Alcon

# Statistical Analysis Plan for CLU484-P002 / NCT05010512
# Title: Clinical Performance of Two Commercial, Daily Disposable Contact Lenses

[redacted]

This version of the Statistical Analysis Plan is based on Version 5.0 of the study protocol.

**Executive Summary:**

Key Objectives:

The primary objective of this study is to demonstrate noninferiority (NI) in visual acuity (VA) at distance when wearing DALIES TOTAL1® (DT1) contact lenses compared to Infuse contact lenses.

Decision Criteria for Study Success:

Success of this study will be based on demonstration of NI in distance VA with DT1 contact lenses when compared to BAUSCH+LOMB INFUSE™ (Infuse) contact lenses, using a margin of 0.05.

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# 1 STUDY OBJECTIVES AND DESIGN

## 1.1 Study Objectives

**PRIMARY OBJECTIVE**

The primary objective of this study is to demonstrate NI in distance VA when wearing DT1 contact lenses compared to Infuse contact lenses.

[redacted]

## 1.2 Study Description

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

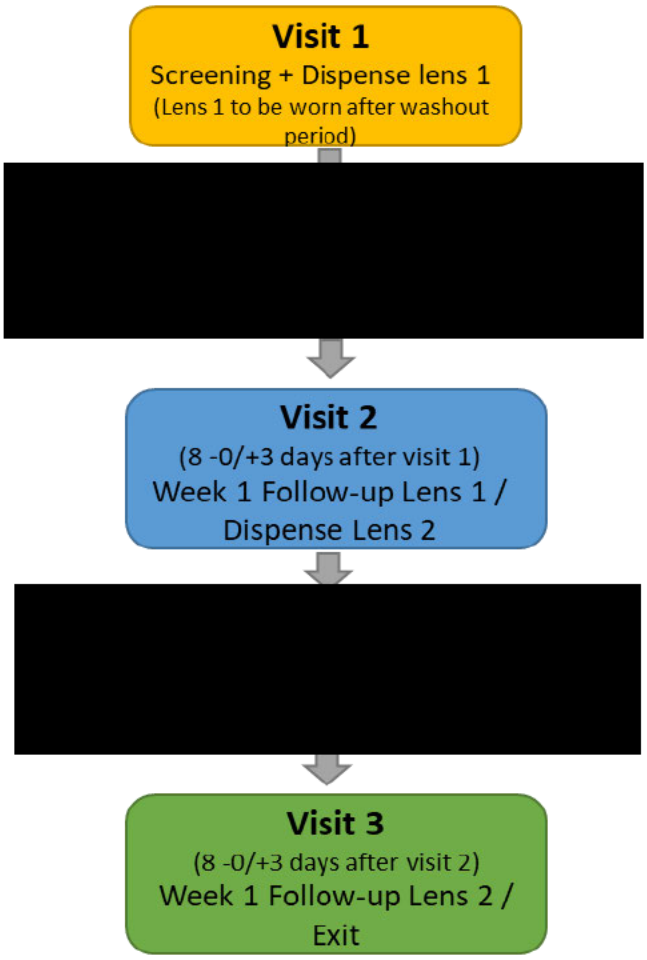
**Table 1-1 Study Description Summary**

| | |
|---|---|
| Study Design | Prospective, randomized, [redacted] controlled, crossover, double-masked |
| Study Population | Habitual soft contact lens wearers in both eyes (excluding current/previous DT1 and Infuse habitual lens wearers), aged 18 or over who have at least 3 months of contact lens wearing experience, and who wear their habitual lenses at least 5 days per week and at least 10 hours per day<br><br>Target to complete: 100; Planned to enroll: ~110 |
| Number of Sites | ~8<br>US |
| Test Product(s) | DAILIES TOTAL1® contact lenses (DT1; [redacted]) |
| Comparator Product(s) | BAUSCH+LOMB INFUSE™ contact lenses (Infuse; [redacted]) |
| Planned Duration of Exposure | 16-22 days total (test and comparator):<br>Test Product: 8 (-0/+3) days<br>Comparator Product: 8 (-0/+3) days |
| Visits | Visit 1 – Screening/Baseline/Dispense Lens 1<br>Visit 2 – Week 1 Follow-up Lens 1/Dispense Lens 2 [8 (-0/+3) days after Visit 1] |

| | |
|---|---|
| | Visit 3 – Week 1 Follow-up Lens 2/Exit [8 (-0/+3) days after Visit 2]<br>[redacted] |

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

**Figure 1–1 Flowchart of Study Visits**




## 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 treatment (lens) sequence

assignment. Randomization will be implemented in the Electronic Data Capture (EDC)/randomization integration system.

