Clareon Toric vs Eyhance Toric

STUDY ID:

ILS241-P002

STATISTICAL ANALYSIS PLAN

Version 2, 14 Nov 2023

ClinicalTrials.gov ID:

NCT05481125

Alcon

Statistical Analysis Plan for ILS241-P002
Title: Clareon Toric vs Eyhance Toric

[redacted]

This is version 2.0 of the Statistical Analysis Plan based on Version 4.0 of the study protocol.

Executive Summary:

Key Objectives:

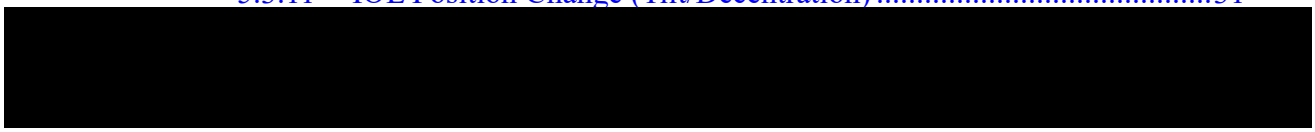
The primary objective of this study is to demonstrate noninferiority of the Clareon/Clareon Toric intraocular lens (IOL) to the Eyhance/Eyhance Toric IOLs in binocular best corrected distance visual acuity (BCDVA) under bright lighting conditions at 3 months postoperative.

[redacted]

Decision Criteria for Study Success:

The study will be considered successful if the data indicate a noninferior visual acuity for the Clareon/Clareon Toric IOLs compared to the Eyhance/Eyhance Toric IOLs. Study success will be concluded if the upper bound of the one-sided 95% confidence interval does not exceed the noninferiority margin of 0.1 logMAR for the BCDVA at 3 months postoperative for Clareon/Clareon Toric IOLs vs the Eyhance/Eyhance Toric IOLs. Primary analysis will be based on All-Implanted Analysis Set (AAS). [redacted]

Table of Contents



[redacted]

List of Tables

List of Figures

[redacted]

1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

Primary effectiveness objective:

To demonstrate noninferiority of the Clareon/Clareon Toric IOLs to the Eyhance/Eyhance Toric IOLs in binocular BCDVA at 3 months postoperative. The corresponding endpoint is the mean difference in binocular BCDVA under bright lighting conditions at 4 m at 3 months postoperative.

Secondary Objective:

Not applicable. There are no secondary objectives in this study.

1.2 Study Description

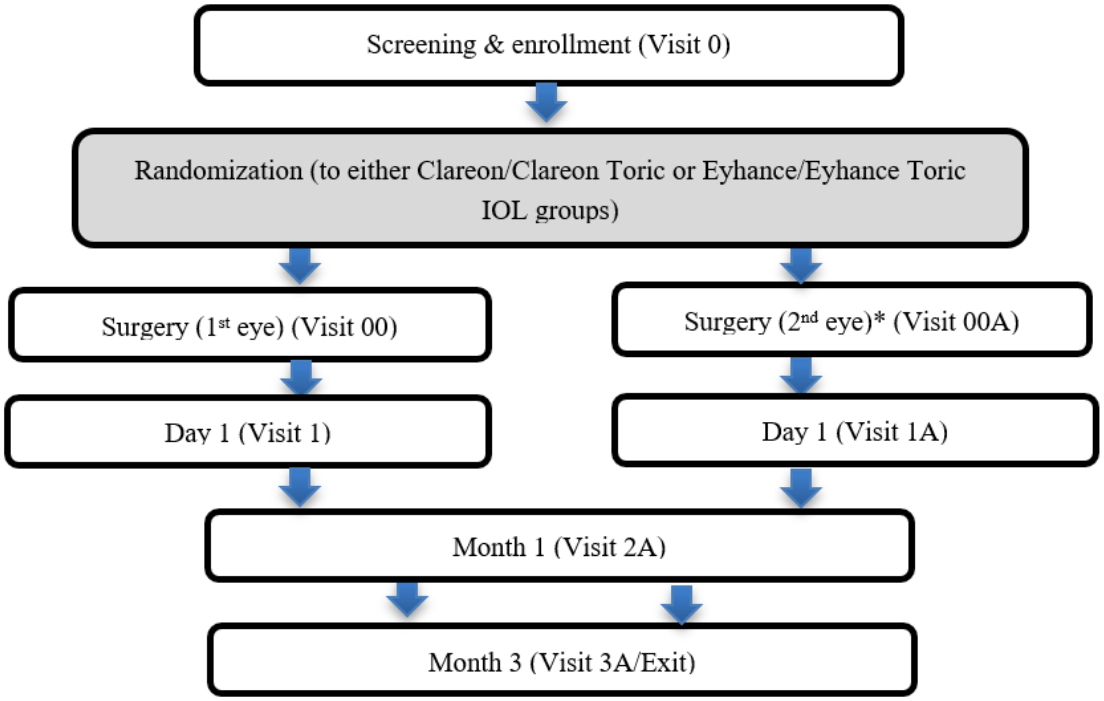
This is a prospective, multi-center, randomized, double-masked (subject and VA assessor), parallel group, postmarket study.

The study will enroll approximately 185 subjects who will be randomized to bilateral implantation of either Clareon/Clareon Toric IOLs or Eyhance/Eyhance Toric IOLs. The study will include adults 22 years of age and older, diagnosed with cataracts in both eyes, and planned bilateral cataract removal by routine small incision phacoemulsification surgery. Patients are required to have at least 1 eye planned for cataract surgery with a toric IOL. The fellow eye may be planned for toric or non-toric IOL implantation. A total of up to 7 scheduled visits (4 postoperative visits) are planned over a period of 5 months.

An overview of study design is depicted in Figure 1.1.

The schedule of visits is included as Table 10-1 in the appendix.

Figure 1-1 Study Diagram



* Option for the 2nd eye to be operated on the same day as the 1st eye. It is recommended that Visit 00 (1st eye surgery) occur within 0 to 30 calendar days after the Preoperative Visit (Visit 0). If not occurring on the same day, the 2nd eye IOL implantation should be conducted within 14 days after 1st eye implantation.

1.3 Randomization

Subjects will be randomized in a 1:1 manner to receive treatment bilaterally with either Clareon/Clareon Toric IOLs or Eyhance/Eyhance Toric IOLs, respectively. Subjects will be block randomized by investigational site.

Only after signing the ICF, a subject will be assigned a subject number by the electronic data capture (EDC) system. If all eligibility criteria are met and the subject desires to continue in the study, randomization will proceed.

