PMCF Evaluation of Clareon Vivity/Vivity Toric

STUDY ID

ILE632-C002

STATISTICAL ANALYSIS PLAN

Version 1

23-May-2023

NCT05852470

Statistical Analysis Plan for ILE632-C002
Title: PMCF Evaluation of Clareon Vivity/Vivity Toric

[redacted]

This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

Executive Summary:

Key Objectives:

The study's co-primary and secondary objectives are listed below. Each objective is assessed at Visit 1 (90-180d post 2nd eye implant).

1. To demonstrate that Clareon Vivity/Vivity Toric IOL is noninferior to Clareon Monofocal/Clareon Toric IOL in mean binocular photopic BCDVA

2. To demonstrate that Clareon Vivity/Vivity Toric IOL is superior to Clareon Monofocal/Clareon Toric IOL in mean binocular photopic DCIVA

3. To demonstrate that Clareon Vivity/Vivity Toric IOL is superior to Clareon Monofocal/Clareon Toric IOL in mean binocular photopic DCNVA

4. To demonstrate that Clareon Vivity/Vivity Toric IOL is superior to Clareon Monofocal/Clareon Toric IOL with respect to proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire

Decision Criteria for Study Success:

A successful outcome on the co-primary effectiveness endpoints is indicated by successful outcomes on the first two of these objectives.

Table of Contents

List of Tables

List of Figures

[redacted]

1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

1.1.1 Primary Objectives

The study's co-primary objectives are listed below. Each objective is assessed at Visit 1 (90-180d post 2nd eye implant).

1. To demonstrate that Clareon Vivity/Vivity Toric IOL is noninferior to Clareon Monofocal/Clareon Toric IOL in mean binocular photopic BCDVA
2. To demonstrate that Clareon Vivity/Vivity Toric IOL is superior to Clareon Monofocal/Clareon Toric IOL in mean binocular photopic DCIVA

1.1.2 Secondary Objectives

The study's secondary objectives are listed below. Each objective is assessed at Visit 1 (90-180d post 2nd eye implant).

1. To demonstrate that Clareon Vivity/Vivity Toric IOL is superior to Clareon Monofocal/Clareon Toric IOL in mean binocular photopic DCNVA
2. To demonstrate that Clareon Vivity/Vivity Toric IOL is superior to Clareon Monofocal/Clareon Toric IOL with respect to proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire

[redacted]

1.1.4 Safety Objectives

Below are listed the study's safety objectives to assess safety of Clareon Vivity/Vivity Toric IOL as compared to Clareon Monofocal/Clareon Toric IOL. Each objective is assessed at Visit 1 (90-180d post 2nd eye implant).

1. Adverse event rates
2. Monocular (1st Eye) and binocular mesopic contrast sensitivity (with and without glare)
3. Rates of severe and most bothersome (separately) visual disturbances as reported by subjects using a questionnaire (QUVID)

1.2 Study Description

This is a prospective/retrospective, multicenter, nonrandomized, parallel group, controlled, assessor masked interventional study. Both eyes of a subject must qualify for enrollment into this study.

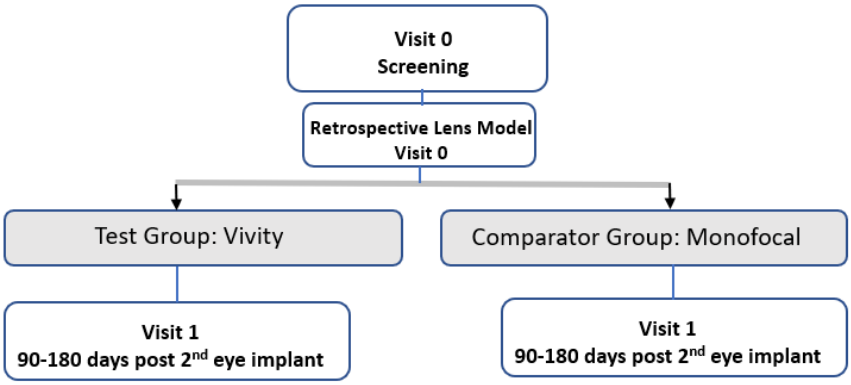
A total of 2 scheduled visits are planned and subject participation is expected to last approximately 2 weeks. The visits include a Screening visit (Visit 0) and 1 visit after screening (Visit 1) that should occur 1 to 14 days after Visit 0. The subject must be 90-180 days post 2nd eye implant at the time of Visit 1. Visit 1 must occur at least one day after the Screening visit and it is recommended that it occurs a maximum of 14 days after screening. The study is expected to be completed in approximately 5 months.

The study population consists of male and female subjects 18 years of age and older that were previously implanted bilaterally with the Clareon Vivity/Clareon Vivity Toric IOLs (Vivity, test article) or Clareon Monofocal/Clareon Toric IOLs (Monofocal, comparator article).

The first operative eye is defined as the eye that was implanted first. The second operative eye is defined as the eye that was implanted second. (Note: Eyes that are implanted on the same day are acceptable in this study.)

An overview of the study design is depicted in Figure 1-1.

Figure 1-1 Study Design Diagram



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

It is aimed to enroll approximately 210 subjects to complete approximately 190 subjects at the final study visit (approximately 95 in each arm). This assumes approximately a 9.5% screen failure rate. Up to 12 US investigative sites are planned for this study. Site specific targets will be adjusted based on individual site capabilities.