Subjects will be [redacted] randomized in a 1:1 manner to receive one of 2 lens sequences:

| Sequence | EDC/randomization integration system | Lens Name |
|---|---|---|
| Sequence 1 | [redacted] | DT1/Infuse |
| Sequence 2 | [redacted] | Infuse/DT1 |

## 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 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, [redacted] 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 set. The visit date for Dispense (Lens 1 or Lens 2) [redacted] 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.

## 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.

# 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 [lens brand; lens solution; lens power: sphere; [redacted]

Subject accounting and demographics characteristics tables will be summarized on the safety, full, and PP analysis sets. Baseline characteristics will be summarized on the full and PP analysis sets.

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

[redacted]

[redacted]

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum, as well as confidence intervals (CI) or confidence limits (CL) where applicable. Categorical variables will be summarized with frequencies 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 [redacted]

[redacted]

## 4.1 Effectiveness Endpoints

**Primary Effectiveness Endpoint**

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

[redacted]

[redacted]

## 4.2 Effectiveness Hypotheses

**Primary Effectiveness**

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

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

where $\mu_{(T)}$ and $\mu_{(C)}$ denote the mean distance VA for DT1 and Infuse, respectively, on the logMAR scale.

[redacted]

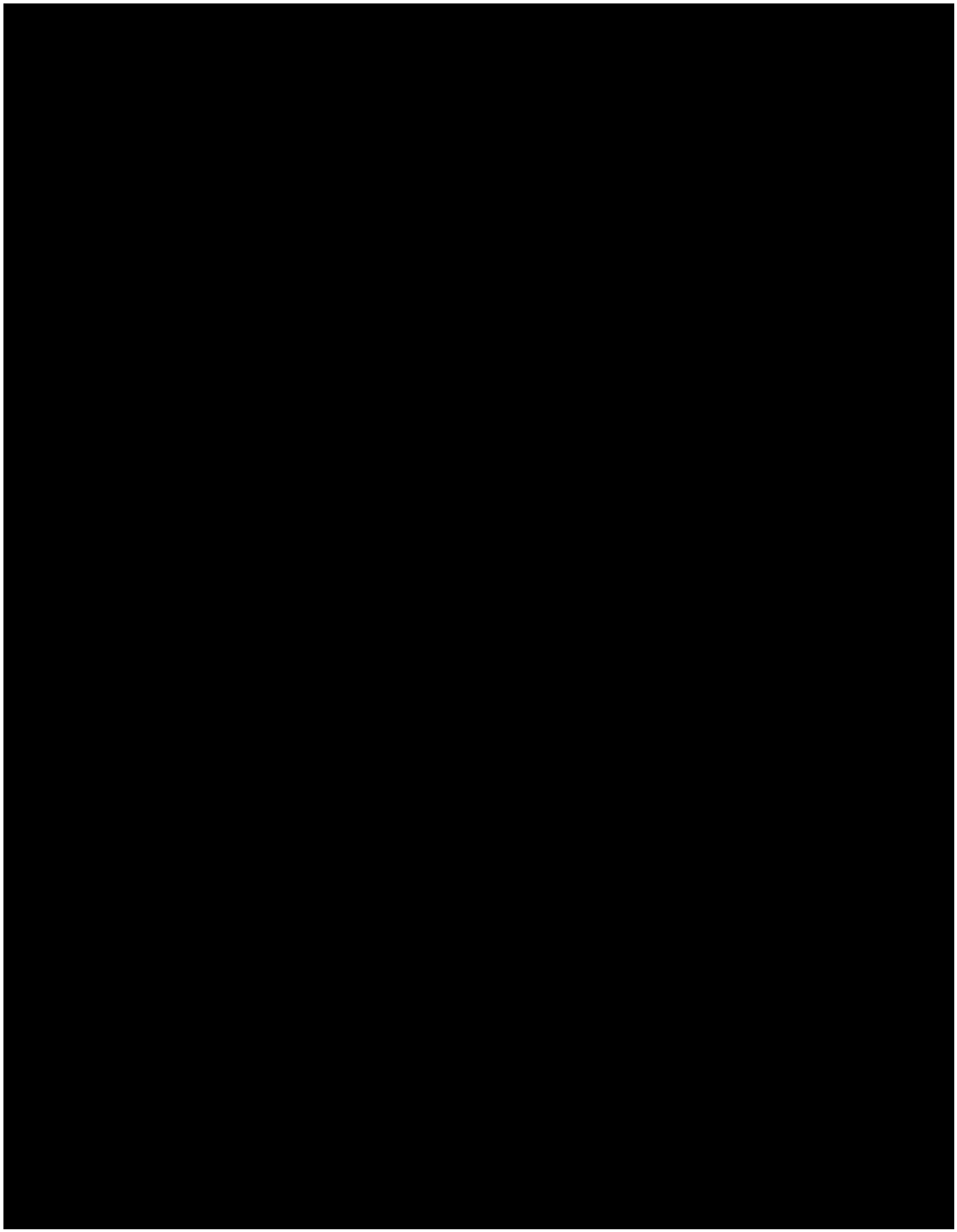
[redacted]

