Short Title:

Statistical Analysis Plan
CLE383-C010

Full Title:

Statistical Analysis Plan
CLE383-C010/NCT03888482

Protocol Title:	Clinical Comparison of DDT2 Contact Lens and a Daily Disposable Contact Lens – Study 2
Project Number:	A01660
Protocol TDOC Number:	TDOC-0056081
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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 of this study is to demonstrate noninferiority in visual acuity (VA) at distance when wearing Daily Disposable T2 Contact Lenses (DDT2) compared to clariti® 1 day Contact Lenses (Clariti 1 Day or Clariti).

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in distance VA with DDT2 when compared to Clariti, using a margin of 0.05.

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

The primary objective is to demonstrate noninferiority in distance VA when wearing DDT2 compared to Clariti.

[redacted]

1.2 Study Description

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

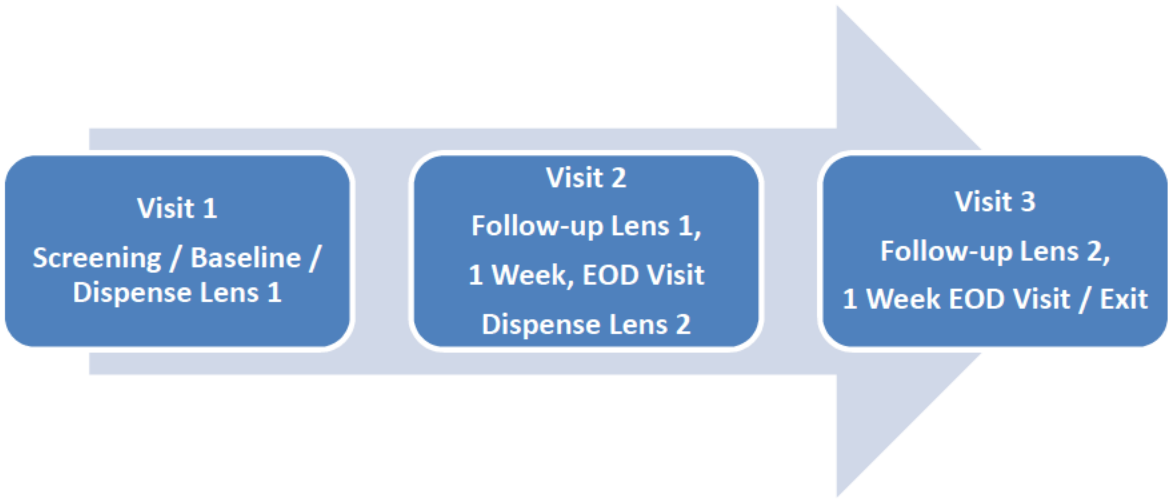
Table 1-1 Study Description Summary

Study Design	Prospective, randomized, bilateral crossover, double-masked, controlled
Study Population	Volunteer subjects aged 18 or over who are spherical soft contact lens wearers (excluding current/previous Clariti and DAILIES TOTAL1® (DT1) lens wearers), and for the last 3 months have worn their habitual lenses at least 5 days per week and at least 8 hours per day in daily wear modality. Target to complete: 138 Planned to enroll: ~154
Number of Sites	~8 (US)
Test Product	Daily Disposable T2 Contact Lenses (Verofilcon A) (DDT2) (LID006841)
Control Product	clariti® 1 day Contact Lenses (somofilcon A) (Clariti 1 Day or Clariti) (LID014044)
Duration of Treatment	Up to 20 days total duration • Test Product: 8 days (-1/+2 days)

	Control Product: 8 days (-1/+2 days)
Visits	Visit 1* – Screening/Baseline/Dispense§ Lens 1 Visit 2 – 1-Week Follow-up Lens 1 at EOD/Dispense§ Lens 2 [8 days (-1/+2 days) from Visit 1] Visit 3 – 1-Week Follow-up Lens 2/Exit [8 days (-1/+2 days) from Visit 2] *Randomization will occur at Visit 1 §Study contact lens wear will commence day after each dispense

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. Randomization will be implemented [redacted]

Qualifying subjects will be randomized in a 1:1 manner to one of 2 lens sequences consisting of the test lens and control lens as described below. For each sequence, subjects wear 1st lens then crossover to 2nd lens.

Sequence 1 = DDT2/Clariti
Sequence 2 = Clariti/DDT2

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, except for the lenses used at Visit 1 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 lenses exposed in the corresponding lens sequence.

Subjects who are lost to follow-up and their exposure to dispensed study lenses is unknown will be included in the safety analysis data set. The visit date for Dispense (Lens 1 or Lens 2) plus the presumed minimum 1 day of washout will be used as the first exposure date for the respective Lens.

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, 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 that have met any of the critical deviation or evaluability criteria identified in the Deviation and Evaluability Plan (DEP).