1.3 Randomization

This study is not randomized.

1.4 Masking

This study is ONLY assessor-masked for manifest refraction, VA, [redacted] and contrast sensitivity. To minimize bias, Alcon personnel (including biostatistics, masked data manager, and clinical project lead) will be masked to the IOLs that have been previously implanted in the subject, to the extent possible. All other members associated with the study (at the site and the study sponsor) are unmasked.

This level of masking will be maintained throughout the conduct of the study. Unmasking will occur only after all planned study data have been validated, and the database locked.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 ANALYSIS SETS

2.1 Effectiveness Analysis Sets

The Full Analysis Set (FAS) will include all eyes for enrolled subjects who are bilaterally implanted with the test or comparator IOL. The FAS will be the primary analysis set for effectiveness.

[redacted]

All effectiveness analyses will be conducted according to actual test or comparator article implanted.

2.2 Safety Analysis Set

The FAS will be used for all safety analyses.

All safety analyses will be conducted according to actual test or comparator article implanted.

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, demographics, surgeon, and baseline characteristics tables (including age, gender, race, ethnicity), listing of IOL group by site, summary of screen failures by reason and listing of subjects excluded from key analysis sets including reasons. All descriptive summary statistics will be displayed with number and percentage for categorical data, and with mean, median, standard deviation, number of subjects, minimum and maximum for continuous data. Tables will be presented by IOL group and overall.

Subject characteristics and study conduct summaries will be presented for the FAS [redacted]

4 EFFECTIVENESS ANALYSIS STRATEGY

A success on co-primary effectiveness endpoints would be indicated by successful outcomes on both 2 of these endpoints (2 hypothesis tests). A total of four hypothesis tests will be conducted to address the co-primary and secondary objectives of the study. [redacted]

[redacted]

4.1 Effectiveness Endpoints

All effectiveness endpoints below are assessed at Visit 1 (90-180d post 2nd eye implant).

4.1.1 Primary Effectiveness

- Mean Binocular photopic BCDVA (logMAR) at 4 m
- Mean Binocular photopic DCIVA (logMAR) at 66 cm

4.1.2 Secondary Effectiveness

- Mean Binocular photopic DCNVA (logMAR) at 40 cm
- Proportion of subjects who respond “Never” to Q1 of the spectacle use questionnaire (IOLSAT)

[redacted]

[redacted]

4.2 Effectiveness Hypotheses

4.2.1 Primary Effectiveness Hypotheses

The null and alternative hypotheses for the first primary effectiveness endpoint are:

$$H_0: \mu_{Vivity} - \mu_{Monofocal} \geq \Delta$$

$$H_1: \mu_{Vivity} - \mu_{Monofocal} < \Delta$$

where μ_{Vivity} and $\mu_{Monofocal}$ are the means for binocular BCDVA for test (Clareon Vivity/Vivity Toric IOL) and comparator (Clareon Monofocal/Clareon Toric IOL), respectively, at Visit 1 (90 to 180 days postoperatively), and Δ is the noninferiority margin set at 0.1 logMAR.

The null and alternative hypotheses for the second primary effectiveness endpoint are:

$$H_0: \mu_{Vivity} \geq \mu_{Monofocal}$$

$$H_1: \mu_{Vivity} < \mu_{Monofocal}$$

where μ_{Vivity} and $\mu_{Monofocal}$ are the means for binocular DCIVA for test (Clareon Vivity/Vivity Toric IOL) and comparator (Clareon Monofocal/Clareon Toric IOL), respectively, at Visit 1 (90 to 180 days postoperatively).

[redacted]

4.2.2 Secondary Effectiveness Hypotheses

The null and alternative hypotheses for the first secondary endpoint are:

$$H_0: \mu_{Vivity} \geq \mu_{Monofocal}$$

$$H_1: \mu_{Vivity} < \mu_{Monofocal}$$

where μ_{Vivity} and $\mu_{Monofocal}$ are the means for binocular DCNVA for test (Clareon Vivity/Vivity Toric IOL) and comparator (Clareon Monofocal/Clareon Toric IOL), respectively, at Visit 1 (90 to 180 days postoperatively).

The null and alternative hypotheses for the second secondary endpoint are:

$$H_0: p_{Vivity} \leq p_{Monofocal}$$

$$H_1: p_{Vivity} > p_{Monofocal}$$

where p_{Vivity} and $p_{Monofocal}$ are the proportion of subjects who respond "Never" to Q1 of the IOLSAT, for test (Clareon Vivity/Vivity Toric IOL) and comparator (Clareon Monofocal/Clareon Toric IOL), respectively, at Visit 1(90 to 180 days postoperatively).

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

The FAS will be used for the primary statistical analyses for both primary effectiveness endpoints. [redacted]

4.3.1.1 Mean Binocular photopic BCDVA (logMAR) at 4 m

Analysis of the first primary effectiveness endpoint (BCDVA) will be based on a two-sample t-test assuming equal variances, [redacted]. The difference in means (Vivity IOL minus Monofocal IOL) and the associated two-sided 90% confidence interval will be presented. Noninferiority is demonstrated if the one-sided p-value for the t-test is less than 0.05 or, equivalently, the upper limit of the two-sided 90% confidence interval is less than the noninferiority margin. A two-sided 95% confidence interval will also be provided for descriptive purposes.

