Clinical Performance of Two Daily Disposable Toric Soft Contact Lenses

CLA306-P002

Statistical Analysis Plan v1

16 Aug 2022

ClinicalTrials.gov ID

NCT05483127

Statistical Analysis Plan for CLA306-P002
Title: Clinical Comparison of Two Daily Disposable Toric Soft Contact Lenses

Author: [redacted]

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 the visual acuity (VA) at distance when wearing PRECISION1™ for Astigmatism soft contact lenses (P1fA) compared to MyDay® toric soft contact lenses (MDT).

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in distance VA with P1fA when compared to MDT, using a margin of 0.05.

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1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

PRIMARY OBJECTIVE(S)

The primary objective of this study is to demonstrate noninferiority in the VA at distance when wearing P1fA contact lenses compared to MDT contact lenses.

[redacted]

1.2 Study Description

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

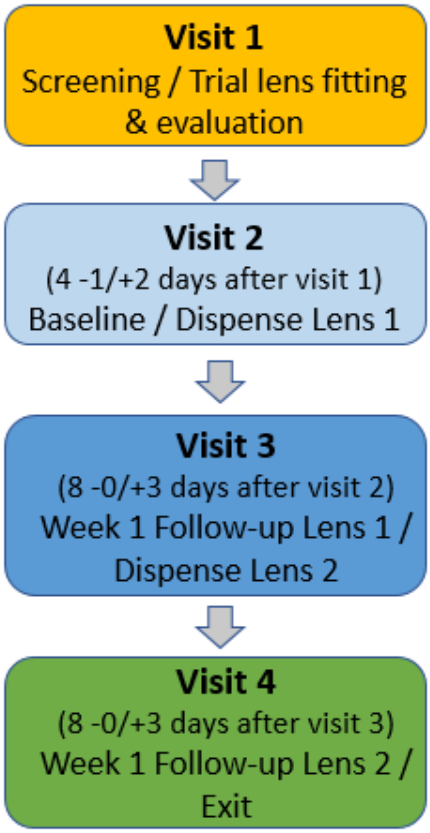
Table 1-1 Study Description Summary

Study Design	Prospective, randomized, controlled, double-masked, bilateral crossover
Study Population	Volunteer subjects aged 18 or over who are habitual toric soft contact lens wearers (excluding current/previous P1fA and MDT habitual lens wearers), 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. One specific group of subjects will be recruited for this study: normal contact lens wearers. [redacted] Target to complete: 130 Planned to enroll: ~150
Number of Sites	~12 US
Test Product(s)	PRECISION1™ for Astigmatism soft contact lenses (P1fA; verofilcon A; [redacted])

Comparator Product(s)	MyDay® toric soft contact lenses (MDT; stenfilcon A; [redacted]
Planned Duration of Exposure	~16 days total (test and comparator): Test Product: 8 (-0/+3) days Comparator Product: 8 (-0/+3) days
Visits	Prescreening Questionnaire (optional) Visit 1 – Screening/Trial Lens Fitting & Evaluation Visit 2 – Baseline/Dispense Lens 1 [Day 1; 4 (-1/+2) days after Visit 1] Visit 3 – Week 1 Follow-up Lens 1/Dispense Lens 2 [8 (-0/+3 days after Visit 2] Visit 4 – Week 1 Follow-up Lens 2/Exit [8 (-0/+3) days after Visit 3]

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

Subjects will be randomized in a 1:1 ratio to receive treatment (lens) in crossover sequence: Test product then Comparator product or Comparator product then Test product, respectively.

Sequence	EDC/randomization integration system	Lens Name
Sequence 1	[redacted]	P1fA/MDT
Sequence 2	[redacted]	MDT/P1fA

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 Sets

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.

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 [redacted] 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 by Lens Sequence
- Baseline Characteristics by Lens Sequence [lens brand; lens power: sphere, cylinder, axis; lens solution; autorefractometry readings]

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] 1 primary [redacted] effectiveness endpoint [redacted] will use the FAS as the primary analysis set.