It is recommended that randomization occur within 14 days prior to 1st eye surgery. A randomization list will be generated using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Subjects will be assigned treatment according to the randomization list uploaded in the EDC system. The randomization list will be generated and maintained by the study sponsor.

1.4 Masking

This study is Visual Acuity (VA) assessor-masked and subject-masked to the IOL group assignment.

The VA assessor associated with vision testing will be masked in this study. This includes manifest refraction [redacted] Any unmasking of the masked assessor or subject must be reported to Alcon.

The subject will remain masked for the duration of his/her trial participation and will be provided with his/her permanent implant card upon study exit.

[redacted]

2 ANALYSIS SETS

2.1 Effectiveness Analysis Sets

The primary analysis set for effectiveness analyses will be the All-Implanted Analysis Set (AAS). The AAS will include all eyes with successful study IOL implantation and with at least one postoperative visit.

All effectiveness analyses will be conducted on an as-treated basis. Eyes will be categorized under the actual study IOL implanted.

2.2 Safety Analysis Set

The Safety Analysis Set (SAS) will include all eyes with attempted study IOL implantation (successful or aborted after contact with the eye). The SAS will be the primary set for all safety analyses.

All analyses for eye-level endpoints (such as ocular adverse events) will be presented separately for first implanted eyes and second implanted eyes, as well as for all eyes

combined. Analyses for subject-level endpoints (such as nonocular adverse events) will be based on the subjects. Additionally, summaries by eye and treatment for toric versus non-toric lenses will be presented as applicable.

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. For treatment-emergent safety analyses, eyes will be categorized under the actual IOL implanted (or attempted to implant).

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Subject characteristics and study conduct summaries include tables and/or listings for subject disposition, demographics and baseline characteristics, targeted medical history and concomitant medications, baseline eye biometry, baseline visual acuity and manifest refraction spherical equivalent (MRSE), and surgical summary. All descriptive summary statistics will be displayed with number of subjects/eyes and percentage for categorical data, and with number of subjects/eyes, mean, standard deviation (SD), median, minimum, and maximum will be presented for continuous data. Tables will be presented by treatment (Clareon/Eyhance) and overall (both IOL groups), as applicable. Descriptive summary statistics for eyes, such as baseline eye biometry, visual acuity, and MRSE, will be presented by treatment, separately for first implanted eyes and second implanted eyes, as well as for all eyes combined.

Baseline will be defined as the last measurement prior to exposure to investigational product, except otherwise stated.

Subject characteristics and study conduct summaries will be presented for the AAS and SAS. [redacted]

3.1 Subject Disposition and Study Conduct

A subject disposition table will be presented that displays the number of subjects enrolled in the study, in addition to the number of screen failures, the number randomized, the number with attempted implantation, successful implantation, completed study, and discontinued study. This table will also contain counts for each reason for premature study discontinuation. A corresponding listing of reasons for early study discontinuation will also be provided.

Subject status by visit for first eyes and second eyes will be presented for AAS, [redacted] and SAS by treatment. Subject accounting by visit will be presented for the primary endpoint

(i.e., binocular BCDVA in bright lighting conditions) for AAS [redacted] by treatment. [redacted] Finally, a summary of IOL exposure will be provided to summarize the number of eyes randomized and implanted with toric and non-toric lenses by treatment and overall.

Summaries of subject eye evaluability for each analysis set will be provided by eye and by subject. Summaries by eye will be presented by treatment for first eyes and second eyes, and all eyes combined. Select summaries by eye and treatment for toric versus non-toric lenses may be presented as applicable. Summaries by subject will be provided by treatment and overall.

In addition, summary tables or subject listings will be provided including:

- Number of subjects randomized by investigator
- Lens model by investigator
- Subjects with screen failure (including reason)
- Eyes receiving treatment different than planned
- Subject eye evaluability
- Subject eyes excluded from analysis
- Subject eyes excluded from study visit
- Protocol deviations

3.2 Demographics

Demographics will be summarized by the number and percentage of subjects for the categorical variables, and descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) for the continuous variables, by treatment and overall based on AAS, [redacted] and SAS. A listing of demographic and baseline characteristics will also be provided.

Demographics (subject-level)

Categorical variables:

- Age (years) (<65, ≥65)

- Sex (Female, Male, Unknown, Undifferentiated)
- Race (per CRF)
- Ethnicity (per CRF)

Continuous variable:

- Age (years)

3.3 Medical History and Concomitant Medications

Targeted medical history and concomitant medications will be listed for all subjects based on the SAS.

Medical history includes all ocular history and targeted systemic history within 30 days prior to screening visit; and concomitant medications include all ocular medications and targeted systemic medications within 30 days prior to screening visit.

3.4 Baseline Eye Biometry

Assessments of eye biometry will be summarized preoperatively by the number and percentage of eyes for categorical variables and descriptive statistics (number of eyes, mean, SD, median, minimum, and maximum) for continuous variables by treatment.

First implanted eyes and second implanted eyes, as well as all eyes combined will be presented based on AAS, [redacted] and SAS.

Continuous variables:

- Axial length (mm)
- Anterior chamber depth (mm)
- Corneal thickness (μm)
- Corneal astigmatism (D) = abs (K1-K2)

Categorical variables:

- Axial length (<21.0 mm (short), ≥21.0 mm to ≤26.0 mm (medium), and >26.0 mm (long))

3.5 Baseline Visual Acuity and MRSE

Baseline visual acuity and MRSE will be summarized preoperatively using descriptive statistics (number of eyes, mean, SD, median, minimum, and maximum) for continuous variables by treatment.

First implanted eyes and second implanted eyes, as well as all eyes combined will be presented based on AAS, [redacted] and SAS.

3.6 Surgical Summary

Surgical factors will be summarized by the number and percentage of eyes for categorical variables and descriptive statistics (number of eyes, mean, SD, median, minimum, and maximum) for continuous variables by treatment.

First implanted eyes and second implanted eyes, as well as all eyes combined will be presented based on AAS.

Continuous variables:

- Target residual refractive error (TRRE) (D)
- Lens power (D) (Median, Min, Max only)
- Incision enlargement (mm) = (final incision size - initial incision size)

Categorical variables:

- Lens model (as per the CRF)
- IOL calculation method (as per the CRF)

Additionally, a listing of incision size (initial, final), enlargement, and position at surgery will be provided.