[redacted]

In addition, the following descriptive statistics (number and percentage in the category) will be provided for each IOL group:

- logMAR categories: the number and percentage of eyes (for monocular endpoints)/subjects (for binocular endpoints) with visual acuity of
    - 0.0 logMAR or better: ≤0.00 logMAR
    - 0.1 logMAR or better: ≤0.10 logMAR
    - 0.2 logMAR or better: ≤0.20 logMAR
    - 0.3 logMAR or better: ≤0.30 logMAR
- Snellen categories: the number and percentage of eyes (for monocular endpoints)/subjects (for binocular endpoints) with visual acuity of
    - 20/20 Snellen or better: ≤0.04 logMAR
    - 20/25 Snellen or better: ≤0.14 logMAR
    - 20/32 Snellen or better: ≤0.24 logMAR
    - 20/40 Snellen or better: ≤0.34 logMAR

4.3.1.2 Mean Binocular photopic DCIVA (logMAR) at 66 cm

Analysis of the second primary effectiveness endpoint (DCIVA) will be based on a two-sample t-test assuming equal variances, with a type I error rate of 5%, 1-sided. The difference in means (Vivity IOL minus Monofocal IOL) and the associated two-sided 90% confidence interval will be presented. Superiority is demonstrated if the one-sided p-value for the t-test is less than 0.05 or, equivalently, the upper limit of the two-sided 90% confidence interval is less than 0. A two-sided 95% confidence interval will also be provided for descriptive purposes.

In addition, the descriptive statistics (number and percentage in the category) will be provided for each IOL group described in Section 4.3.1.1.

4.3.2 Secondary Effectiveness Analyses

The FAS will be used for the primary statistical analyses for both secondary effectiveness endpoints. [redacted]

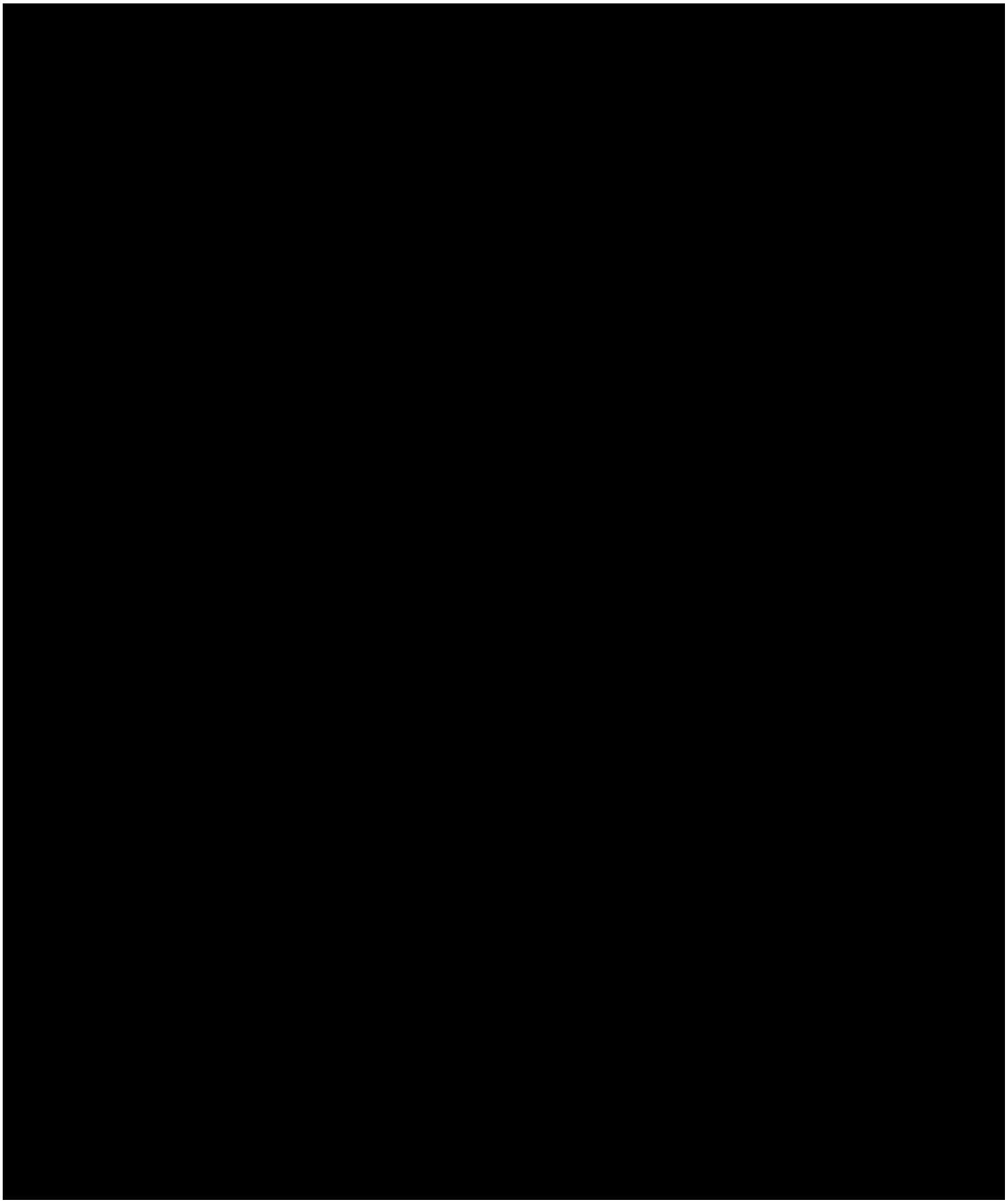
4.3.2.1 Mean Binocular photopic DCNVA (logMAR) at 40 cm

