Short Title:

Statistical Analysis Plan
ILJ466-C001/NCT03170154

Full Title:

Statistical Analysis Plan
ILJ466-C001

Protocol Title:	Clinical Investigation of the Clareon® IOL
Project Number:	██████
Protocol TDOC Number:	TDOC-0052273
Author:	████████████
	████████████████
Approvals:	See last page for electronic approvals.
Job Notes:	

This is Version 2.0 of Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 4.0 of the study protocol TDOC-0052273. ████████ ████████████████

Executive Summary:

Key Objectives:

The objective of this study is to demonstrate favorable visual acuity and adverse event outcomes for the Clareon IOL compared to historical safety and performance endpoint (SPE) rates as reported in EN ISO 11979-7:2014.

The primary effectiveness objectives are to demonstrate that the percentage of subjects with monocular best corrected distance visual acuity of 0.3 logMAR or better at 12 months postoperative is greater than or equal to the SPE rate of 92.5% for the All-implanted Analysis Set and 96.7% for the Best-case Analysis Set using the one-sided exact 95% upper confidence limit.

The secondary effectiveness objectives are to demonstrate IOL rotational stability using IOL rotation at 6 months postoperative and to describe IOL misplacement, IOL rotation and IOL misalignment.
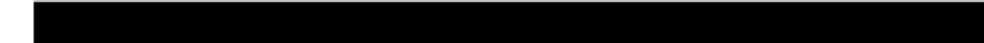
The primary safety objective is to estimate the rate of adverse events (ocular and nonocular, serious and non-serious) including secondary surgical interventions (SSIs).

Decision Criteria for Study Success:

The study will be considered successful if the data indicate a favorable outcome 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 (BCDVA) of 0.3 logMAR or better at 12 months postoperative (Visit 5) is greater than or equal to the SPE rates of 92.5% for the All-implanted Analysis Set and 96.7% for the Best-case Analysis Set (as reported in EN ISO 11979-7:2014).

Table of Contents

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 01-Mar-2018
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 01-Mar-2018
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

List of Tables

List of Figures

Alcon - Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

1   Study Objectives and Design

1.1   Study Objectives

Primary Effectiveness Objectives:

To show that the percentage of subjects with monocular best corrected distance visual acuity (BCDVA) of 0.3 logMAR or better at 12 months postoperative (Visit 5) is greater than or equal to the SPE rate of 92.5% for the AAS and 96.7% for the BAS using the one-sided exact 95% upper confidence limit.

Secondary Effectiveness Objectives:

To assess the rotational stability using IOL rotation at 6 months postoperative (Visit 4) and to describe IOL misplacement, IOL rotation and IOL misalignment

Primary Safety Objective:

To estimate the rate of adverse events (ocular and nonocular, serious and non-serious) including secondary surgical interventions (SSIs) at 12 months postoperative (Visit 5)

1.2   Study Description

This study is a prospective, multi-center, single-group safety and performance clinical study, requiring no masking. The trial will evaluate the safety and performance of the new monofocal IOL model ███████ in approximately 350 implanted subjects. Only one eye will be implanted with the study lens. Subjects will attend a total of 7 study visits (5 postoperative) over a period of approximately 13 months.

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

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

Alcon - Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

Figure 1–1   Study Design

1.3   Randomization

1.4   Masking

This is an open-label single-group study. All subjects will be implanted with the ▮▮▮ IOL in one eye.

1.5   Interim Analysis

▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮
▮▮▮▮▮▮▮▮▮▮▮▮▮▮

Alcon - Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

2   Analysis Sets

2.1   Efficacy 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. Additional analyses, including the co-primary analysis, will be conducted using the Best-Case Analysis Set (BAS). BAS includes all eyes successfully implanted with the test article that had:

- at least 1 postoperative visit

- no pre-operative ocular pathology

- no macular degeneration at any time

- no previous surgery for the correction of refractive errors

The Rotation Analysis Set (RAS) will include all eyes with successful test article implantation from a sub-set of approximately 6 clinical sites that examine subjects for rotational stability.

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.

2.3   Pharmacokinetic Analysis Set

Not applicable.

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 12 months postoperative (Visit 5) will be summarized along with the corresponding one-sided exact 95% upper confidence limit. The one-sided exact 95% upper confidence limit will be compared to the SPE rate of 92.5% for AAS and 96.7% for BAS.

Descriptive statistics will be provided for the secondary and supportive effectiveness endpoints.

4.1   Effectiveness Endpoints

<u>Co-Primary Effectiveness Endpoints</u>

- Percentage of all-implanted subjects achieving best corrected monocular distance visual acuity (BCDVA) of 0.3 logMAR or better at 12 months postoperative (Visit 5)

- Percentage of best-case subjects achieving best corrected monocular distance visual acuity (BCDVA) of 0.3 logMAR or better at 12 months postoperative (Visit 5)

<u>Secondary Effectiveness Endpoint</u>

The secondary effectiveness endpoints are IOL rotation, IOL misplacement, and IOL misalignment.

4.2   Effectiveness Hypotheses

Not Applicable.

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

In general, for visual acuity endpoints, the number and percentage of the logMAR categories and Snellen categories will be provided respectively.

- 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

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 (BCDVA) of 0.3 logMAR or better (logMAR category) at 12 months postoperative (Visit 5) is greater than or equal to the SPE rates of 92.5% for the AAS and 96.7% for the BAS (as reported in EN ISO 11979-7:2014). A successful outcome on the co-primary effectiveness endpoints is indicated by successful outcomes on both of these endpoints. The number and percentage of subjects with BCDVA of 0.3 logMAR or better at 12 months postoperative (Visit 5) will be presented with the corresponding two-sided exact 95% confidence interval as well.