[redacted]

[redacted]

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

All data obtained in evaluable subjects/eyes will be included in the analysis. No imputation for missing values will be carried out f[redacted]

[redacted]

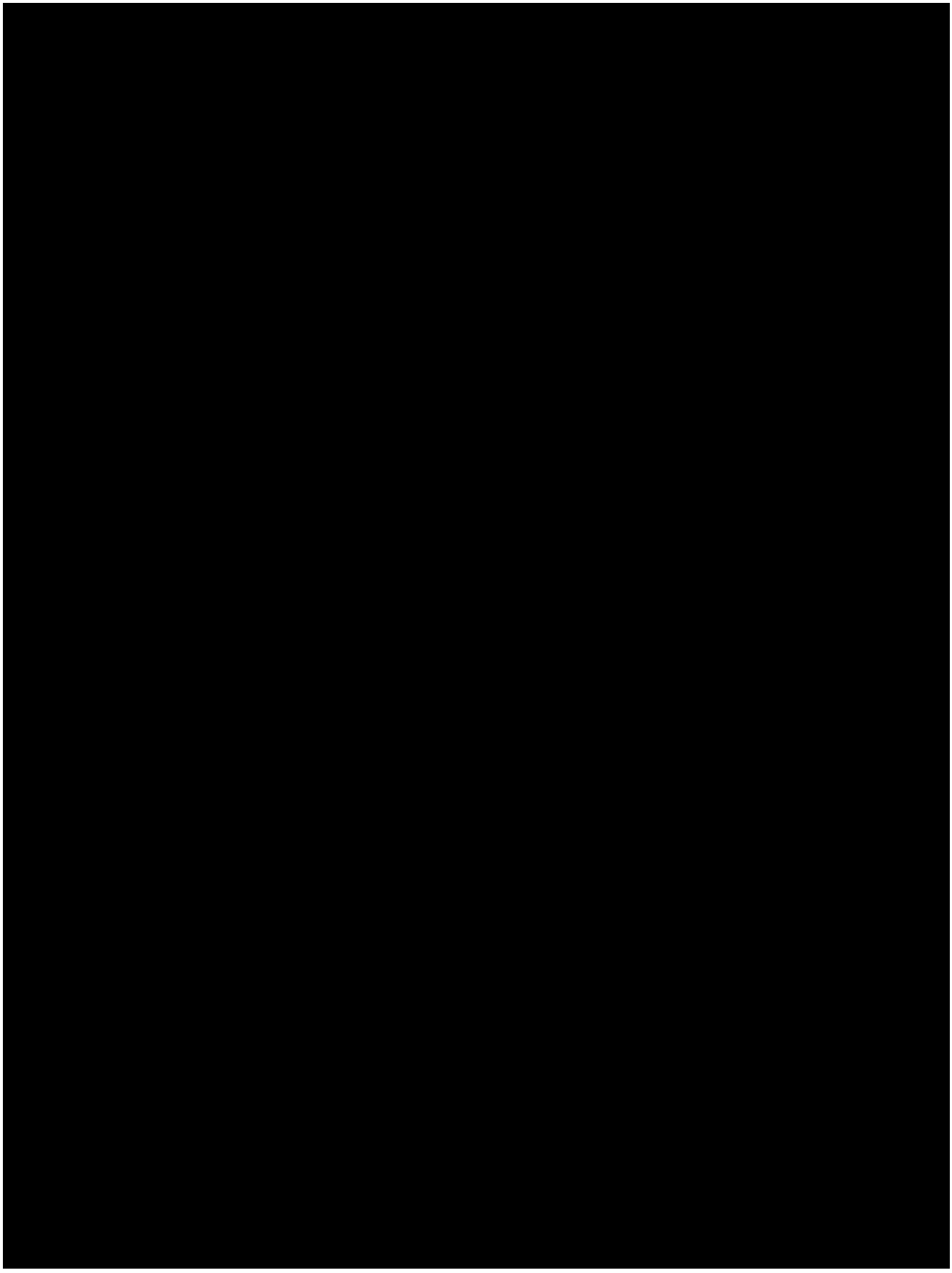
A listing of select effectiveness data will also be provided.

4.1 Effectiveness Endpoints

Primary Effectiveness Endpoint

The primary effectiveness endpoint is distance VA with study lenses at Week 1, 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 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 at Week 1 for P1fA and MDT, respectively, on the logMAR scale.