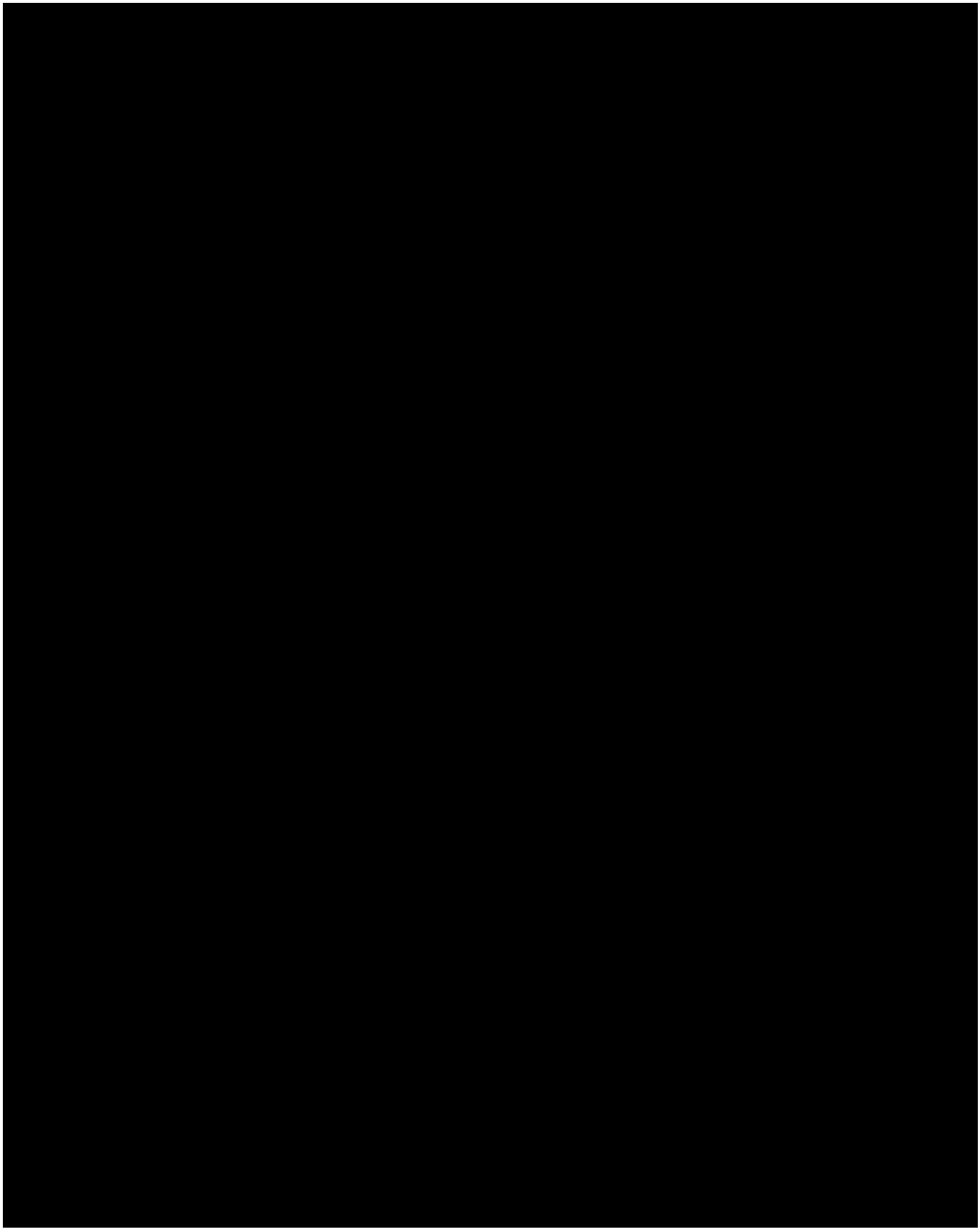
Analysis of the first secondary effectiveness endpoint (DCNVA) will be based on a two-sample t-test assuming equal variances, with a type I error rate of 5%, 1-sided. The difference in means (Vivity IOL minus Monofocal IOL) and the associated two-sided 90% confidence interval will be presented. Superiority is demonstrated if the one-sided p-value for the t-test is less than 0.05 or, equivalently, the upper limit of the two-sided 90% confidence interval is less than 0. A two-sided 95% confidence interval will also be provided for descriptive purposes.

In addition, the descriptive statistics (number and percentage in the category) will be provided for each IOL group described in Section 4.3.1.1.