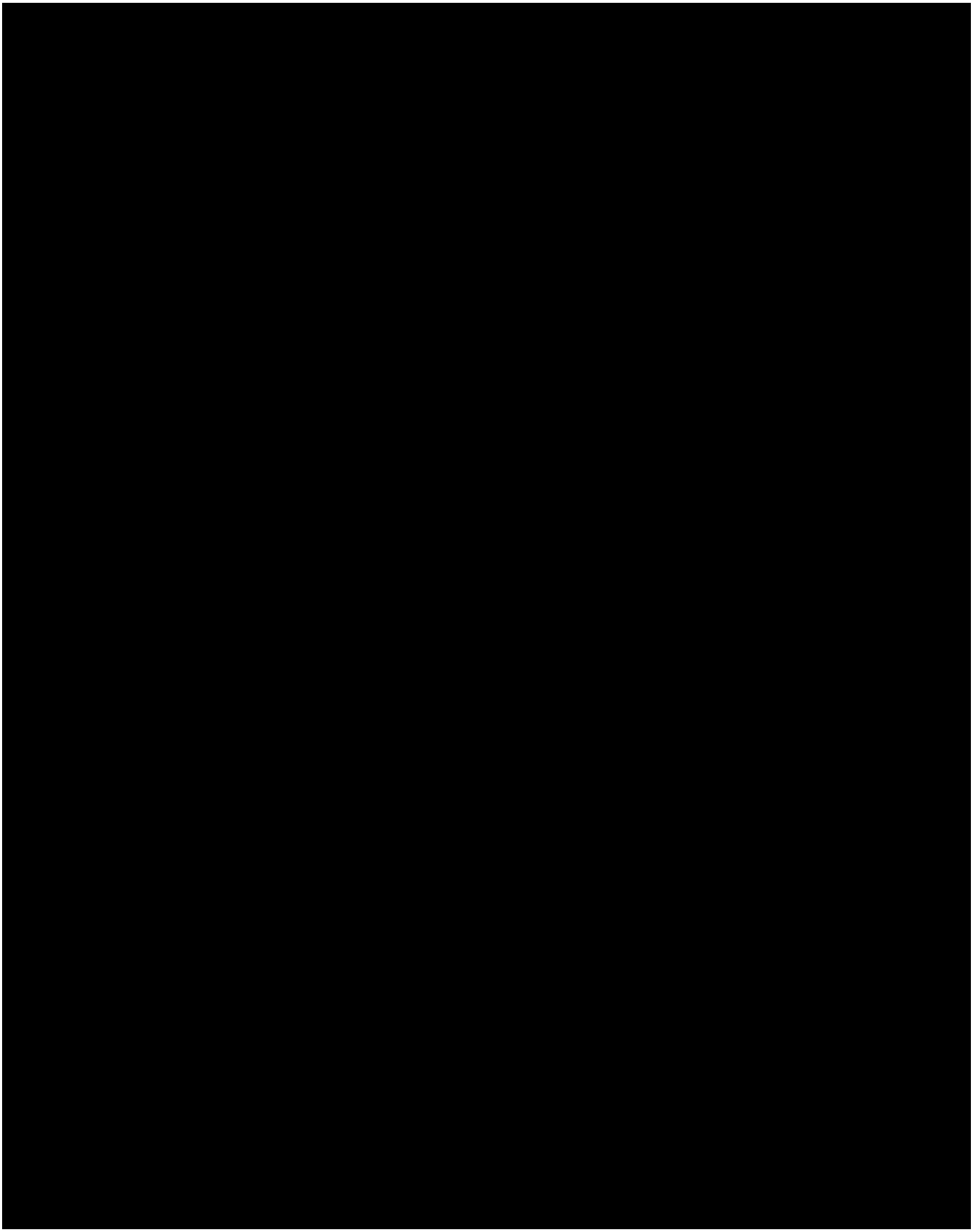
## 4.3 Statistical Methods for Effectiveness Analyses