4 EFFECTIVENESS ANALYSIS STRATEGY

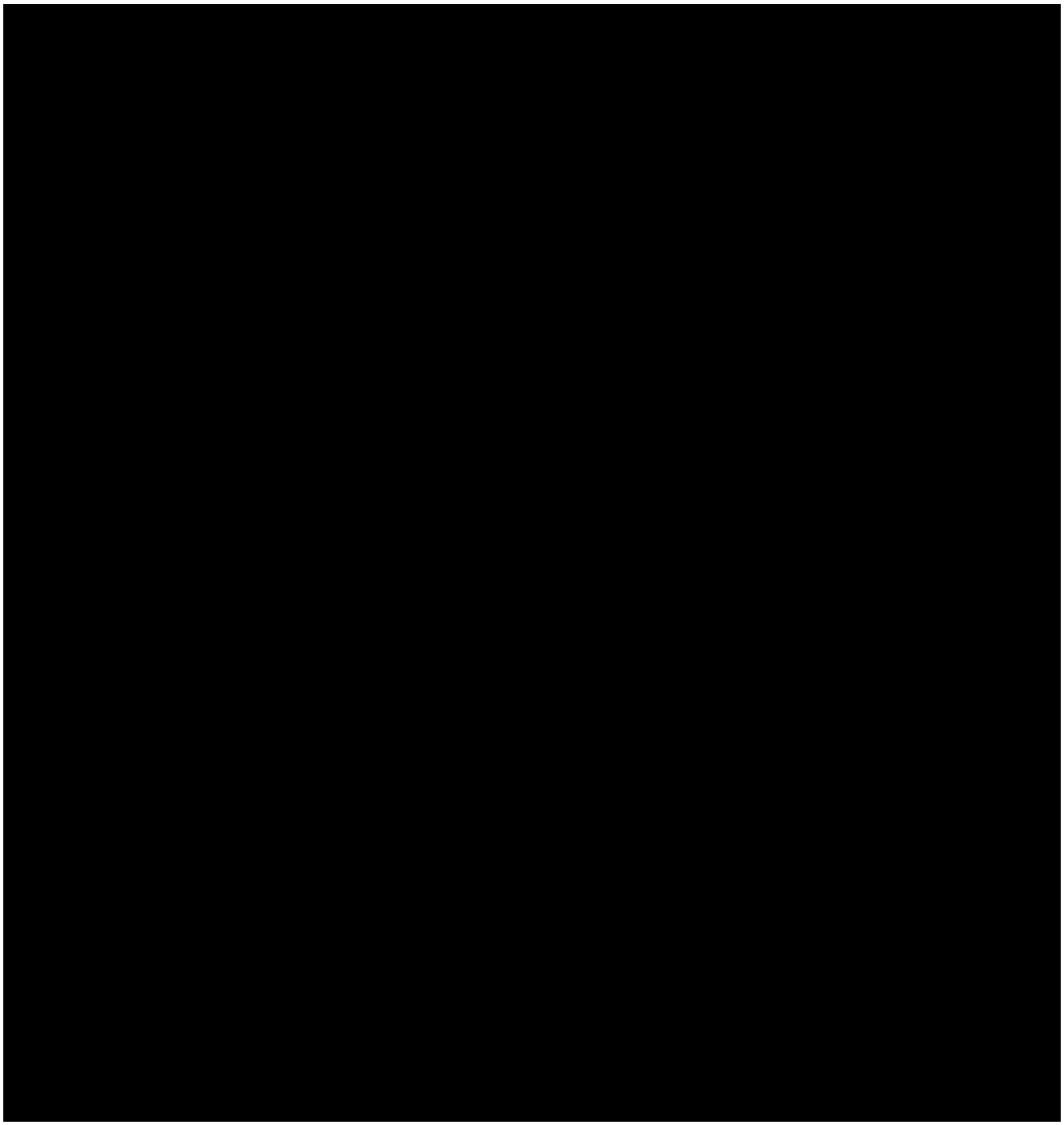
A success on the primary effectiveness endpoint would be indicated by achieving noninferiority of the Clareon/Clareon Toric IOLs to the Eyhance/Eyhance Toric IOLs in binocular BCDVA in bright lighting conditions at 3 months postoperative. [redacted]

4.1 Effectiveness Endpoints

Primary endpoint:

- Mean binocular BCDVA in logMAR at 4 m under bright lightning conditions at 3 months postoperative

[redacted]



4.2 Effectiveness Hypotheses

4.2.1 Primary Effectiveness Hypothesis

The primary objective of this study is to demonstrate noninferiority of the Clareon/Clareon Toric IOLs to the Eyhance/Eyhance Toric IOLs in binocular BCDVA at 3 months postoperative. The primary effectiveness endpoint is mean binocular BCDVA under bright lightning conditions at 4 m at 3 months postoperative.

The null (H_0) and alternative (H_1) hypotheses to be evaluated in support of the primary noninferiority objective are:

$$H_0: \mu_{Test} - \mu_{Comparator} \geq \Delta$$

$$H_1: \mu_{Test} - \mu_{Comparator} < \Delta$$

Where, Δ refers to the noninferiority margin, set at 0.1 logMAR, and μ_{Test}, $\mu_{Comparator}$ refers to the mean values of binocular BCDVA for the test (Clareon/Clareon Toric) and comparator (Eyhance/Eyhance Toric) IOLs respectively at 3 months post implantation.

[redacted]

