Short Title:

Statistical Analysis Plan IlJ466-P003 / NCT03316885

Full Title:

Statistical Analysis Plan IlJ466-P003

Protocol Title: Post-Market Clinical Investigation of the Clareon® IOL

[redacted] [redacted]

Protocol TDOC Number: TDOC-0053438

[redacted] [redacted]

[redacted]

Approvals: See last page for electronic approvals.

Job Notes:

This is the second (Version 2.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 of the study protocol TDOC-0053438.

Executive Summary:

Key Objectives:

The objective of this study is to evaluate the long-term (3 years) favorable visual acuity and adverse event outcomes for the Clareon IOL. A comparison to historical safety and performance endpoint (SPE) rates as reported in EN ISO 11979-7:2014 will be conducted for Visual Acuity and Adverse Events at one year.

The performance target in support of the primary effectiveness objective is to demonstrate that the one-sided exact 95% upper confidence limit for the percentage of subjects with monocular best corrected distance visual acuity of 0.3 logMAR or better at 1 year postoperative is not worse than the SPE rate of 92.5% for All-Implanted Analysis Set (as reported in EN ISO 11979-7:2014).

The secondary effectiveness objective is to evaluate visual acuity outcomes obtained with up to 3 years follow up in eyes implanted with the Clareon IOL.

The primary safety objective is to evaluate the safety of the Clareon IOL for first and second operative eyes separately up to 3 years postoperative. Adverse Events rates at 1 year (Visit 5A) will be compared to historical safety and performance endpoint (SPE) rates as reported in EN ISO 11979-7:2014.

Decision Criteria for Study Success:

The study will be considered successful if the data indicate a favorable outcome at one year in relation to the SPE rates as reported in EN ISO 11979-7:2014.

Categorical statistics (sample size, number in the category, percent in the category, and the corresponding one-sided exact 95% upper confidence limit) will be provided for the primary endpoint of monocular best corrected distance visual acuity. Study success will be concluded if the one-sided exact 95% upper confidence limit for the percentage of subjects with monocular best corrected distance visual acuity of 0.3 logMAR or better at 1 year postoperative is not worse than the SPE rate of 92.5% for All-Implanted Analysis Set (as reported in EN ISO 11979-7:2014).

Table of Contents

[redacted]

[redacted]

[redacted]

List of Tables

List of Figures

1 Study Objectives and Design

1.1 Study Objectives

Primary Effectiveness Objective:

The performance target in support of the primary effectiveness objective is to show that the one-sided exact 95% upper confidence limit for the percentage of subjects with monocular best corrected distance visual acuity of 0.3 logMAR or better at 1 year postoperative (Visit 5A) is not worse than the SPE rate of 92.5% as reported in EN ISO 11979-7:2014.

Secondary Effectiveness Objective:

The secondary effectiveness objective is to evaluate the visual acuity outcomes obtained with up to 3 years follow up in eyes implanted with the Clareon IOL.

Primary Safety Objective:

The primary safety objective is to evaluate the safety of the Clareon IOL for first and second operative eyes separately up to 3 Years (Visit 7A). Adverse Events rates at 1 year (Visit 5A) will be compared to historical safety and performance endpoint (SPE) rates as reported in EN ISO 11979-7:2014.