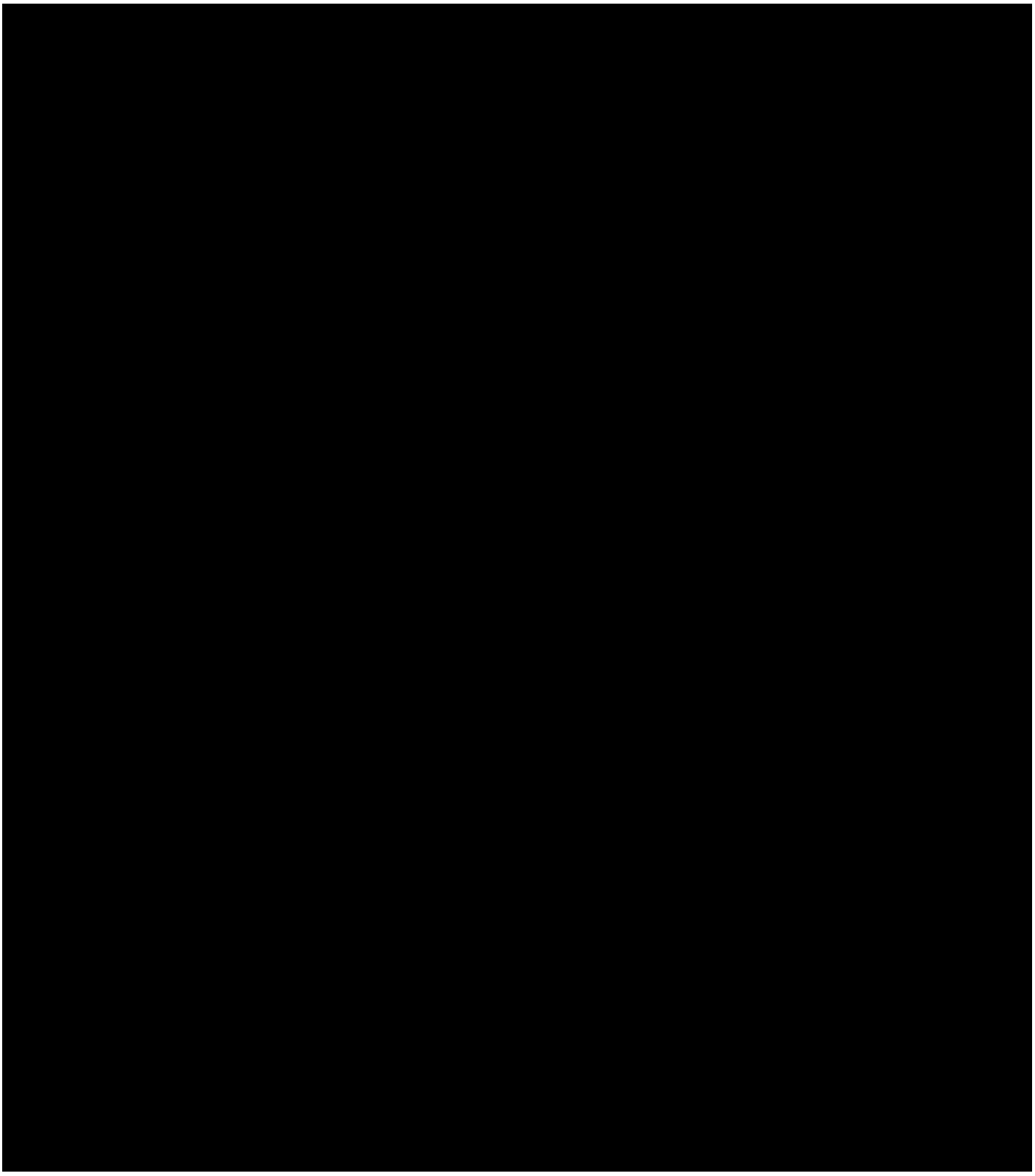
4.3.2.2 Proportion of subjects who respond “Never” to Q1 of the spectacle use questionnaire (IOLSAT)