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

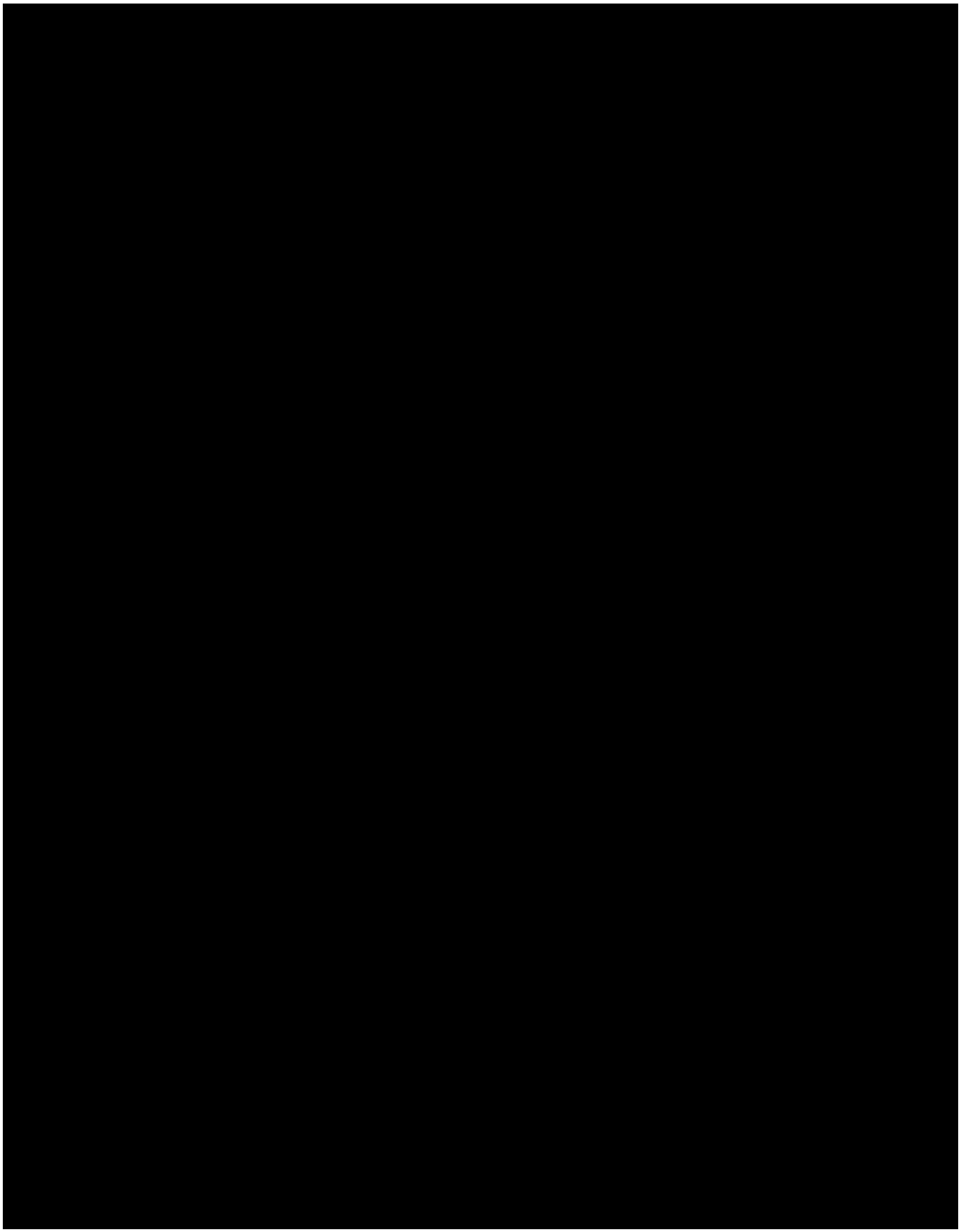
4.3.1 Primary Effectiveness Analysis

The noninferiority hypothesis of the primary endpoint will be evaluated based on the difference in means (Clareon/Clareon Toric *minus* Eyhance/Eyhance Toric) and the associated 95% upper confidence limit using a two-sample t-test. Using Levene's test, equality of variance between the two treatments will be assessed. If the test for equality of variance is not rejected, equal variance can be assumed. The null hypothesis is rejected, and noninferiority is claimed, if the upper bound of the one-sided 95% confidence interval does not exceed the noninferiority margin of 0.1 logMAR. The primary analysis will be based on AAS. [redacted]

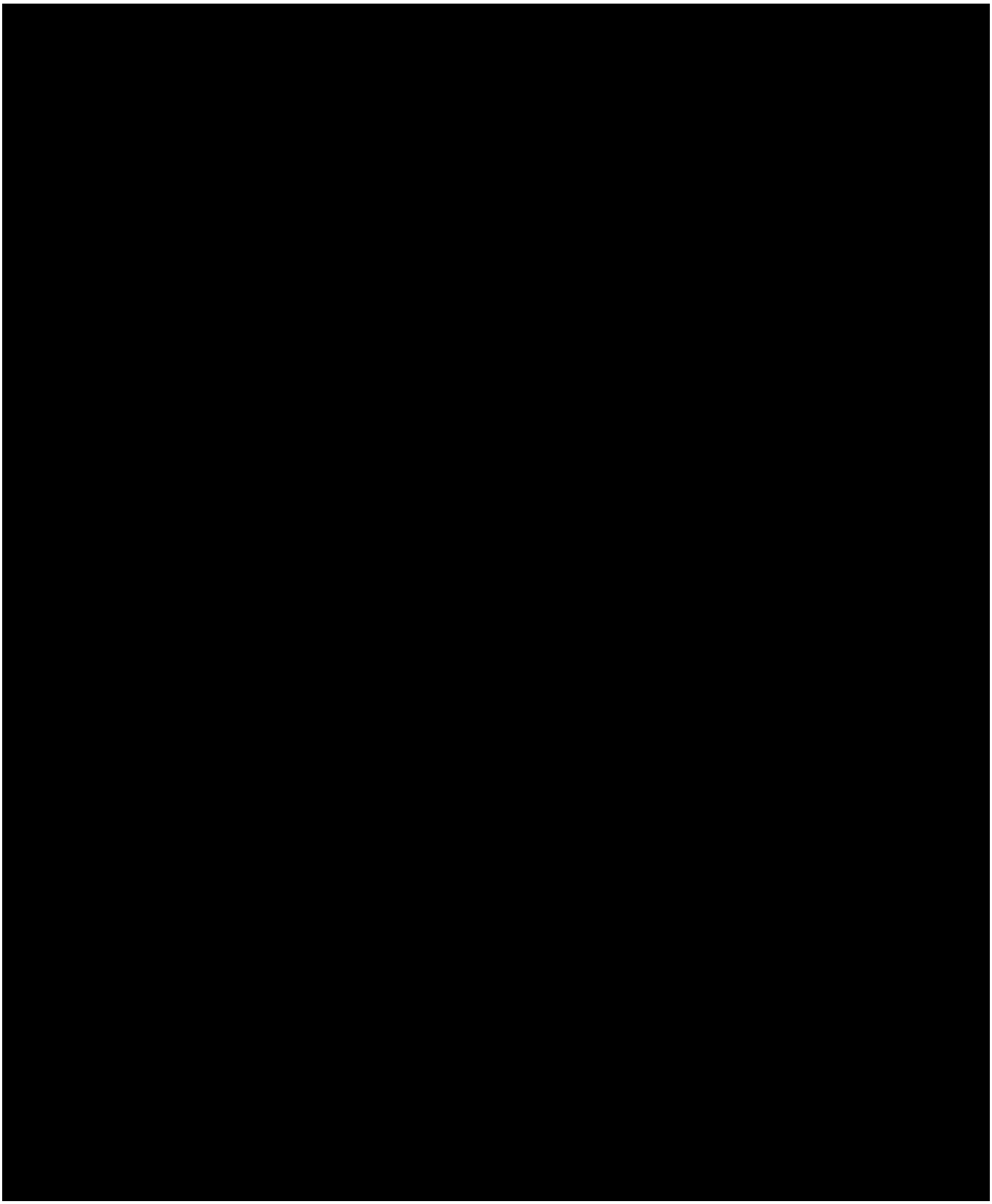
The mean difference between treatments, the associated standard error, and 95% upper confidence limit will be presented for the primary endpoint based on AAS [redacted] at the 3-month visit.