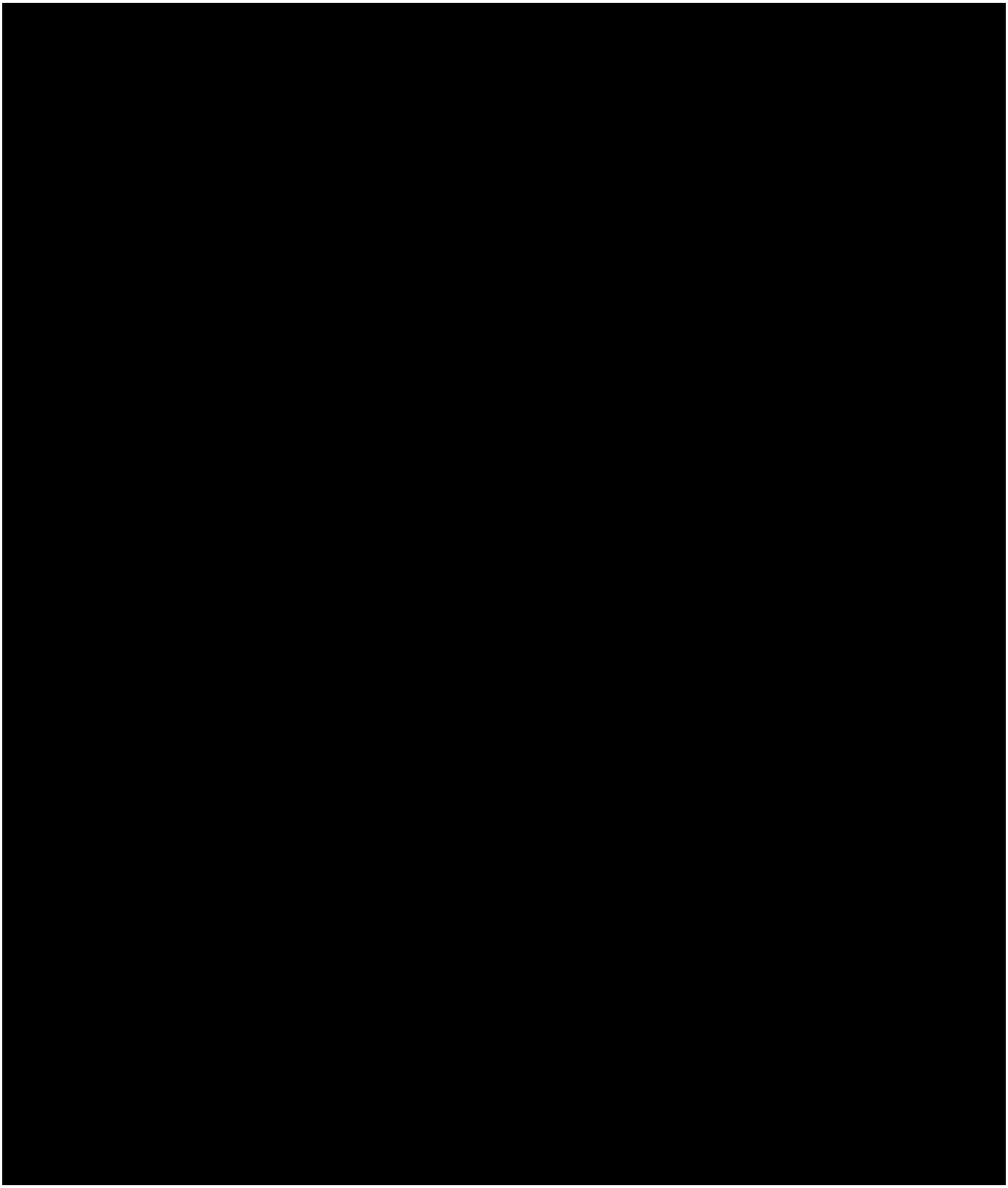
### 4.3.1 Primary Effectiveness Analysis