[redacted]

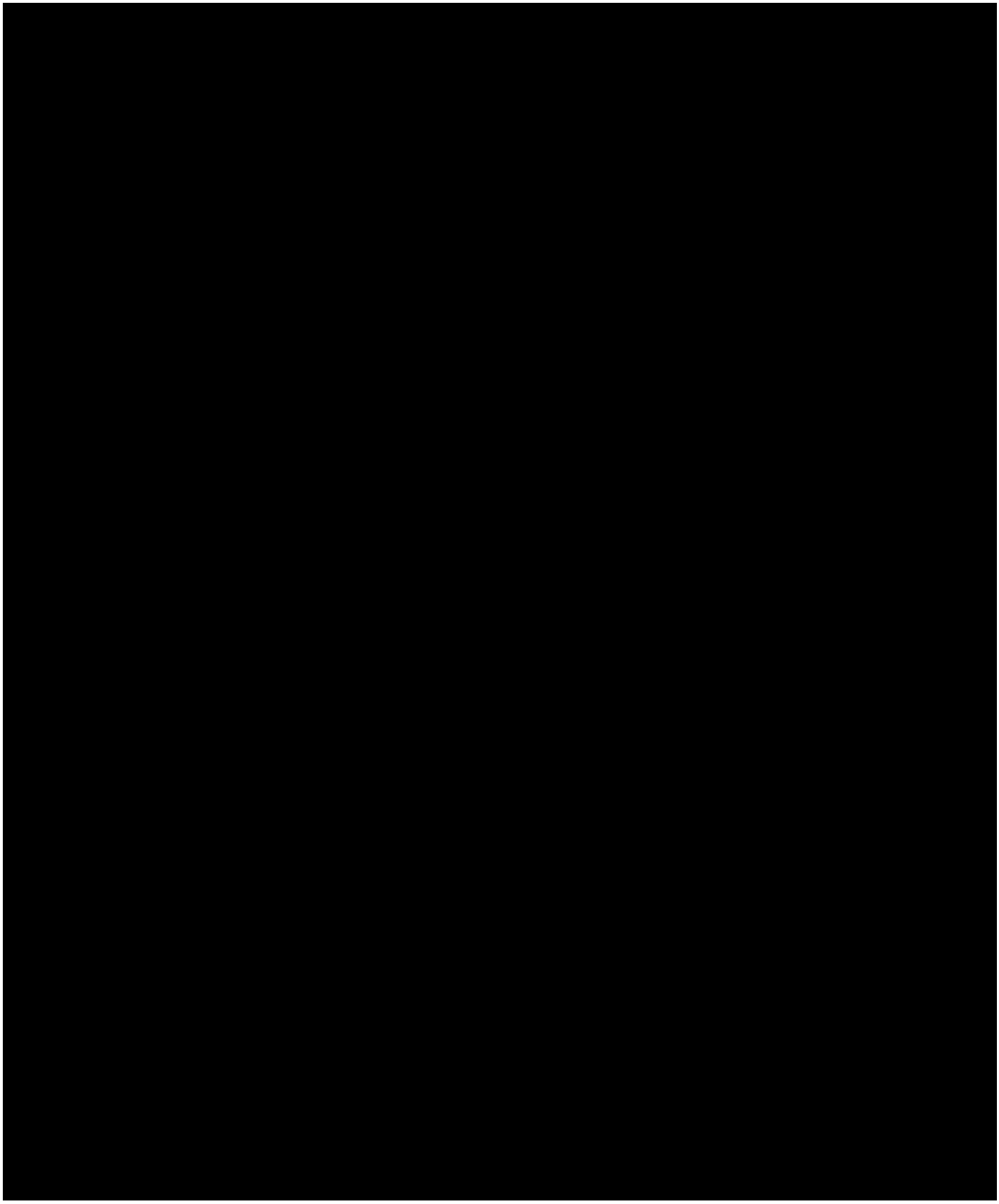
[redacted]

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, visit, and lens by visit interaction, period, and sequence. Within-subject correlation due to eye and the crossover design will also be accounted for in the model. Lens difference (P1fA minus MDT) and the corresponding one-sided 95% upper confidence limit will be computed at Week 1. Noninferiority in distance VA will be declared if upper confidence limit is less than 0.05.

[redacted]



[redacted]

4.5 Subgroup Analyses and Effect of Baseline Factors

It is not expected that demographics 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 effectiveness endpoints.

5 SAFETY ANALYSIS STRATEGY

The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events (AE) 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

- 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 lenses. For biomicroscopy data, baseline will be defined as the last measurement prior to exposure to study lenses. 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.