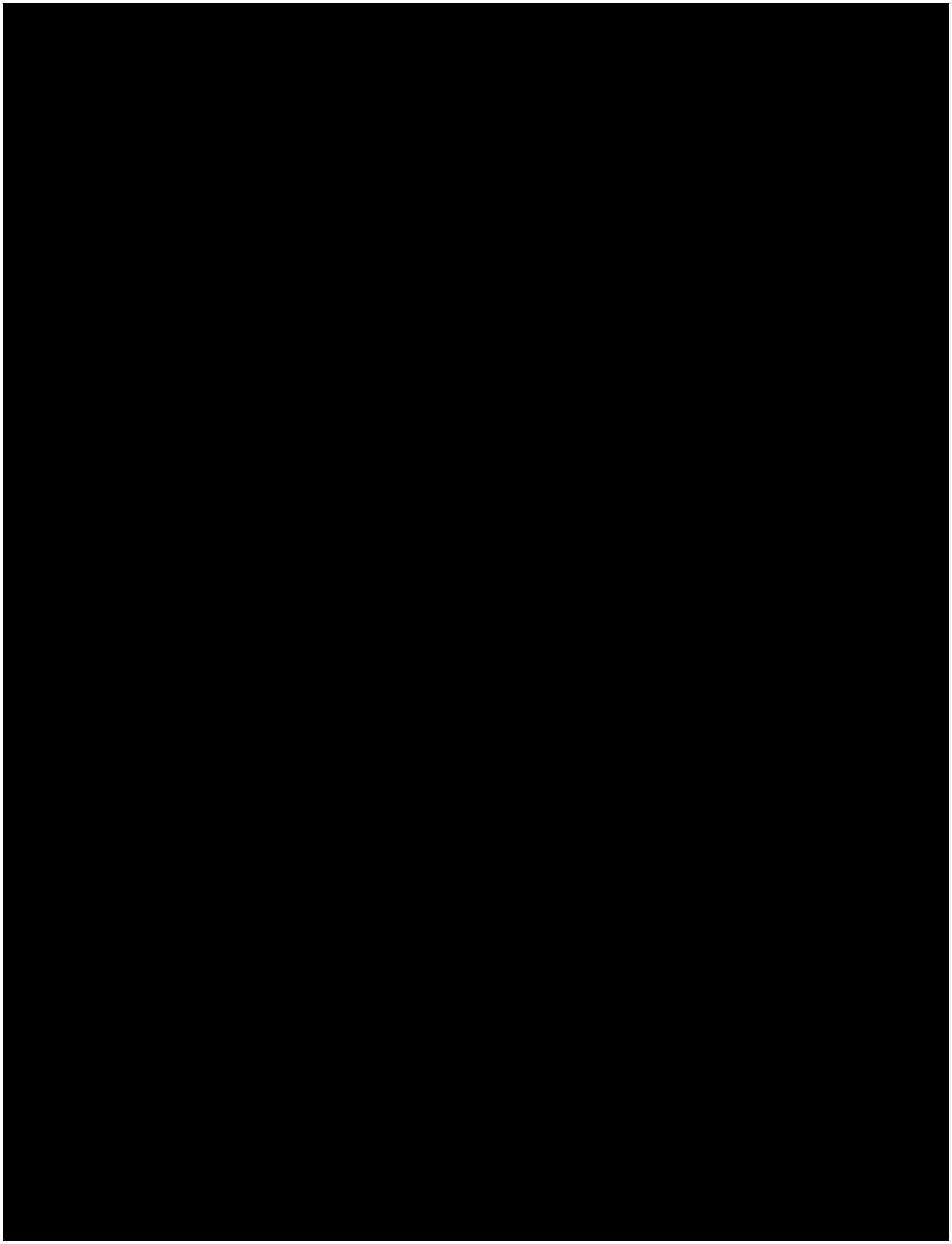
[redacted]

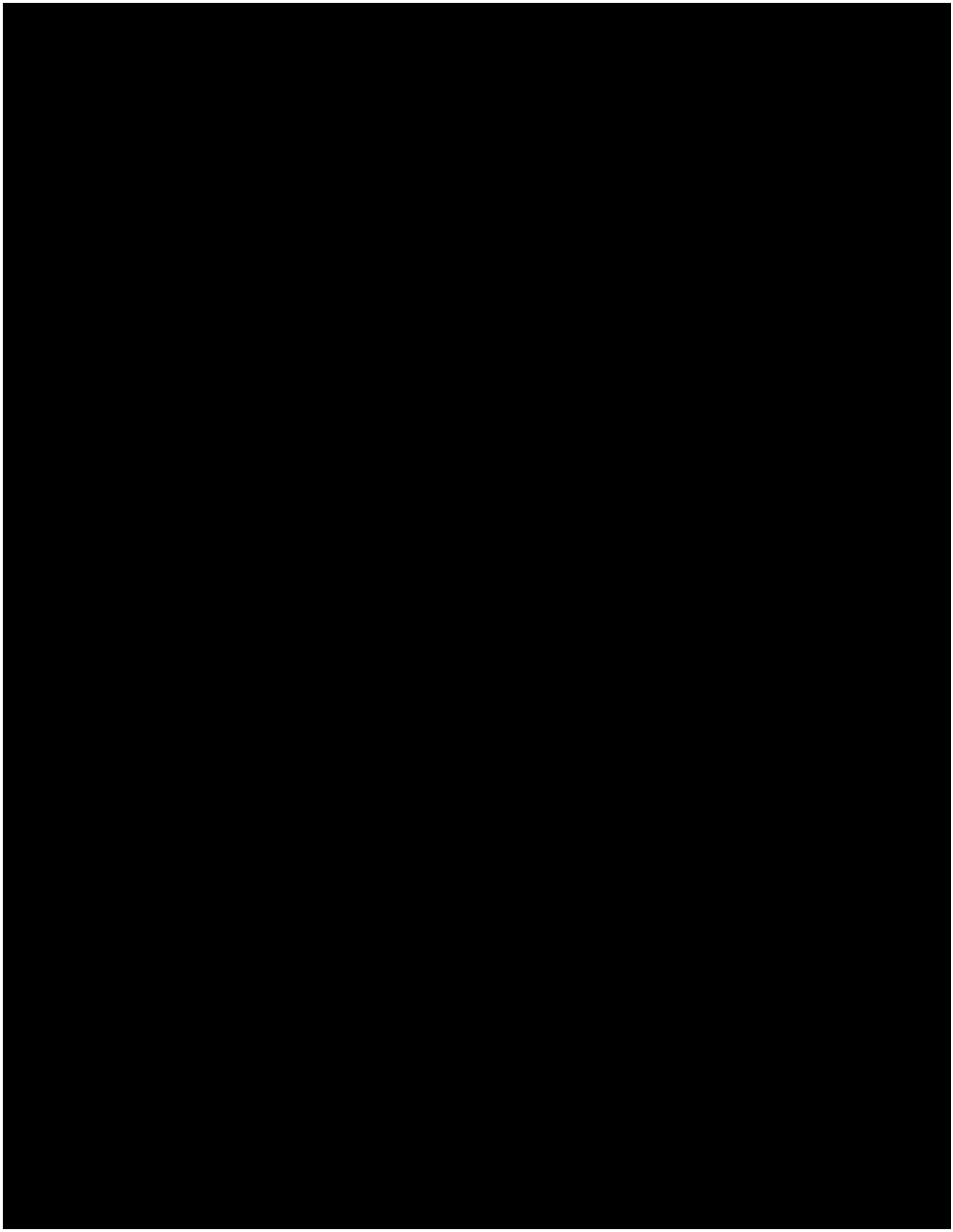
[redacted]