A mixed effects repeated measures model will be utilized to test these hypotheses. The model will include terms for lens, period, and sequence as fixed effects. Within-subject correlation due to eye and the crossover design will also be accounted for in the model. Lens difference (DT1 minus Infuse) and the corresponding one-sided 95% upper confidence limit will be computed. NI in distance VA will be declared if upper confidence limit is less than 0.05.

[redacted]







## 4.6 Interim Analysis for Effectiveness

No interim analysis is planned for the effectiveness endpoints.

# 5 SAFETY ANALYSIS STRATEGY

The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters. Therefore, no inferential testing will be done for the safety analysis.

## 5.1 Safety Endpoints

The safety endpoints are

- Adverse events (AE)
- Biomicroscopy Findings/Slit Lamp Examinations
    - 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 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 the time of their study exit will be accounted for in the reporting.

Pre-treatment AEs and between-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 study lenses. 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 study lenses for Period 1 or Period 2 until the subject completes the respective period or is discontinued from the study. Each AE will be summarized under the exposed lens based upon the event onset date/time up until the start of the next lens in the crossover sequence.

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 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/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 Conjunctival Compression/Indentation or Chemosis
- Listing of Subjects With Increased Severity by 2 or More Grades in Biomicroscopy Findings [This listing will include all relevant visit within the crossover period]
- Listing 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

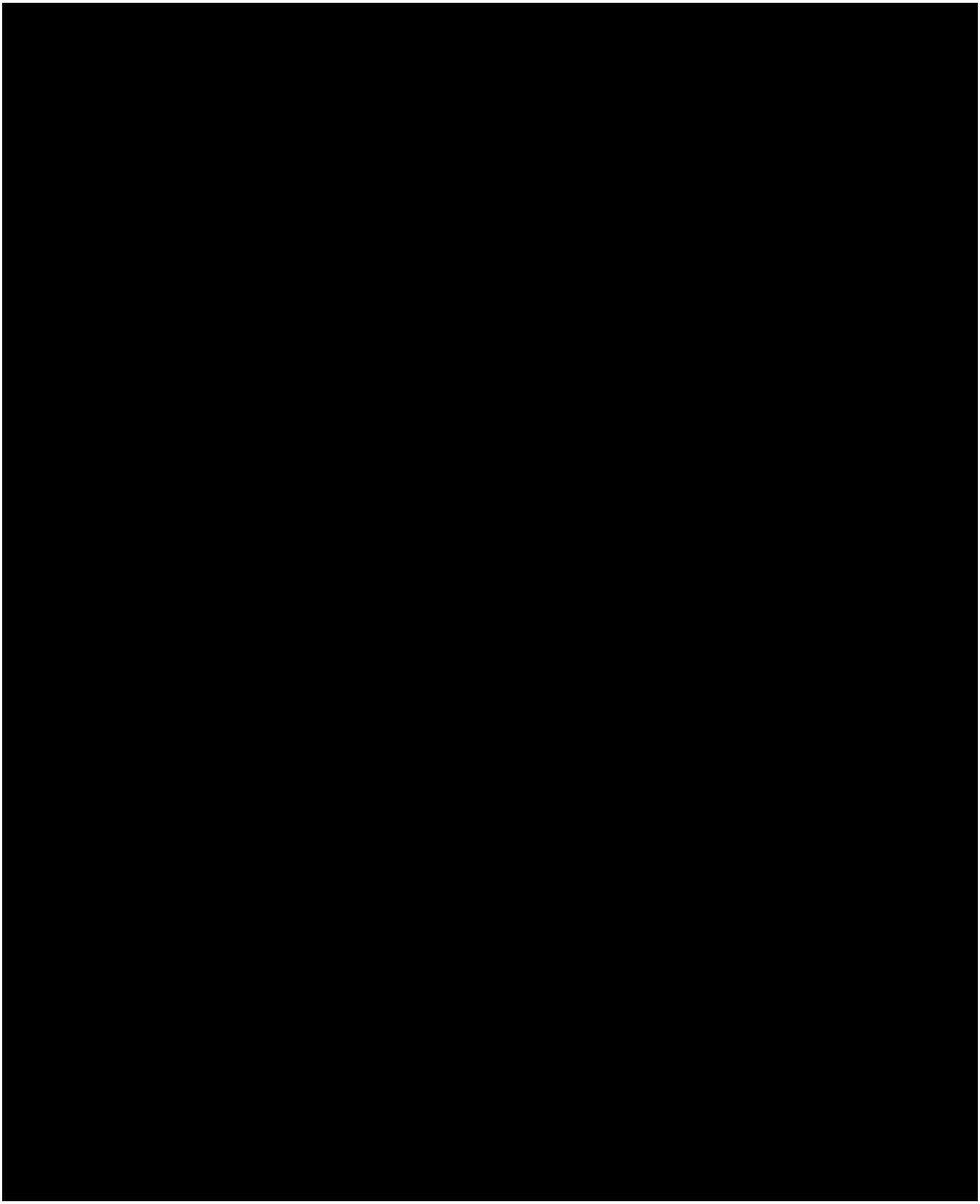
Not Applicable.