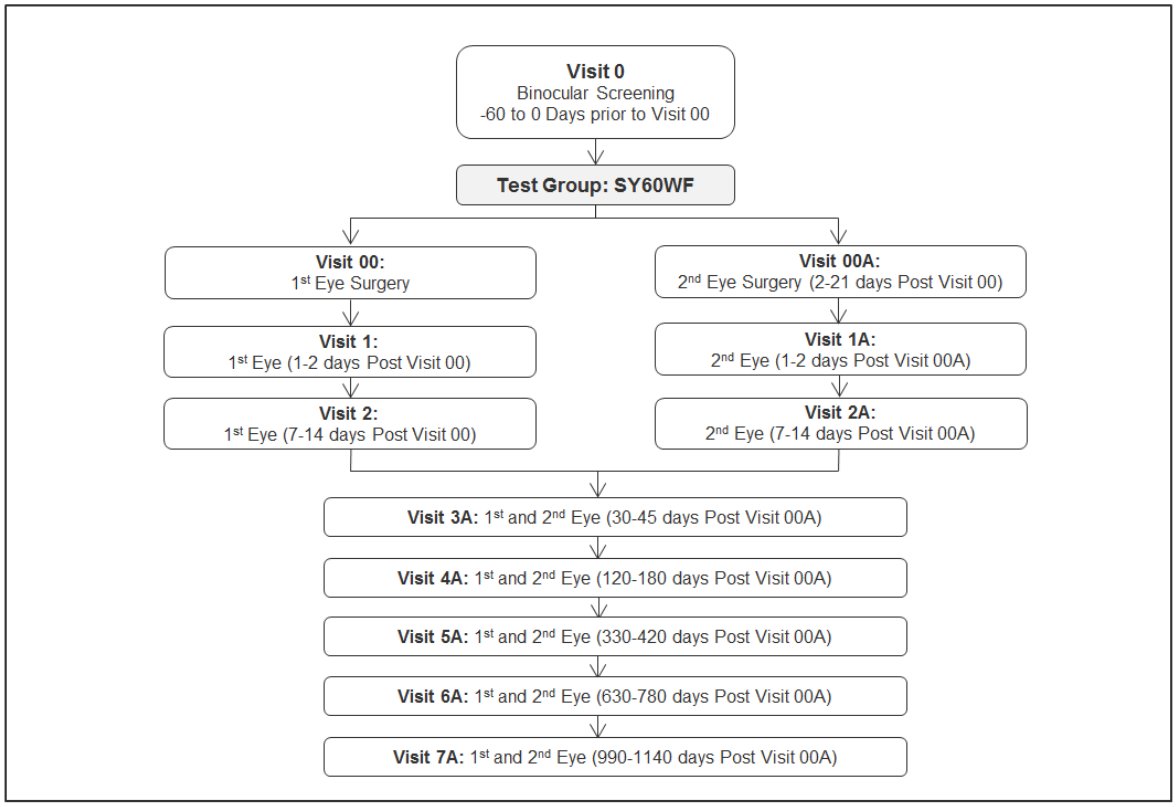
1.2 Study Description

This study is a prospective, multicenter, single-arm safety and performance clinical study, requiring no masking. The trial will evaluate the safety and performance of the Clareon IOL in approximately 200 bilaterally implanted subjects. To qualify for enrollment into the trial, adult (≥ 22 years of age) subjects must require routine, bilateral cataract surgery. Potential subjects will be screened for enrollment into the trial in accordance with the entry criteria found in Section 10 (SUBJECT POPULATION) of the protocol. Subjects will attend a total of 12 study visits (7 post-implantation) over a period of approximately 3 years.

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

The schedule of visits is available in Section 6 (SCHEDULE OF VISITS) of the protocol.

Figure 1-1 Study Design



1.3 Randomization

No randomization is performed in this study.

1.4 Masking

This is an open-label single-arm study. All subjects will be implanted with the Clareon IOL in both eyes.

[redacted]

2 Analysis Sets

2.1 Effectiveness Analysis Sets

The primary analysis set for effectiveness analyses will be the All-Implanted Analysis Set (AAS). AAS includes all eyes with successful test article implantation. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

2.2 Safety Analysis Set

The Safety Analysis Set will include all eyes with attempted implantation with the test article (successful or aborted after contact with the eye) and will be used for the safety analyses.

3 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, demographics and baseline characteristics tables (including age, gender, race, and ethnicity), 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 n and % for categorical data, and with mean, median, standard deviation, number of subjects, minimum, and maximum for continuous data.

Subject characteristics and study conduct summaries will be presented for the AAS, the BAS and the safety analysis set.

4 Effectiveness Analysis Strategy

The number and percentage of subjects with BCDVA of 0.3 logMAR or better at 1 year, 2 years, and 3 years postoperative will be summarized along with the corresponding one-sided exact 95% upper confidence limit. Only the one-sided exact 95% upper confidence limit for the rate at 1 year will be compared to the SPE rate of 92.5% for AAS.

Descriptive statistics will be provided for the secondary effectiveness endpoints.