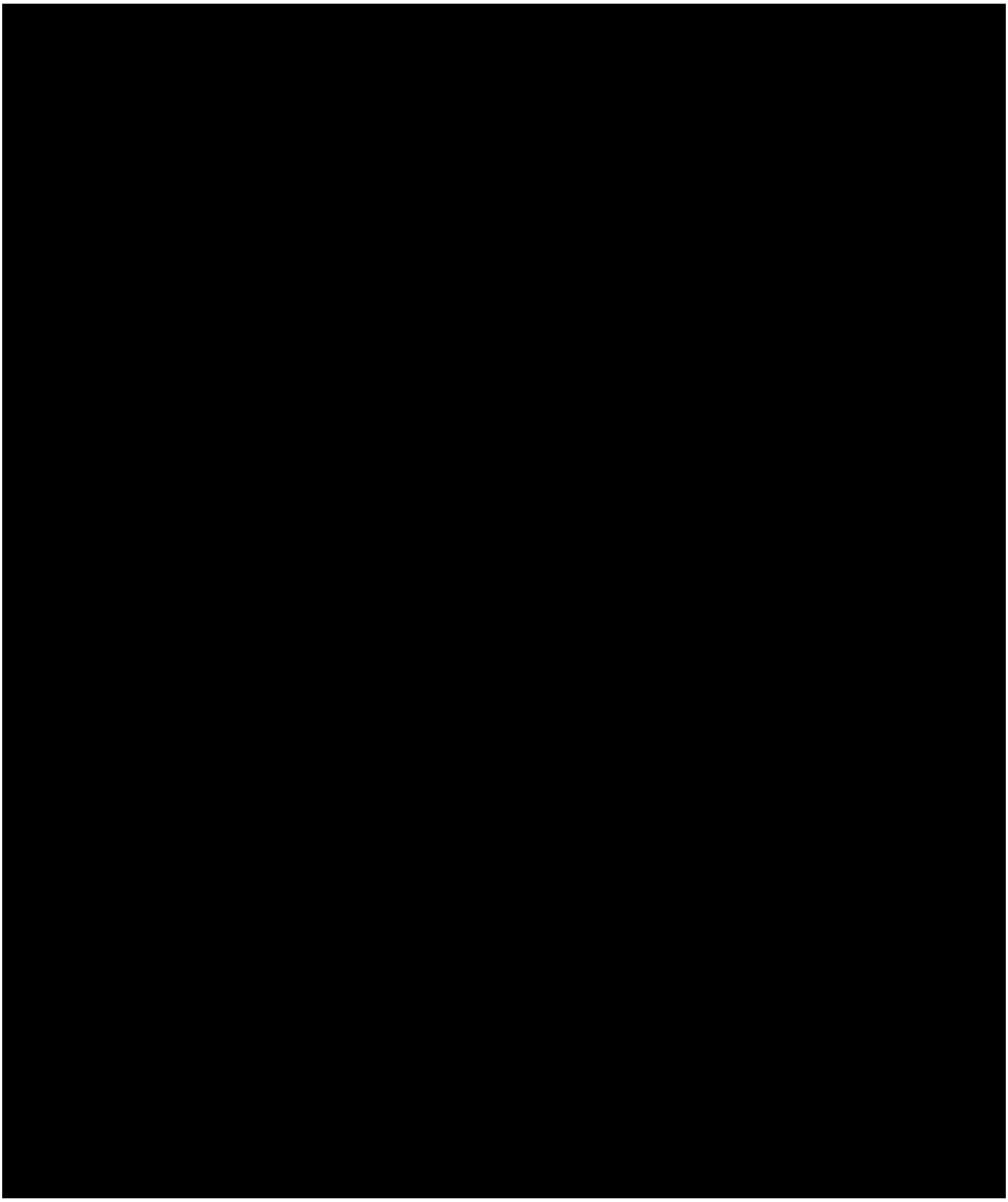


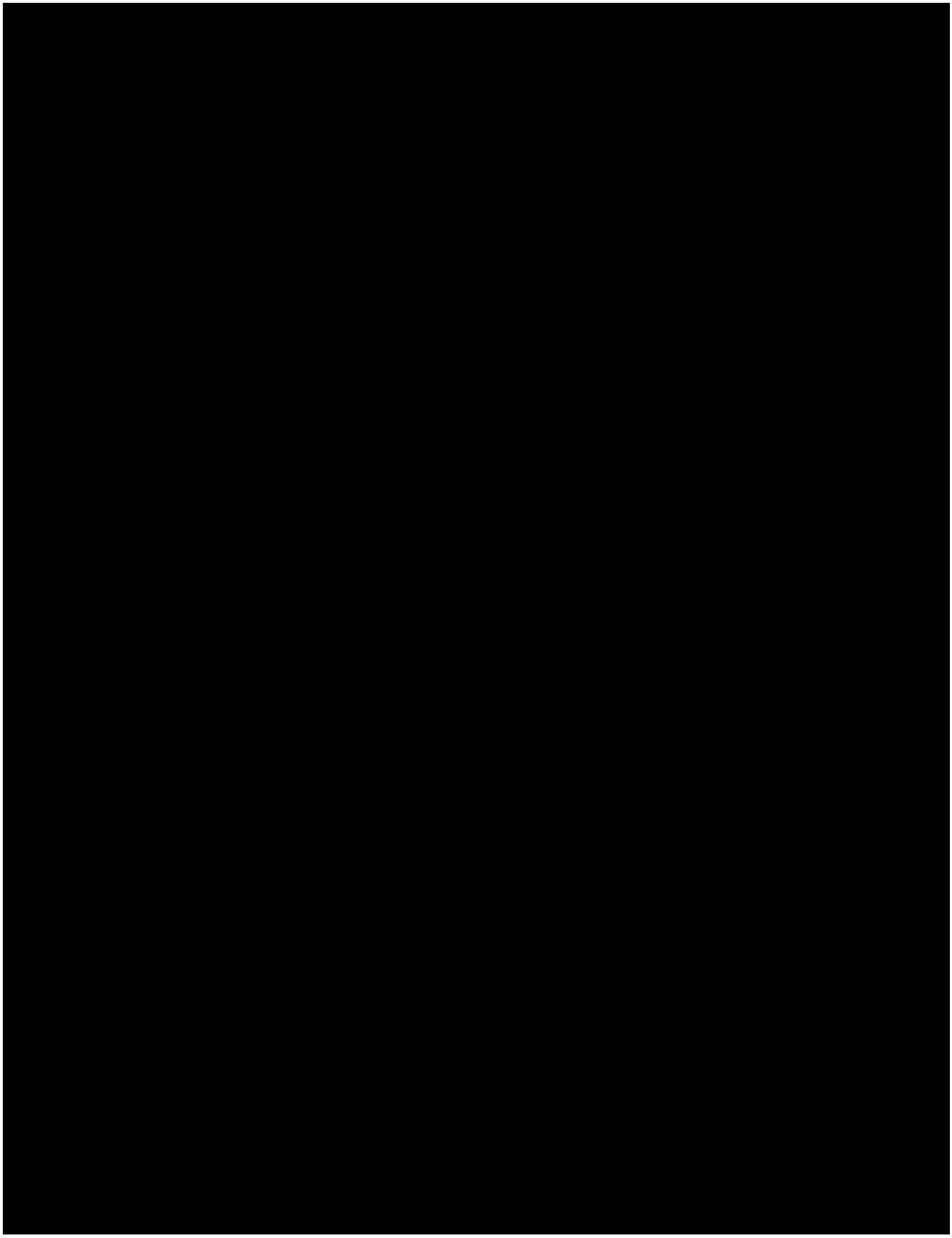
[redacted]











5 SAFETY ANALYSIS STRATEGY

5.1 Safety Endpoints

Safety endpoints are:

- All adverse events (ocular and nonocular, serious and non-serious)
- Secondary surgical interventions (SSIs)
- Device deficiencies
- IOL observations

- IOL position change (tilt and decentration)
- Posterior Capsule Opacification (PCO)
- Posterior capsulotomy
- Surgical problems
- Other surgical procedures at surgery
- Slit lamp examination
- Dilated fundus examination
- Intraocular Pressure (IOP) (mmHg)

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

Except otherwise stated, the analysis set for all safety analyses is the SAS as defined in Section 2.2. Baseline will be defined as the last measurement prior to exposure to investigational product, except otherwise stated.

Unless otherwise specified, all eye-level safety endpoints will be summarized by treatment, separately for first implanted eyes and second implanted eyes, as well as for all eyes combined. When combining eyes, mixed effects models will be utilized to account for the correlation between subject-eyes when estimating confidence intervals.

In addition to the analyses presented below a listing of all monocular BCDVA for eyes with a loss of 10 letters or more at 3 months compared to 1 month will be provided; where a 10 letter loss (decrease) is a change in BCDVA of at least 0.2 logMAR.

5.3.1 Adverse Events

The applicable definition of an Adverse Event (AE) is in the study protocol. The number and percentage of all ocular adverse events will be tabulated for any event and by MedDRA Preferred Term by treatment. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term. The number of events will also be presented. Adverse events related to the study IOL are referred to as adverse device effects.

Additionally, adverse events associated with SSI, specifically with preferred terms indicating secondary IOL intervention, will be summarized by relatedness to the study device by treatment. For SSIs, the number of events is not applicable and therefore will not be presented.

Adverse events will be summarized in the following tables, by treatment:

1. All Adverse Events (Serious and Non-Serious Combined)
    a. Ocular
    b. Nonocular

2. All Adverse Device Effects
    a. Ocular
    b. Nonocular

3. All Serious Adverse Events (including Serious Adverse Device Effects)
    a. Ocular
    b. Nonocular