## 7 SAMPLE SIZE AND POWER CALCULATIONS

Sample size calculation is based on a prior clinical study [redacted] which evaluated performance of DT1 and Infuse.

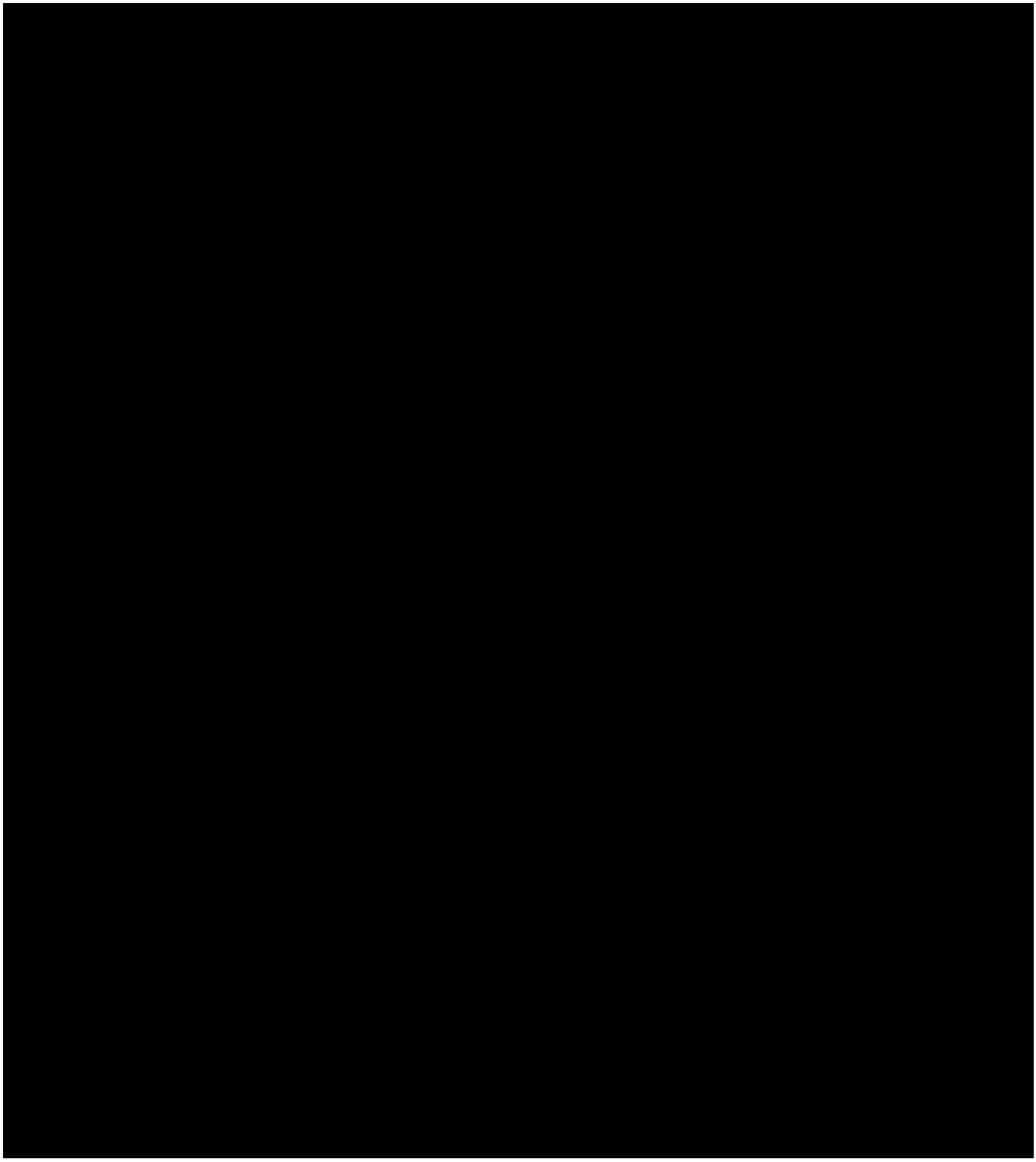
**Primary Effectiveness**

To demonstrate NI (margin = 0.05 in logMAR; ½ line in Snellen) in distance VA as a one-tailed hypothesis with $\alpha$=0.05, and using a standard deviation of 0.0497 for paired differences, 80% power can be attained with a sample size of 8 (4 per sequence).



# 8 REFERENCES

Not Applicable.



# 10 APPENDIX

**Table 10-1 Schedule of Study Procedures and Assessments**

| Visit | **Visit 1** Screening/Baseline/ Dispense Lens 1 [redacted] | **Visit 2** Week 1 Follow-up Lens 1 / Dispense Lens 2 | **Visit 3** Week 1 Follow-up Lens 2 / Exit | **Early Exit** | **Unscheduled Visit** |
|---|---|---|---|---|---|
| | [redacted] | 8 (-0/+3) days after Visit 1 [redacted] | 8 (-0/+3) days after Visit 2 | **N/A** | **N/A** |
| Informed Consent | X | | | | |
| Demographics | X | | | | |
| Medical History | X | X | X | X | X |
| Concomitant Medications‡ | X | X | X | X | X |
| Inclusion/Exclusion | X | | | | |
| Habitual lens information (brand, power) | X | | | | |