4.1 Effectiveness Endpoints

Primary Effectiveness Endpoint

Percentage of subjects achieving BCDVA of 0.3 logMAR or better at 1 year post-implantation (Visit 5A)

Secondary Effectiveness Endpoints

- Percentage of subjects achieving BCDVA of 0.3 logMAR or better at 2 years post-implantation (Visit 6A)
- Percentage of subjects achieving BCDVA of 0.3 logMAR or better at 3 years post-implantation (Visit 7A)
- UCDVA at 1 year (Visit 5A) post-implantation
- UCDVA at 2 years (Visit 6A) post-implantation
- UCDVA at 3 years (Visit 7A) post-implantation

4.2 Effectiveness Hypotheses

Not applicable.

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

4.3.1.1 Monocular BCDVA at 1 year post-implantation

The performance target in support of the primary effectiveness objective is to show that the one-sided exact 95% upper confidence limit for percentage of subjects with monocular BCDVA of 0.3 logMAR or better at 1 year postoperative (Visit 5A) is not worse than the SPE rate of 92.5% for the AAS. As a supportive analysis, the one-sided exact 95% upper confidence limit for percentage of subjects with monocular BCDVA of 0.3 logMAR or better at 1 year postoperative (Visit 5A) will be compared against SPE rate of 96.7% for the BAS.

For visual acuity endpoints, the following descriptive statistics will be provided:

- logMAR categories: the number and percentage of eyes 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 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

In addition, descriptive statistics including mean, median, standard deviation, number of eyes, minimum, maximum, and the two-sided 95% confidence interval will be presented.

4.3.2 Secondary Effectiveness Analyses

4.3.2.1 Monocular BCDVA at 2 years post-implantation

Analyses performed on this endpoint will be the same as the analyses described in Section 4.3.1.1 except that the observed rates will not be compared to the SPE rates (i.e. no one-sided confidence interval will be computed).

4.3.2.2 Monocular BCDVA at 3 years post-implantation

Analyses performed on this endpoint will be the same as the analyses described in Section 4.3.1.1 except that the observed rates will not be compared to the SPE rates (i.e. no one-sided confidence interval will be computed).

4.3.2.3 Monocular UCDVA at 1 year post-implantation

The following descriptive statistics will be provided:

- logMAR categories: the number and percentage of eyes 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 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

In addition, descriptive statistics including mean, median, standard deviation, number of eyes, minimum, maximum, and the two-sided 95% confidence interval will be presented.

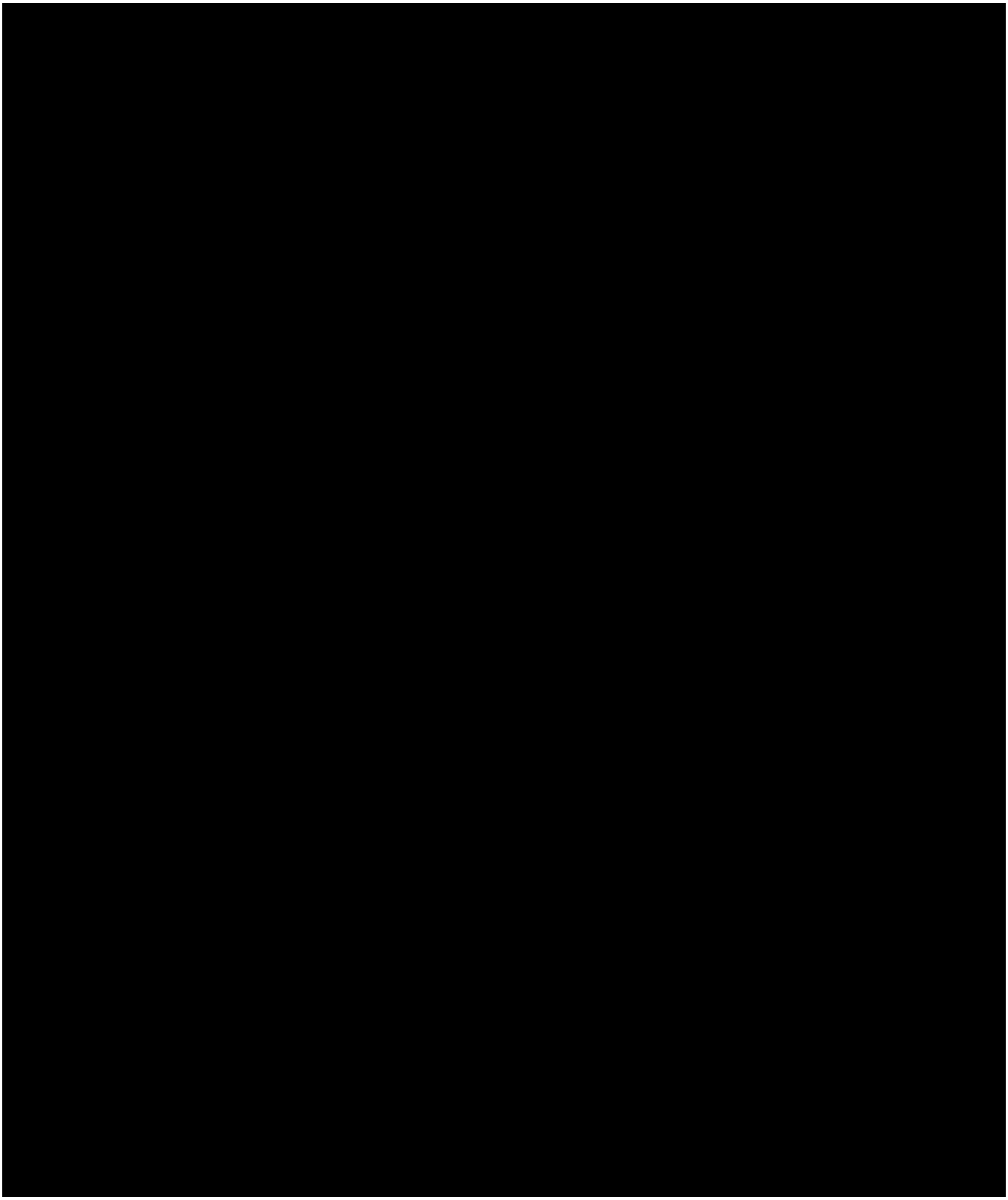
4.3.2.4 Monocular UCDVA at 2 years post-implantation