4. Secondary Surgical Interventions (SSIs)

3. Subject/Eye Listings
    a. Non-serious Ocular
    b. Non-serious Nonocular
    c. Serious Ocular
    d. Serious Nonocular
    e. SSIs

In addition, listings of treatment-emergent and non-treatment emergent adverse events will be provided separately. The treatment-emergent AE listings will include, but are not limited to, the following variables: IOL model, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), days from surgery, AE duration, and corresponding AE details.

Individual subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to investigational product (i.e., non-treatment emergent). The non-treatment emergent AE listings will include, but are not limited to, the following variables: subject identification number, age, sex, eye (if applicable), days prior to planned surgery, duration, and corresponding AE details.

A listing of all SSIs will also be presented and will include, but is not limited to, the following variables: IOL model, subject identification number, age, sex, eye, days from surgery, duration, and corresponding AE details

Ocular AEs and SSIs will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.2 Device Deficiencies

The applicable definition of a device deficiency is presented in the study protocol. The number and percentage of all device deficiencies will be tabulated by treatment. A listing of all device deficiencies will also be provided. Device deficiencies will be summarized and listed for all randomized subjects.

Device deficiencies will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.3 IOL Observations

The number and percentage of IOL observations reported at each scheduled visit will be tabulated by treatment. A listing of all IOL observations will also be provided.

IOL observations will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.4 Subjective Posterior Capsule Opacification (PCO) Assessment

The number and percentage of eyes representing the maximum rating for an eye during the study will be tabulated by the response categories presented on the CRF (i.e., none, clinically nonsignificant, clinically significant, clinically significant requiring a YAG) and summarized by treatment. Similarly, eyes with a ‘worst case’ rating of clinically significant PCO or posterior capsulotomy (YAG) will be summarized by the response categories on the CRF. The summaries described above will also be further summarized by toric and non-toric lenses, for all eyes combined only.