Presentation of AEs will be separated into pre-treatment AEs and treatment-emergent AEs as defined below:

- Pre-treatment: an event that occurs after signing informed consent but prior to exposure to study lenses
- Treatment-emergent: an event that occurs from exposure to Period 1 study lenses until subject exits 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 All Nonocular 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

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 Conjunctival Compression/Indentation or Chemosis
- Listing of Subjects With Increased Severity by 2 or More Grades in Biomicroscopy Findings
- 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

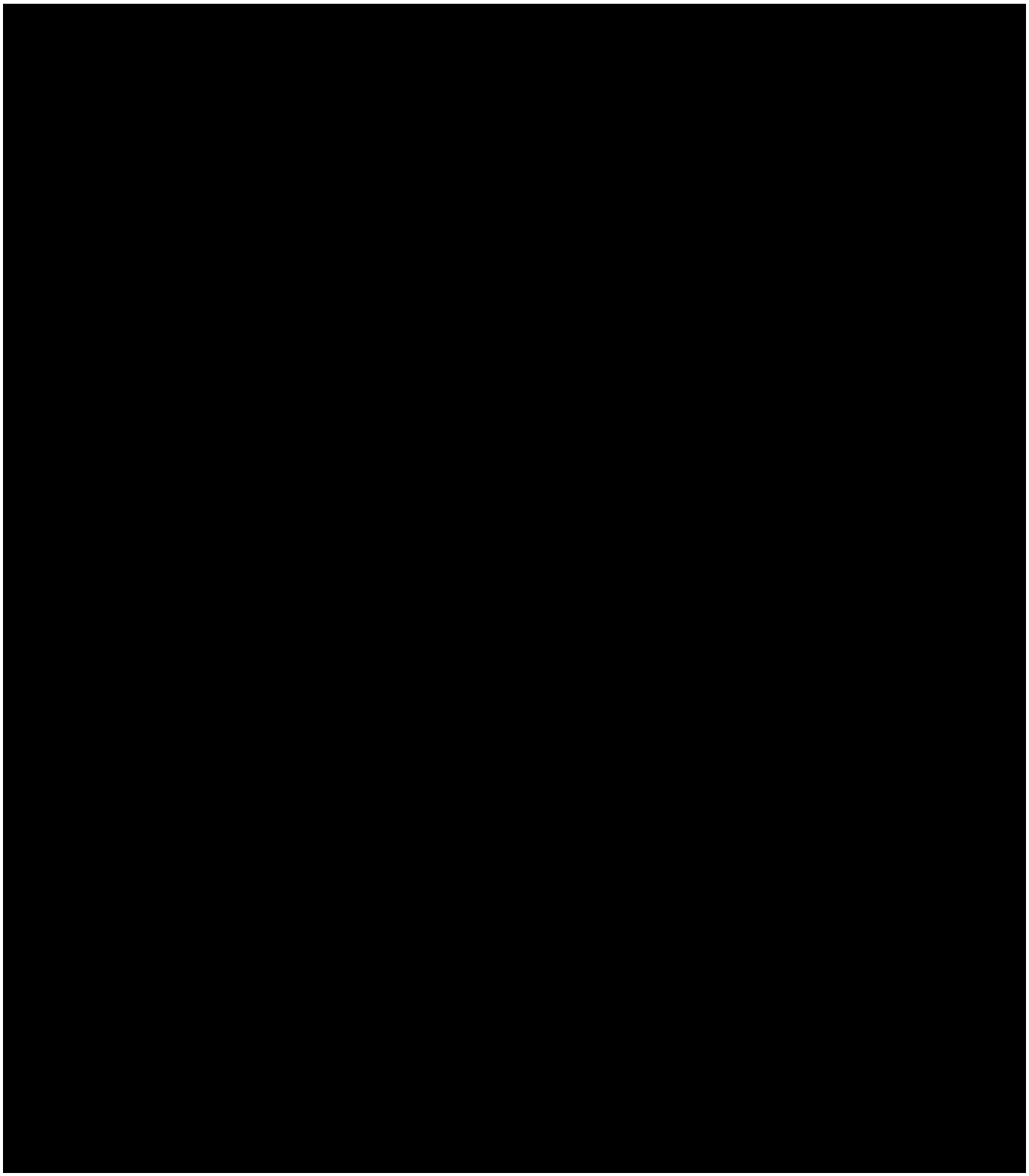
Not Applicable

7 SAMPLE SIZE AND POWER CALCULATIONS

Sample size calculation is based on a prior clinical study [redacted] which evaluated performance of P1fA and MDT. [redacted]

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 0.0692 for paired differences, 90% power can be attained with a sample size of 18 (9 per sequence).