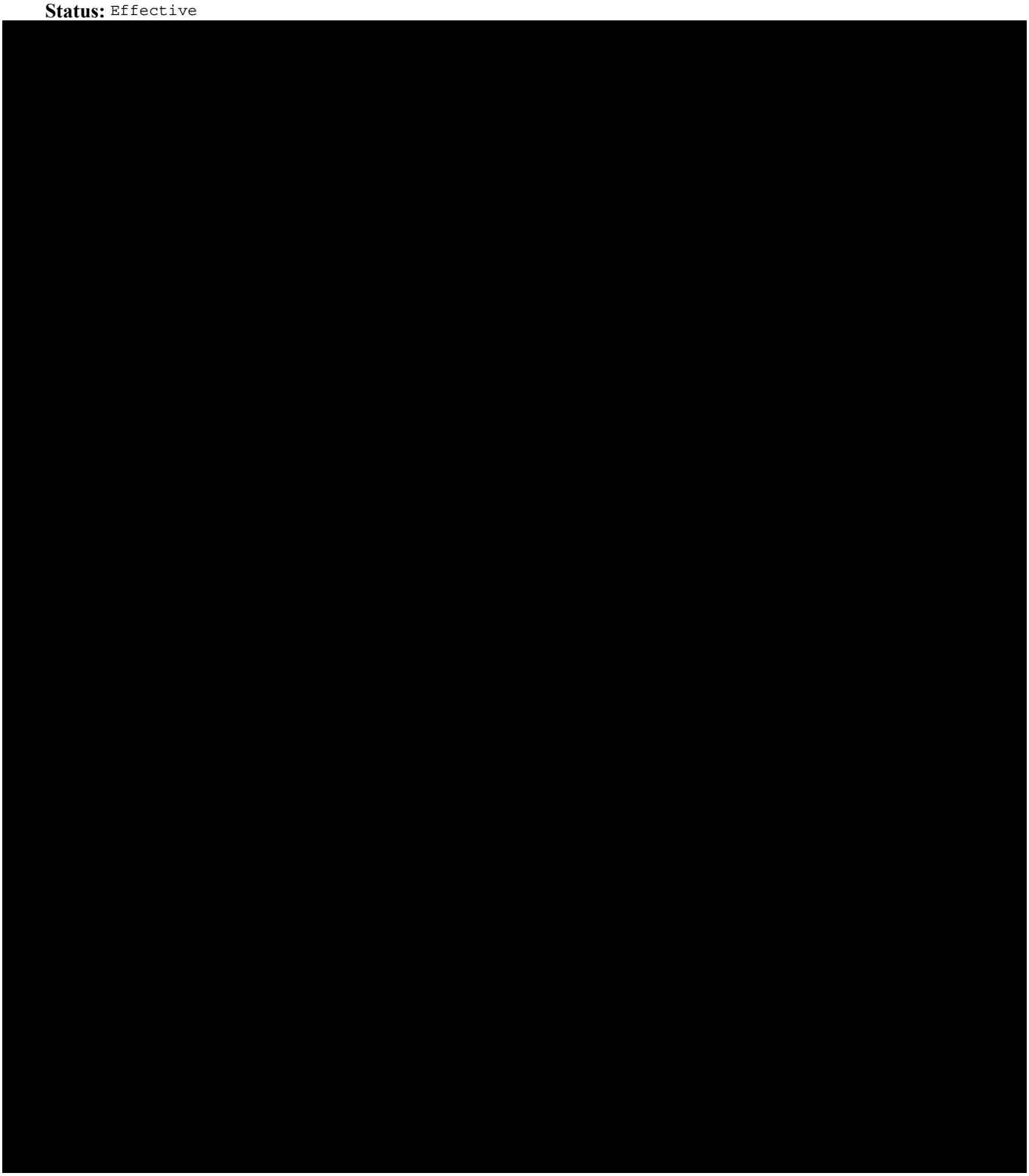
Analyses performed on this endpoint will be the same as the analyses described in Section 4.3.2.3.

