plus® (nelfilcon A) Multifocal contact lens (DACP MF)
Control Product(s)	Progressive addition lens spectacles (PALs)
Duration of Treatment	Test product(s): Up to 3 hours Control product(s): Up to 3 hours
Visits	Visit 1 – Screening Visit 2 – Exposure/Exit [0 - 14 days from Visit 1] * *Randomization for subjects in the contact lens group will occur at Visit 2

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

Figure Error! No text of specified style in document.**–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 assignment. Randomization will be implemented in Medidata Rave RTSM.

Qualifying subjects in the contact lens group will be randomized in a 1:1:1 ratio to one of 3 parallel groups to receive either AOHG MF, DT1 MF, or DACP MF, respectively. Habitual PALs wearing subjects will not be randomized.

1.4 Masking

This study is double-masked for contact lens group and single-masked for PALs group (investigators will be masked to type and brand of PAL).

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 product evaluated in this study, except for the lenses used at Visit 2 for the purpose of parameter optimization and fitting as they are not intended for the assessment of safety. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study product exposed.

Adverse events occurring from the time of informed consent but prior to first exposure to study products will be summarized in subject listings.

2.2 Full Analysis Set

The full analysis set (FAS) is the set of all subjects assigned to PALs or randomized to the contact lens group who are exposed to any study product evaluated in this study, except for the lenses used for optimization and fitting.

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 Deviations and Evaluability Plan (DEP).

3 Subject Characteristics and Study Conduct Summaries

The following tables will be presented:

- Subject Disposition
- Analysis Sets
- Subject Accounting
- Demographic Characteristics
- Baseline Characteristics [redacted]

Demographic characteristics and subject accounting tables will be summarized on the safety, full, and per protocol analysis datasets. Baseline characteristics will be summarized on the full and per protocol analysis datasets.

In addition, the following subject listings will be provided:

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

4 Effectiveness Analysis Strategy

This study defines 1 primary, [redacted] All effectiveness evaluations will use the FAS as the primary analysis set. [redacted] analyses of the primary [redacted] 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.

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum and maximum, as well as confidence intervals/limits as applicable. Categorical variables will be summarized with counts 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 primary [redacted]

For all planned inferential analyses, alternative models/methods may be considered, for instance, if convergence cannot be achieved.

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is the average transition time, calculated from all (maximum of 3) voice recorded readings, recorded in seconds, during alternate viewing from distance (4 m) to intermediate (80 cm) and vice versa.

[redacted]

4.2 Effectiveness Hypotheses

Primary Effectiveness

The null and alternative hypotheses for the primary analysis are formulated in terms of the predefined margin of 0.5 for noninferiority:

H_0: $\mu_{(MF)} - \mu_{(PAL)} \geq 0.5$
H_a: $\mu_{(MF)} - \mu_{(PAL)} < 0.5$

where $\mu_{(MF)}$ and $\mu_{(PAL)}$ denote the mean of average transition time between distance and intermediate viewing for MF contact lenses and PALs, respectively.

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

A mixed effect repeated measures model will be utilized to test these hypotheses, with a term for treatment (4 levels: AOHG MF, DT1 MF, DACP MF, and PAL). Within-subject correlation due to multiple observations per subject will be accounted for. Difference between MF (pooling all 3 MF groups) and PAL and the corresponding one-sided 95% upper confidence limit (UCL) will be computed. Noninferiority in transition time will be declared if the UCL is less than 0.5. Furthermore, if noninferiority is demonstrated, subsequent superiority will be tested and declared if UCL is less than 0. Otherwise, no further testing will be carried out on this endpoint.

Analysis of the mixed effect repeated measures model will be implemented in SAS. The pseudocode is provided below.

```
proc sort data = studydata;
by subject;
run;

proc mixed data = studydata;
      class subject lens;
      model transitiontime = lens;
      random subject;
     repeated / subj = subject type = cs;
```

lsmeans lens;
contrast 'Compare MF vs PALs' lens 1 1 1 -3;
run;

Additionally, descriptive statistics will also be provided summarize:

- Average transition time for each individual MF lens group
- Average transition time for distance to intermediate viewing
- Average transition time for intermediate to distance viewing

[redacted]

[redacted]

[redacted]

4.6 Interim Analysis for Effectiveness

No interim analysis is planned for the effectiveness endpoints.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events (AE)
- 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 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 products on Visit 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.