| VA with habitual correction (OD, OS, LogMAR distance)* | X | | X (Exit procedure) | X | (X) |
| Manifest refraction and BCVA with manifest refraction (OD, OS, logMAR distance) * | X | (X) | (X) | (X) | (X) |
| Biomicroscopy | X | X | X | X | X |
| Trial lens fitting (DT1 and Infuse) [redacted] | X | | | | |
| [redacted] | [redacted] | | | | |
| Randomize | X | | | | |
| Dispense (provide) study lenses* | X | X | | | (X) |
| VA (logMAR distance) with study lenses, OD, OS | | X | X | (X) | (X) |
| [redacted] | | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] | [redacted] | [redacted] |

| Visit | **Visit 1** Screening/Baseline/ Dispense Lens 1 | **Visit 2** Week 1 Follow-up Lens 1 / Dispense Lens 2 | **Visit 3** Week 1 Follow-up Lens 2 / Exit | **Early Exit** | **Unscheduled Visit** |
|---|---|---|---|---|---|
| | | 8 (-0/+3) days after Visit 1 | 8 (-0/+3) days after Visit 2 | **N/A** | **N/A** |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| AEs | X | X | X | X | X |
| Device Deficiencies | X | X | X | X | X |
| Exit Form | (X) | (X) | X | X | (X) |

(X) assessment performed as necessary, e.g., decrease of VA by 2 lines or more with investigational product (IP)

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