4.3.2.5 Monocular UCDVA at 3 years post-implantation

Analyses performed on this endpoint will be the same as the analyses described in Section 4.3.2.3.

4.3.3 Exploratory Effectiveness Analyses





5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- AEs (ocular and nonocular, serious and nonserious) including SSIs
- Device deficiencies
- IOL observations
- Surgical problems
- Intraocular pressure
- Posterior capsular opacification
- Posterior capsulotomy
- IOL position change (tilt and decentration)
- Slit lamp examination
- Dilated fundus exam
- Other procedures during surgery

5.2 Safety Hypotheses

The rate at one year (Visit 5A) of cumulative and persistent AEs listed in IS EN ISO 11979-7:2014 will be compared with the historical control SPE rates. 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 safety analysis set as defined in Section 2.2. Baseline will be defined as the last measurement prior to exposure to investigational product, except otherwise stated.

5.3.1 AEs (including SSIs)

All information obtained on adverse events (AEs) will be displayed by subject and eye, where appropriate.

The number and percentage of all ocular adverse events, including secondary surgical interventions (SSIs) for either eye, will be tabulated by preferred term, 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 tabulated, separately for first and second implanted eyes.

Adverse events will be summarized in the following tables:

1. All Adverse Events (Serious and Nonserious 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. Nonserious Ocular
    b. Nonserious Nonocular
    c. Serious Ocular
    d. Serious Nonocular

In addition, descriptive summaries (counts and percentages) for specific AEs will be presented. The one-sided exact 95% lower confidence limit of incidence rates (proportion of eyes with events) observed up to one year of follow up (i.e. after all implanted subjects have completed Visit 5A) will be compared to the cumulative and persistent adverse event safety and performance endpoint (SPE) rates shown in Table 5–1. An eye with multiple ocular adverse events of the same preferred term is only counted once toward the total of this preferred term. A similar table will be constructed with all and persistent AEs listed in IS EN ISO 11979-7:2014 observed through the entire 3 year follow up, but no comparison will be made between these 3-year rates and the SPE rates (i.e. no one-sided confidence intervals will be computed).

Table 5–1 Adverse Event Safety and Performance Endpoint Rates

Adverse Event	SPE Rate (%)
Cumulative	
Cystoid Macular Oedema	3.0
Hypopyon	0.3
Endophthalmitis[a]	0.1
Lens dislocated from posterior chamber	0.1
Pupillary block	0.1
Retinal detachment	0.3
Secondary surgical intervention[b]	0.8

Persistent	
Corneal stroma oedema	0.3
Cystoid macular oedema	0.5
Iritis	0.3
Raised IOP requiring treatment	0.4

[a]Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.
[b]Excludes posterior capsulotomies.
SPE = Safety and Performance Endpoint
SPE rates are from Table B.2 – Posterior Chamber IOL Adverse Event Rates in IS EN ISO11979-7:2014.