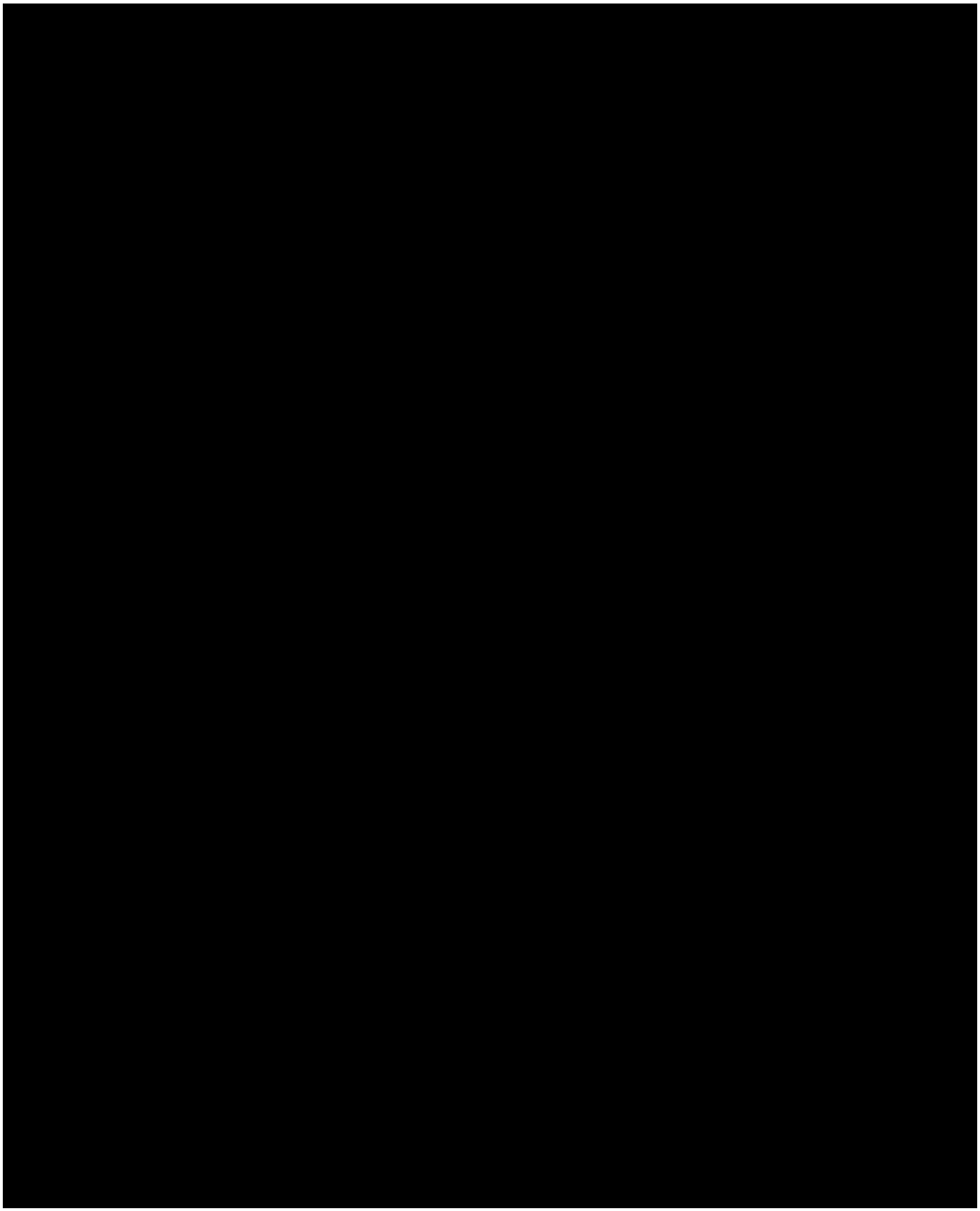
A two-sided 90% confidence interval for the difference in proportions (Vivity IOL – Monofocal IOL) will be calculated using the Miettinen-Nurminen method (1985), and Vivity IOL will be determined to be superior to Monofocal IOL if the lower boundary of the confidence interval is greater than zero. This is equivalent to using a type I error rate of 5%, 1-sided. A two-sided 95% confidence interval will also be provided for descriptive purposes.





[redacted]





4.6 Handling of Missing Data

All key effectiveness endpoints are assessed at Visit 1 (90-180d post 2nd eye implant). The influence of missing data is expected to be minimal. Missing values for co-primary and secondary effectiveness endpoints by IOL group will be summarized. Missing values will not be imputed.

4.7 Interim Analysis for Effectiveness

Not applicable.

5 SAFETY ANALYSIS STRATEGY

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events
- Device deficiencies
- QUVID subject survey

- Binocular and monocular (first eye implanted) mesopic contrast sensitivity test (with and without glare)
- IOP
- Slit lamp examination findings including:
    - IOL observations
    - Absolute IOL position change (tilt and decentration)
    - Subjective posterior capsular opacification (PCO)
    - Posterior capsulotomy rates
- Dilated fundus examination, including fundus visualization

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 focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events and other safety parameters. Descriptive summaries (number and percentage) and listings will be presented. Individual subject listings will be provided for AEs that occur after signing informed consent. In addition to the specific requested variable/outcome of interest, all listings will include the following common variables (if appropriate): site, subject, age, sex, race, ethnicity, IOL group/model, visit, implant eye and eye.

5.3.1 Extent of Exposure

Retrospective exposure durations are collected at Visit 0 (screening visit) and will be summarized as a continuous measure (N, mean, median, standard deviation, minimum and maximum) by IOL group. Duration is defined as the day of Visit 1 minus the day of 2nd eye implant, plus 1.

5.3.2 Adverse Events

Adverse events are collected at both Visit 0 (screening visit) and Visit 1 (90-180d post 2nd eye implant).

Descriptive summaries (number and percentage) for all ocular adverse events will be presented by preferred term with a breakdown by IOL group, separately for first and second eyes. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term.

The number and percentage of all adverse events will also be summarized with a breakdown by IOL group, separately for first and second implanted eyes.

Adverse events will be summarized in the following tables:

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. Subject Listings
    a. Non-Serious Ocular
    b. Non-Serious Nonocular
    c. Serious Ocular
    d. Serious Nonocular

5.3.3 Device Deficiencies

Device deficiencies are collected at both Visit 0 (screening visit) and Visit 1 (90-180d post 2nd eye implant).

The number and percentage for each device deficiency category will be summarized with a breakdown by IOL group, separately for first and second implanted eyes. A listing of all device deficiencies, as recorded on the Device Deficiency Form, will also be provided.

5.3.4 QUVID Subject Survey

QUVID questionnaire will be conducted at Visit 1 (90-180d post 2nd eye implant).

Descriptive summaries (number and percentages) for the severe and most bothersome (separately) visual disturbances as presented by the subjects using the QUVID questionnaire

will be presented by IOL group. These rates will be accompanied by two-sided exact 95% confidence intervals.

Descriptive summaries (number and percentage) for each category of responses to each question on the QUVID questionnaire will be presented by IOL group.

5.3.5 Mesopic Contrast Sensitivity (With and Without Glare)

Binocular and monocular (first eye implanted) mesopic contrast sensitivity test (with and without glare) will be conducted at Visit 1(90-180d post 2nd eye implant).