Analysis and presentation of pre-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 products. The period for treatment-emergent AE analysis starts from exposure to study products until the subject completes or is discontinued from the study.

The following tables and supportive listings will be provided:

- Incidence of All Ocular Treatment-Emergent Adverse Device Effects
- Incidence of All Ocular Treatment-Emergent Adverse Events, Not Related
- Incidence of All Ocular Treatment-Emergent Adverse Events, Overall
- Incidence of Ocular Serious Treatment-Emergent Adverse Device Effects
- Incidence of Ocular Serious Treatment-Emergent Adverse Events, Not Related
- Incidence of Ocular Serious Treatment-Emergent Adverse Events, Overall
- Incidence of Ocular Significant Nonserious Treatment-Emergent Adverse Device Effects

- Incidence of Ocular Significant Nonserious Treatment-Emergent Adverse Events, Not Related
- Incidence of Ocular Significant Nonserious Treatment-Emergent Adverse Events, Overall
- Incidence of All Nonocular Treatment-Emergent Adverse Device Effects
- Incidence of All Nonocular Treatment-Emergent Adverse Events, Not Related
- Incidence of All Nonocular Treatment-Emergent Adverse Events, Overall
- Incidence of Nonocular Serious Treatment-Emergent Adverse Device Effects
- Incidence of Nonocular Serious Treatment-Emergent Adverse Events, Not Related
- Incidence of Nonocular Serious Treatment-Emergent Adverse Events, Overall
- 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/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
- Listings of Subjects with Infiltrates

5.3.3 Device Deficiencies

The following tables and supportive listings will be provided for contact lens group only:

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

6 Analysis Strategy for Other Endpoints

Not applicable

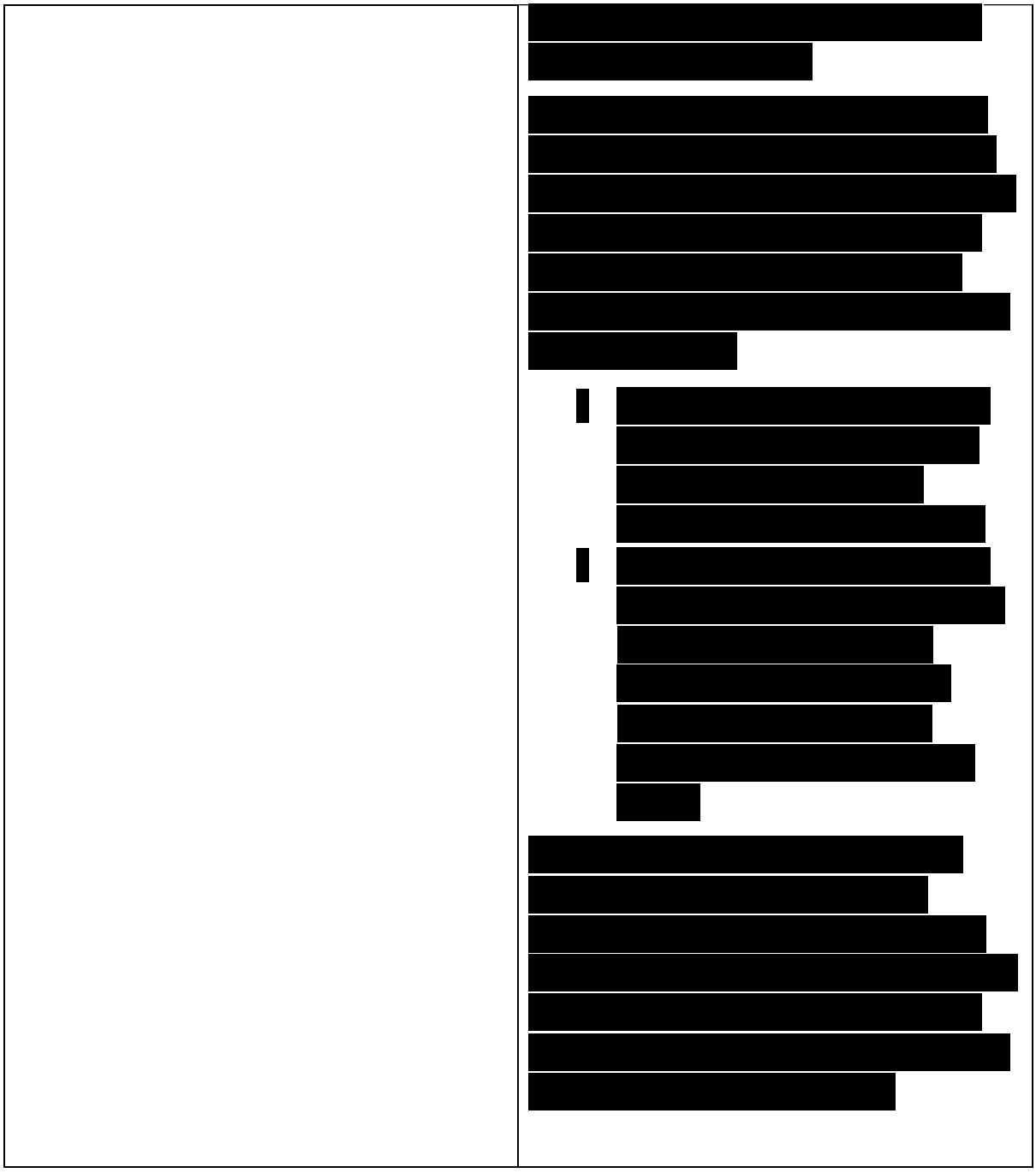
7 Sample Size and Power Calculations

Sample size calculation is based on published results regarding response time for distance and near visual acuity, with high and low contrast.

To demonstrate noninferiority (margin = 0.5 seconds) as a one-tailed hypothesis with $\alpha = 0.05$, and using a common standard deviation of 0.456, 80% power can be attained with a sample size of 48 (12 per group). For a comparison using a 3:1 ratio, required sample sizes for 80% power are 24:8 (test:control).

8 References

Not applicable



10 Appendix

Table 10–1 Overview of Study Plan

	ALL SUBJECTS	MULTIFOCAL CONTACT LENS WEARERS	PROGRESSIVE ADDITION LENS SPECTACLE WEARERS	ALL SUBJECTS
Visit	**Visit 1/ Screening**	**Visit 2/ Exposure/Exit**	**Visit 2/ Exposure/Exit**	**Unscheduled Visit**
Procedure/Assessment	**Day 1 (May be performed same day as Visit 2)**	**0-14 Days from Visit 1**	**0-14 Days from Visit 1**	
Informed Consent	✓			
Demographics	✓			
Medical History	✓	✓	✓	✓
Concomitant Medications	✓	✓	✓	✓
Inclusion/Exclusion	✓	✓	✓	
Randomize		✓		
Habitual correction (type/brand, power)		✓	✓	
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]	

	ALL SUBJECTS	MULTIFOCAL CONTACT LENS WEARERS	PROGRESSIVE ADDITION LENS SPECTACLE WEARERS	ALL SUBJECTS
Visit	**Visit 1/ Screening**	**Visit 2/ Exposure/Exit**	**Visit 2/ Exposure/Exit**	**Unscheduled Visit**
Procedure/Assessment	**Day 1 (May be performed same day as Visit 2)**	**0-14 Days from Visit 1**	**0-14 Days from Visit 1**	
[redacted]				
[redacted]		■	■	
[redacted]		■	■	
[redacted]		■	■	
[redacted]		■		
[redacted]		■	■	
[redacted]		■		
[redacted]		■	■	
[redacted]		■		
Transition time during alternate distance (4 m) and intermediate		✓	✓	

	ALL SUBJECTS	MULTIFOCAL CONTACT LENS WEARERS	PROGRESSIVE ADDITION LENS SPECTACLE WEARERS	ALL SUBJECTS
Visit	**Visit 1/ Screening**	**Visit 2/ Exposure/Exit**	**Visit 2/ Exposure/Exit**	**Unscheduled Visit**
Procedure/Assessment	**Day 1 (May be performed same day as Visit 2)**	**0-14 Days from Visit 1**	**0-14 Days from Visit 1**	
(80 cm) viewing				
[redacted]		■	■	
[redacted]		■	■	■
[redacted]		■	■	■
[redacted]		■	■	■
AEs	✓	✓	✓	✓
Device deficiencies	✓	✓		(✓)
Exit form†	(✓)	✓	✓	(✓)

(✓) assessment performed as necessary, eg, decrease of VA by 2 lines or more with investigational product (IP)
*source only; † must be performed as a screening assessment and prior to study exit

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]