The number and percentage of secondary surgical interventions will be presented. In addition, the number and percentage of secondary IOL interventions will be presented in each of the following categories:

1) Related to IOL - due to optical properties
2) Related to IOL - not due to optical properties

A listing of secondary IOL interventions and secondary surgical interventions unrelated to IOL will also be presented, respectively.

5.3.2 Device deficiencies

The number and percentage of all device deficiencies will be tabulated, separately for first and second implanted eyes. A listing of all device deficiencies, as recorded on the Device Deficiency Form, will also be provided.

5.3.3 IOL observations

IOL observations will be summarized using descriptive statistics, including frequency (N) and percent of eyes, separately for first and second implanted eyes, at each scheduled and unscheduled visit where the data were collected. A listing of all IOL observations will be provided.

5.3.4 Surgical problems

Descriptive statistics (number and percentages) on eyes with surgical problems will be presented, separately for first and second implanted eyes. In addition, a listing of subjects with surgical problems will be provided.

5.3.5 Intraocular pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole mmHg.

Descriptive summaries (N, mean, median, standard deviation, standard error, minimum, and maximum) of observed values and change from baseline values will be presented at each study visit, separately for first and second implanted eyes.

A summary table with number and percentages of eyes in each category of IOP change from baseline to last on-treatment IOP assessment and to any visit by implanted eye will be presented according to the following categories: >30 mmHg increase, 21 to 30 mmHg increase, 11 to 20 mmHg increase, 6 to 10 mmHg increase, -5 mmHg decrease to 5 mmHg increase, 6 to 10 mmHg decrease, 11 to 20 mmHg decrease, 21 to 30 mmHg decrease, and >30 mmHg decrease, separately for first and second implanted eyes. For change to any visit, an eye will be counted only in the category that represents maximum change from baseline across all post-baseline assessments.

A listing will be provided, which presents all eyes with an increase or decrease in IOP of more than 10 mmHg at any visit compared to the same eye at baseline.

5.3.6 Posterior capsular opacification and Posterior Capsulotomy

A frequency and incidence table of the “worst case” posterior capsule opacification (including capsulotomy) will be presented, separately for first and second implanted eyes. Posterior capsule opacification will be summarized using descriptive statistics, including number and percent of eyes, at each scheduled and unscheduled visit where the data were collected, separately for first and second implanted eyes.

[redacted]

5.3.7 IOL position change (tilt and decentration)

Descriptive statistics (number and percentages) on eyes with a change from baseline in IOL position category (Tilted, Decentered) will be presented, separately for first and second implanted eyes. In addition, a listing of eyes with IOL position change will be provided.

5.3.8 Slit-Lamp Examination

The number and percentage of all slit lamp examination findings will be tabulated by IOL group and implanted eye.

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

5.3.9 Dilated Fundus Examination

The number and percentage of all dilated fundus examination findings will be tabulated by IOL group and implanted eye.

A listing will be provided which presents all eyes with abnormality in any fundus parameter at any postoperative visit.

5.3.10 Other Procedures at Surgery

A listing of all other procedures at surgery will be provided.

8 Sample Size and Power Calculations

If more than 110 of 125 eyes show monocular best corrected distance visual acuity (BCDVA) of 0.3 logMAR or better at 1 year (Visit 5A), the one-sided exact 95% upper confidence limit for the rate is not worse than SPE rate of 92.5%. Assuming that the mean and the standard deviation of monocular BCDVA are 0.0 and 0.18 logMAR respectively, the study has greater than 99% chance to meet this performance target.

For any event where zero incidence is observed in 125 first-operative eyes with Clareon IOL, the upper limit of the 95% one-sided exact binomial upper confidence limit is less than 2.4%. Thus, with 95% confidence, the true adverse event rate is less than 2.4%.

Approximately 200 subjects will be bilaterally implanted with the Clareon IOL in order to ensure at least 125 evaluable subjects complete the study.

9 References

Michael Simpson and W. Neil Charman. The effect of testing distance on intraocular lens power calculation. *J Refract Surg*. 2014 Nov;30(11):726

[redacted]

[redacted]

Signature Page for V-CLN-0004312 v1.0