3 Subject Characteristics and Study Conduct Summaries

The following tables will be presented:

- Subject Disposition by Lens Sequence
- Analysis Sets by Lens Sequence
- Analysis Sets by Lens
- Subject Accounting by Lens Sequence
- Demographics Characteristics by Lens Sequence
- Baseline Characteristics by Lens Sequence (eg, summary statistics for subjective ratings)

Demographic characteristics and subject accounting tables will be summarized by lens sequence and overall on the safety, full, and per protocol analysis datasets. Baseline characteristics will be summarized by lens sequence and overall 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 Sequence Assignment by Investigator
- Listing of Subjects Discontinued from Study

4 Effectiveness Analysis Strategy

This study defines one primary, [redacted] effectiveness endpoin [redacted] All effectiveness evaluations will use the FAS as the primary analysis set. [redacted]

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] analyses.

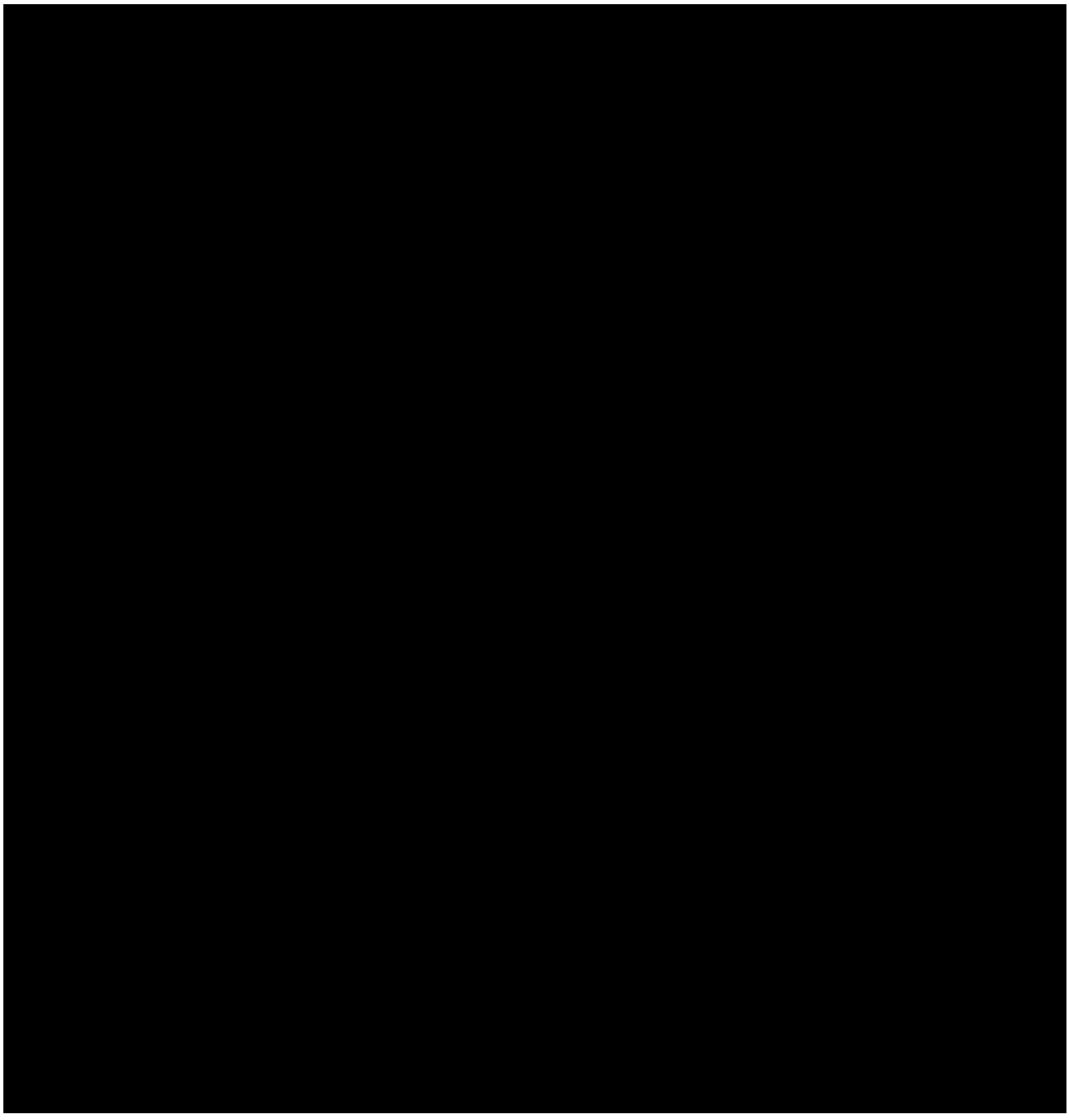
For all planned inferential analyses, alternative models/methods may be considered if convergence cannot be achieved. Furthermore, if significant carryover effects are noted

(confounded with sequence effect), results will be examined by period to ensure the overall conclusion is valid.

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is VA at distance with study lenses, collected separately for each eye in logMAR.