A listing of eyes with clinically significant PCO, clinically significant PCO requiring YAG, or posterior capsulotomy will be presented which includes the PCO or capsulotomy results at all visits. The listing will include, but are not limited to, the following variables: treatment, IOL model, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), visit, days from surgery, and PCO or capsulotomy details at each visit.

5.3.5 Posterior Capsulotomy

The number and percentage of eyes with posterior capsulotomy (overall and by reason) will be tabulated by treatment.

Posterior capsulotomy will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.6 Surgical Problems

The number and percentage of eyes with surgical problems as per the CRF (e.g., anterior capsular tear) will be presented by treatment. In addition, a listing of subjects with surgical problems will be provided. The listing will include the following variables: treatment, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), and description of surgical problem.

Surgical problems will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.7 Other Procedures at Surgery

A listing of all other surgical procedures will be provided. The listing will include the following variables: treatment, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), and type of other surgical procedure.

5.3.8 Slit Lamp Examination

For each slit lamp parameter as per the CRF, numbers and percentages of eyes that experience an abnormality at each scheduled visit will be presented by treatment.

A listing will be provided which presents all eyes with an abnormality in any slit-lamp parameter at any postoperative visit. The listing will include all slit-lamp data from all visits with the following variables: treatment, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), visit, days from surgery, and slit lamp parameter.

Slit lamp abnormalities will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.9 Dilated Fundus Examination

For each dilated fundus parameter as per the CRF, numbers and percentages of eyes that experience abnormality at each scheduled visit will be presented by treatment.

A listing will be provided which presents all eyes with an abnormality in any fundus parameter at any postoperative visit. The listing will include all fundus examination data from all visits with the following variables: treatment, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), visit, days from surgery, and fundus parameter.

Dilated fundus abnormalities will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.10 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole mmHg. All analyses will be presented by treatment.

Descriptive statistics (number of eyes, mean, median, SD, minimum, maximum, and two-sided 95% confidence interval) of observed values and change from baseline values will be presented at each study visit.

A listing will be provided which presents all eyes with an increase or decrease in IOP of more than 10 mmHg at any postoperative visit compared to the same eye at baseline. The listing will include the following variables: treatment, IOL model, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), visit, days from surgery, value at the visit, baseline value, and a change from baseline value.

IOP will also be summarized by toric and non-toric lenses for all eyes combined only.

5.3.11 IOL Position Change (Tilt/Decentration)

The number and percentage of eyes with a change from last visit (per CRF) in IOL position category (Tilted $\geq$ 1 degree, Decentered $\geq$ 0.5 mm) will be presented by treatment.

In addition, a listing of eyes with any IOL position change will be provided. The listing will include the following variables: treatment, subject identification number, age, sex, surgery eye (first or second implanted eye), eye (OD or OS), visit, days from surgery, and amount of tilting or decentration.

IOL position change will also be summarized by toric and non-toric lenses for all eyes combined only.

6 ANALYSIS STRATEGY FOR OTHER ENDPOINTS

Not Applicable.

8 REFERENCES

No references.

9 REVISION HISTORY

This is the second (Version 2.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 4.0 of the study protocol.

10 APPENDIX

Table 10-1 Schedule of Study Procedures and Assessments

	Both Eyes	First Operative Eye[1]	Second Operative Eye[1]	First Operative Eye	Second Operative Eye	Both eyes		Applicable eye
	Pre-op Visit 0	Visit 00	Visit 00A	Visit 1	Visit 1A	Visit 2A	Visit 3A/Exit Visit	Unscheduled visit
		Day 0	Day 0A	Day 1-2	Day 1-2	Day 30-60 (1month)	Day 90-120 (3months)	N/A
Informed consent	X							
Demographics	X							
Medical history[2]	X							
Concomitant medications[2]	X	X	X	X	X	X	X	(√)
Urine pregnancy test[3]	X							
Inclusion/exclusion criteria	X							
Target refractive error (aiming for emmetropia or first minus)	X							
Manifest refraction	X					X	X	(√)
Corneal Tomography	X					X	X	
Biometry (Keratometry, AL, and ACD with corneal thickness)	X					X	X	
[redacted]								
Dilated pupil size	X							
Toric IOL calculator	X							
Lens information		X	X					
Randomization[5]	X							
Cataract surgery		X	X					
Incision size and location		X	X					
[redacted]								
Distance Visual Acuity								

	Both Eyes	First Operative Eye[1]	Second Operative Eye[1]	First Operative Eye	Second Operative Eye	Both eyes		Applicable eye
	Pre-op Visit 0	Visit 00	Visit 00A	Visit 1	Visit 1A	Visit 2A	Visit 3A/Exit Visit	Unscheduled visit
		Day 0	Day 0A	Day 1-2	Day 1-2	Day 30-60	Day 90-120	N/A
[redacted]								
Binocular UCDVA • Bright lighting conditions						X	X	
[redacted]								

	Both Eyes	First Operative Eye[1]	Second Operative Eye[1]	First Operative Eye	Second Operative Eye	Both eyes		Applicable eye
	Pre-op Visit 0	Visit 00	Visit 00A	Visit 1	Visit 1A	Visit 2A	Visit 3A/Exit Visit	Unscheduled visit
		Day 0	Day 0A	Day 1-2	Day 1-2	Day 30-60	Day 90-120	N/A
[redacted]								
Safety								
All adverse events including SSI	X	X	X	X	X	X	X	(√)
Device deficiencies		X	X	X	X	X	X	(√)
IOL observations				X	X	X	X	(√)
PCO assessment				X	X	X	X	(√)
Posterior capsulotomy assessment				X	X	X	X	(√)
Surgical problems		X	X					
Other surgical procedures at surgery		X	X					
Reasons for discontinuation during surgery		X	X					
Slit lamp examination	X			X	X	X	X	(√)
Dilated fundus examination	X					X	X	(√)
IOP	X			X	X	X	X	(√)
IOL position change (tilt and decentration)				X	X	X	X	(√)

NOTES:

1 It is recommended that Visit 00 (1st eye surgery) occur within 0 to 30 calendar days after the Preoperative Visit (Visit 0). Visit 00A (2nd eye surgery) may have the option to occur same day as Visit 00 (1st eye surgery) and it is recommended that the 2nd eye surgery occur within 14 days after the 1st eye surgery.

2 CRF data will be targeted:

Medical History: All ocular history, targeted systemic history within 30 days prior to screening visit

Concomitant medications: All ocular medications, targeted systemic medications within 30 days prior to screening visit

3 In women of childbearing potential only.

4 Preoperative pupil size is the ability to constrict with a penlight.

5 It is recommended that randomization occur within 14 days prior to 1st eye surgery.

[redacted]

(√) Assessment performed as necessary