8 REFERENCES

Not Applicable.

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 Schedule of Study Procedures and Assessments

Procedure / Assessment	Prescreening Questionnaire (Optional)	Visit 1 Screening /Trial lens fitting & evaluation	Visit 2 Baseline / Dispense Lens 1	Visit 3 Week 1 Follow-up Lens 1/Dispense Lens 2		Visit 4 Week 1 Follow-up Lens 2/Exit	USV	Early Exit Visit
		Subjects should discontinue habitual contact lenses after Visit 1; habitual spectacles should be worn.	Day 1 4 (-1/+ 2) days after Visit 1	8 (-0/+3) days after Visit 2 Lens 1 follow up	Lens 2 Dispense	8 (-0/+3) days after Visit 3	N/A	N/A
			Period 1		Period 2			
Informed Consent		✓						
Demographics		✓						
Medical History€		✓	✓	✓		✓	✓	✓
Concomitant Medications €		✓	✓	✓		✓	✓	✓
Inclusion / Exclusion		✓						
Habitual lens information (brand, power [sphere, cylinder, axis], solution (if applicable))		✓						
VA with habitual contact lens correction (OD, OS, logMAR distance)*		✓				✓	(✓)	✓
Keratometry*		✓						
Autorefractometry		✓						
Manifest refraction* (OD, OS; sphere, cylinder, axis)		✓		(✓)		(✓)	(✓)	(✓)
BCVA (OD, OS logMAR distance with manifest refraction)*		✓		(✓)		(✓)	(✓)	(✓)
Biomicroscopy		✓	✓	✓		✓	✓	✓
Symptomatology questionnaire ‡	(✓)*	✓						

Procedure / Assessment	Prescreening Questionnaire (Optional)	Visit 1 Screening /Trial lens fitting & evaluation	Visit 2 Baseline / Dispense Lens 1	Visit 3 Week 1 Follow-up Lens 1/Dispense Lens 2		Visit 4 Week 1 Follow-up Lens 2/Exit	USV	Early Exit Visit
		Subjects should discontinue habitual contact lenses after Visit 1; habitual spectacles should be worn.	Day 1 4 (-1/+ 2) days after Visit 1	8 (-0/+3) days after Visit 2 Lens 1 follow up	Lens 2 Dispense	8 (-0/+3) days after Visit 3	N/A	N/A
Fitting lens (Test and Comparator) trial fitting and evaluation* (LogMAR VA {with spherical OR as needed} and lens fitting assessments)		✓						
Randomize		✓						
Order study lenses*		✓					(✓)	
Dispense study lenses (Record lens information in EDC)			✓		✓		(✓)	
[redacted]								
VA (logMAR distance) with study lenses, OD, OS			✓	✓	✓	✓	(✓)	✓
[redacted]								

Procedure / Assessment	Prescreening Questionnaire (Optional)	Visit 1 Screening /Trial lens fitting & evaluation	Visit 2 Baseline / Dispense Lens 1	Visit 3 Week 1 Follow-up Lens 1/Dispense Lens 2		Visit 4 Week 1 Follow-up Lens 2/Exit	USV	Early Exit Visit
		Subjects should discontinue habitual contact lenses after Visit 1; habitual spectacles should be worn.	Day 1 4 (-1/+ 2) days after Visit 1	8 (-0/+3) days after Visit 2		8 (-0/+3) days after Visit 3	N/A	N/A
				Lens 1 follow up	Lens 2 Dispense			
[redacted]								
AEs [α]		✓	✓	✓	✓	✓	✓	✓
Device Deficiencies		✓ Trial fit lenses	✓	✓	✓	✓	✓	✓
Exit Form						✓		✓

(✓) assessment performed as necessary, e.g., decrease of VA by 2 lines or more with investigational product (IP)
* Source only
€ Option 3 (all ocular and targeted systemic meds/ medical history)
α Comprehensive details of all AEs will be documented in the source records; however, targeted collection will be utilized in the eCRF.

[redacted]

‡ Sites will be provided optional prescreening questionnaire

[redacted]