[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 0.05 for noninferiority:

H_0: $\mu_{(T)} - \mu_{(C)} \geq 0.05$
H_a: $\mu_{(T)} - \mu_{(C)} < 0.05$

where $\mu_{(T)}$ and $\mu_{(C)}$ denote the mean distance VA for DDT2 and Clariti, respectively, on the logMAR scale.

[redacted]

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

A mixed effects repeated measures model will be utilized to test these hypotheses. The model will include terms for lens, period, and sequence. Within-subject correlation due to eye and the crossover design will also be accounted for in the model. Lens difference (DDT2 minus Clariti) and the corresponding one-sided 95% upper confidence limit will be computed. Noninferiority in distance VA will be declared if upper confidence limit is less than 0.05.

[redacted]

[redacted]

[redacted]

[redacted]

4.4 Multiplicity Strategy

[redacted]

The primary endpoint of distance VA will be tested at one-sided α=0.05 for noninferiority [redacted]

[redacted]

[redacted]

[redacted]

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

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events (AE)
- Biomicroscopy 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 lenses. For biomicroscopy data, baseline will be defined as Visit 1 for Period 1 and Visit 2 for Period 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 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. A between-treatment AE is an event that occurs after last exposure to Period 1 lenses but prior exposure to Period 2 lenses. The period for treatment-emergent AE analysis starts from exposure to study lenses for Period 1 or Period 2 until the subject completes the respective period or is discontinued from the study.

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 Non-serious 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
- Listing of All Ocular Between-Treatment Adverse Events
- Listing of All Nonocular Between-Treatment Adverse Events

5.3.2 Biomicroscopy Findings

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 [This listing will include all relevant visits within the crossover period]
- Listing of Subjects With Increased Severity by 2 or More Grades in Biomicroscopy Findings [This listing will include all relevant visits within the crossover period]
- Listings of Subjects with Infiltrates

5.3.3 Device Deficiencies

The following tables and supportive listings will be provided:

- 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 a prior clinical study (CLE383-C006) which evaluated performance of DDT2 and Clariti.

Primary Effectiveness

To demonstrate noninferiority (margin = 0.05 in logMAR; ½ line in Snellen) in distance VA as a one-tailed hypothesis with α=0.05, and using a standard deviation of 0.074 for paired differences, 80% power can be attained with a sample size of 16 (8 per sequence).

[redacted]

[redacted]

[redacted]

[redacted]

8 References

[redacted]

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

Procedure / Assessment	**Visit 1** Screening / Baseline / Dispense Lens 1 (Lens 1 to be worn after washout period)	**Visit 2** 1-Week Follow-up Lens 1 at EOD□ / Dispense Lens 2	**Visit 3** 1-Week Follow-up Lens 2 at EOD□ / Exit	**Unscheduled Visit / Early Exit**
	Washout period: Subjects will discontinue habitual lens wear after the screening visit until the next day when they commence wearing study Lens 1∞	8 (-1/+2) days after Visit 1 Washout period: Subjects will wear spectacles after Visit 2 until the next day when they commence wearing study Lens 2.∞	8 (-1/+2) days after Visit 2	N/A
Informed Consent	✓	-	-	-
Demographics	✓	-	-	-
Medical History	✓	✓	✓	✓
Concomitant Medications	✓	✓	✓	✓
Inclusion / Exclusion	✓	-	-	-
Habitual lens information (brand, power)*	✓	-	-	-
VA with habitual contact lens correction (OD, OS, Snellen distance)*	✓	-	✓ (Exit procedure)	(✓)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BCVA (Snellen distance with manifest refraction) OD, OS*	✓	(✓)	(✓)	(✓)
Biomicroscopy	✓	✓	✓	✓
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dispense (provide) study lenses	✓	✓	-	(✓)
VA (logMAR distance) with study lenses, OD, OS	✓* (with both fitting set lens types)	✓	✓	(✓)
[redacted]	[redacted]	[redacted]		

Procedure / Assessment	Visit 1 Screening / Baseline / Dispense Lens 1 (Lens 1 to be worn after washout period)	Visit 2 1-Week Follow-up Lens 1 at EOD□ / Dispense Lens 2	Visit 3 1-Week Follow-up Lens 2 at EOD□ / Exit	Unscheduled Visit / Early Exit
	Washout period: Subjects will discontinue habitual lens wear after the screening visit until the next day when they commence wearing study Lens 1∞	8 (-1/+2) days after Visit 1 Washout period: Subjects will wear spectacles after Visit 2 until the next day when they commence wearing study Lens 2.∞	8 (-1/+2) days after Visit 2	N/A
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs	✓	✓	✓	✓
Device Deficiencies	✓	✓	✓	✓
Exit Form	(✓)	(✓)	(✓)	(✓)

□ End of Day (8 – 16 hours of wear) *** source only** (✓) assessment performed as necessary, eg, decrease of VA by 2 lines or more with investigational product (IP)

† Time points +/- 15 minutes [redacted]

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