Linear sine grating binocular and monocular mesopic contrast sensitivity testing will be undertaken for spatial frequencies of 12, 6, 3 and 1.5 cycles per degree (cpd) without glare and then with glare using the eVA system. For each subject, the contrast sensitivity function (CSF) at each spatial frequency will be determined (with and without glare) automatically by the eVA system.

Analyses of log contrast sensitivity will be performed for each testing condition (with and without glare) and spatial frequency. [redacted]

In addition, for mesopic contrast sensitivity, descriptive summary statistics will be presented by IOL group and 3 mesopic pupil size ranges [≤ 3.0 mm (small), > 3.0 mm to < 4.0 mm (medium), and ≥ 4.0 mm (large)].

[redacted]

5.3.6 IOP

Intraocular pressure (IOP) measurements will be recorded in mmHg and recorded by the corresponding whole number (e.g., A measurement of 12.8 mmHg or 12.2 mmHg will each be recorded as 12 mmHg). IOP measurements will be conducted at Visit 0 (screening visit).

Descriptive summaries (N, mean, median, standard deviation, standard error, minimum and maximum) of observed values be presented by IOL group, separately for first and second implanted eyes.

5.3.7 Slit-Lamp Examination

Slit-Lamp Examination is performed at Visit 0 (screening visit). Record any slit lamp findings, absolute IOL position change (tilt and decentration), any IOL observations, any subjective PCO and the subject has the presence of a posterior capsulotomy.

The number and percentage of all abnormal slit lamp examination findings and “worst case” grading for aqueous cells and flare will be presented by IOL group and implanted eye.

A listing will be provided which presents all eyes with an abnormality in any slit-lamp parameter.

5.3.8 IOL observations

IOL observations will be summarized by lens model using descriptive statistics, including frequency (N) and percent of eyes, separately for first and second implanted eyes, at Visit 0 (screening visit). “Other” IOL observations will be summarized and sorted by subject identification (site number, subject number), and by IOL group, separately for first and second implanted eyes.

5.3.9 Absolute IOL position change (Tilt/Decentration)

Descriptive statistics (number and percentages) on eyes with an absolute change at Visit 0 (screening visit) in IOL position category (Tilted, Decentered) will be presented by IOL group, separately for first and second implanted eyes.

In addition, a listing of subjects with absolute IOL position change will be provided.

5.3.10 Subjective posterior capsular opacification (PCO)

Descriptive statistics including number and percentage of eyes at Visit 0 (screening visit) of the “worst case” posterior capsule opacification (including capsulotomy) will be presented by IOL group, separately for first and second implanted eyes.

A listing of eyes with clinically significant posterior capsule opacification, clinically significant posterior capsule opacification requiring YAG or posterior capsulotomy will be presented which includes the posterior capsule opacification or capsulotomy values.

5.3.11 Posterior Capsulotomy

The number and percentage of eyes with posterior capsulotomy at Visit 0 (screening visit) will be presented with a breakdown by IOL group, separately for first and second implanted eyes.

5.3.12 Dilated Fundus Examination

Dilated Fundus Examination is performed at Visit 0 (screening visit).

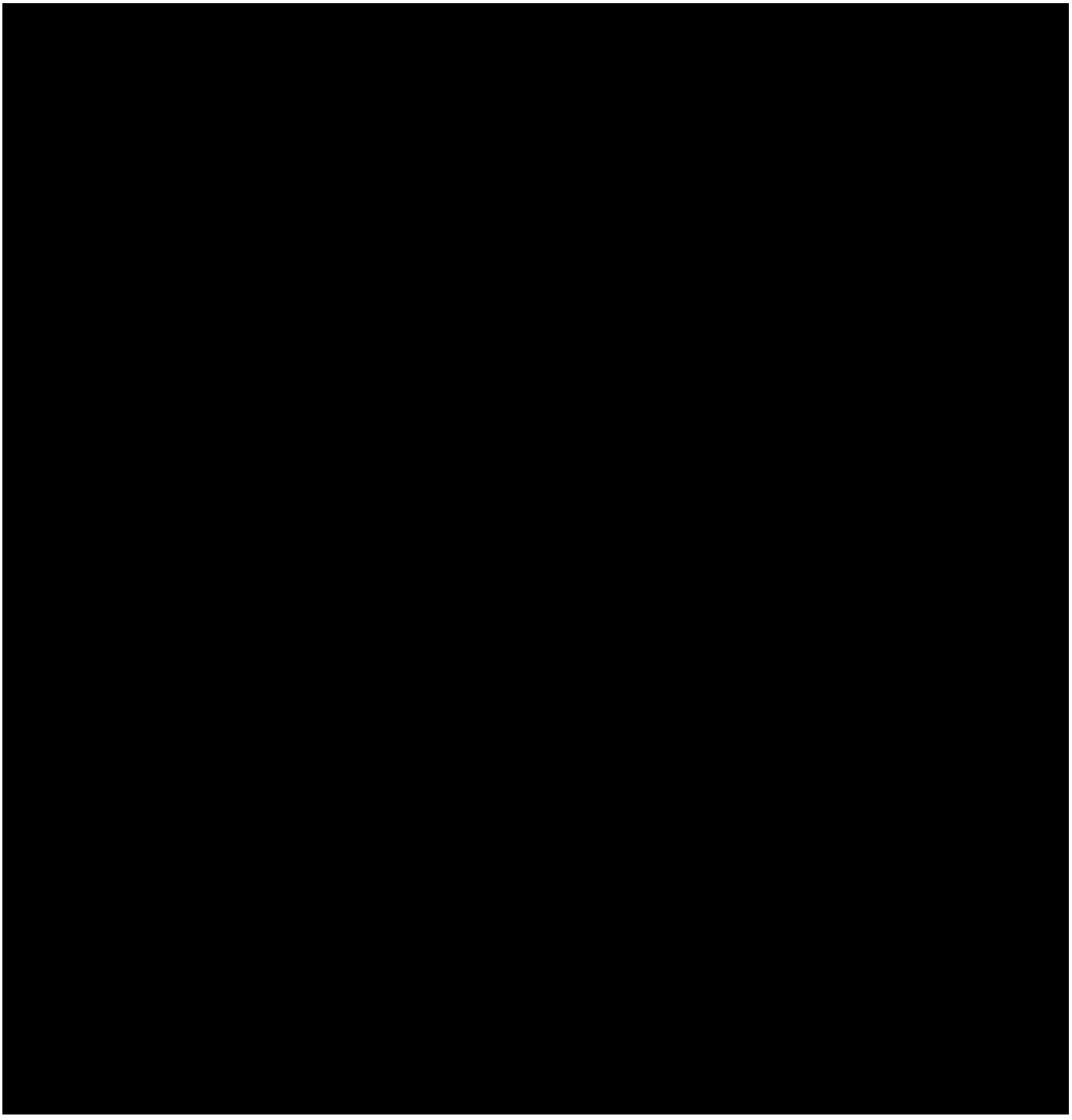
The number and percentage of all dilated fundus examination findings or visualization difficulty will be presented by IOL group, separately for first and second implanted eyes.

A listing will be provided which presents all eyes with abnormality or visualization difficulty in any fundus parameter.

5.3.13 Photopic Pupil Size

Photopic pupil size at Visit 0 (screening visit) will be presented as number and percentage in the following categories, respectively: ≤ 3.0 mm (small), > 3.0 mm to < 4.0 mm (medium), and ≥ 4.0 mm (large).

Descriptive statistics including mean, median, standard deviation, number of eyes, minimum, maximum and two-sided 95% confidence interval will be presented by IOL group, separately for first and second implanted eyes.



7 SAMPLE SIZE AND POWER CALCULATIONS

A total of 210 subjects will be enrolled (approximately 105 per arm). Assuming a screen failure rate of 9.5%, approximately 190 subjects will be evaluable at Visit 1 (95 per arm). The power estimates for the planned analyses are presented below:

Table 7-1 Power (%) Under Various Assumptions with Evaluable Sample Size of the difference between Vivity vs Monofocal IOL

Order	Endpoint	Comparison	Noninferiority Margin	Expected difference	SD[redacted]	Power
Co Primary	Binocular BCDVA	Noninferiority	0.10	0.04	0.14	90%
Co Primary	Binocular DCIVA at 66 cm	Superiority	NA	0.085	0.14	> 98%
1st Secondary	Binocular DCNVA at 40 cm	Superiority	NA	0.14	0.14	> 99%
2nd Secondary	Q1 of IOLSAT = NEVER	Superiority	NA	0.14	NA	> 96%
[redacted]						

Overall power is estimated based on the assumption that each hypothesis test is independent.

8 REFERENCES

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

	Visit 0 (Screening Visit)	**Visit 1**
	Study Day 0	**Study Day 1 to 14** [e]
Procedure/ Assessment		**3 to 6 months (90-180 days) post 2nd eye implant** [e]
Informed Consent	X	
Demographics	X	
Medical History [c]	X	
Concomitant Medications [c]	X	X
Inclusion/Exclusion	X	
Urine pregnancy test [d]	X	
Photopic Pupil Size	X	
Slit Lamp Examination	X	
Tonometry	X	
Dilated Fundus Examination	X	
Subjective PCO	X	
Presence of Posterior Capsulotomy	X	
IOL Observations	X	
Absolute IOL Position Change (Tilt/Decentration)	X	
Pre-Operative/Operative Information from Chart: • Lens model & power • IOL calculation method • Corneal topography and/or aberrometry (if available) • Biometry & keratometry • Predicted residual refractive error • Operating surgeon (first eye) • 1st eye implanted (OD or OS) • Date of Surgery for second eye	X (retrospective)	

	Visit 0 (Screening Visit)	**Visit 1**
QUVID questionnaire		X
IOLSAT questionnaire		X
Manifest refraction		X
• Binocular BCDVA [redacted]		X [redacted]
• Binocular DCIVA [redacted]		X [redacted]
• Binocular DCNVA [redacted]		X [redacted]
[redacted]		[redacted]
Binocular Mesopic Contrast Sensitivity (with and without glare) Monocular Mesopic Contrast Sensitivity (with and without glare) [b]		X X
Adverse Events	X	X
Device Deficiencies	X	X

[a] First and Second Eye Implanted, [b] First Eye Implanted only, [c] Medical History and Concomitant Meds will be reviewed in source only, [d] in women of childbearing potential only, [e] Visit 1 must occur at least one day after the Screening visit and it is recommended that is occur a max of 14 days after screening. The subject must be 90-180 days post 2nd eye implant at the time of Visit 1.