In addition, descriptive statistics (sample size, mean, median, standard deviation, number of subjects/eyes, minimum, maximum, and the two-sided 95% confidence interval) will be provided.

4.3.2 Secondary Effectiveness Analyses

The performance target in support of the secondary effectiveness objective is to show that IOL rotation at 6 months postoperative (Visit 4) is,

Alcon - Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

- less than 10° in 90 % of eyes in the RAS
- less than 20° in 95 % of eyes in the RAS
- less than 30° in 99 % of eyes in the RAS

In order to summarize IOL rotation, IOL misplacement and IOL misalignment, sample size, number, percent and cumulative percent for the following categories will be provided: (<10, <20, and <30 degrees, respectively). Additional tables using the following categories will also be provided: (0-5, >5-10, >10-15, >15-20, >20-30, and >30 degrees, respectively).

IOL rotation at Visit [x] is defined as the difference between axis of IOL orientation on the day of surgery and the postoperative Visit [x]. IOL misplacement is defined as the difference between intended axis of placement and actual axis of IOL orientation on the day of surgery. IOL misalignment at Visit [x] is defined as the summation of IOL misplacement and IOL rotation at Visit [x]. IOL misalignment at Visit 0 is the same as IOL misplacement.

IOL rotational stability will be assessed at a sub-set of approximately six clinical trial sites on a total of at least 100 subjects.

Alcon - Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 01-Mar-2018
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Table 4-1 summarizes the efficacy analyses.

Alcon - Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

Table 4–1   **Summary of Analysis Strategy for All Effectiveness Endpoints**

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method	Analysis Set	Missing Data Approach
Primary				
BCDVA at 4 m	M	One-sided exact 95% UCL compared to SPE rate of 92.5%	AAS	Observed data only
BCDVA at 4 m	M	One-sided exact 95% UCL compared to SPE rate of 96.7%	BAS	Observed data only
Secondary				
IOL rotation	M	Continuous and Categorical statistics	RAS	Observed data only
IOL misplacement	M	Continuous and Categorical statistics	RAS	Observed data only
IOL misalignment	M	Continuous and Categorical statistics	RAS	Observed data only
██████	█	████████	█	██
██████	█	████████	█	██
██████	█	████████	█	██
██████	█	████████	█	██
██████	█	████████	█	██
[a]M=Main analysis approach; ████████				

4.4   Multiplicity Strategy

Not applicable.

██ ████████████████████████

██

████

Alcon – Business Use Only Statistical Analysis Plan   **Effective Date:** 01-Mar-2018
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

▮ ██████████████████

▮ ██████████████

▮ ████████████████████████████████
████████████████

▮ ████████████████████████████████
██████████████████████

4.6   Interim Analysis for Efficacy

███████████████████████████████████████
████████████████

5   Safety Analysis Strategy

5.1   Safety Endpoints

The safety endpoints are:

- Adverse events (ocular and non-ocular, serious and non-serious) including Secondary Surgical Interventions

▮ ████████████

▮ ██████████

▮ █████████████████

▮ ███████████████

▮ ████████████

▮ ██████████████████

▮ ████████████████

▮ ██████████

5.2   Safety Hypotheses

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.

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 01-Mar-2018
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

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.

The primary safety objective is to estimate the rate of adverse events (ocular and nonocular, serious and non-serious) including secondary surgical interventions (SSIs).

5.3.1   Adverse Events

All information obtained on AEs will be displayed by subject.

The rates of all adverse events will be provided with counts and percentages, and these rates will be accompanied by two-sided exact 95% confidence intervals.

Adverse events will be summarized in the following tables:

1. All Adverse Events (Serious and Non-Serious Combined)
   a. Ocular
   b. Non-Ocular
2. All Adverse Device Effects
   a. Ocular
   b. Non-Ocular
3. All Serious Adverse Events (including Serious Adverse Device Effects)
   a. Ocular
   b. Non-Ocular
4. Subject Listings
   a. Non-Serious Ocular
   b. Non-Serious Non-Ocular
   c. Serious Ocular
   d. Serious Non-Ocular

In addition, descriptive summaries (counts and percentages) for specific AEs, such as ISO-defined ocular AEs, will be presented. The one-sided exact 95% lower confidence limit for incidence rates observed for study eyes will be compared to the cumulative and persistent adverse event SPE rates that include SSIs (as reported in EN ISO 11979-7:2014). The frequency of adverse events, separately for cumulative and persistent, will be presented overall, stratified by age (<65 years vs. ≥65 years), and by investigative site.

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 ISO 11979-7:2014.

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.

████ ████████████████████

███████████████████████████████████████
██
███
████████████████████████████

███████████████████████████████████████
███
████████████

████ █████████████████
███
███
██████████████████████

████ ███████████████████████
███
████████████████████████

6   Pharmacokinetic Analysis Strategy

Not applicable.

7   Sample Size and Power Calculations

With a sample size of 300 evaluable eyes, the probability to demonstrate that at least 270 (90%) of evaluable subjects implanted with the Clareon IOL having monocular best corrected distance visual acuity (BCDVA) of 0.3 logMAR or better at 12 months postoperative (Visit 5), hence showing the one-sided exact 95% upper confidence limit is greater than or equal to the SPE rate of 92.5%, is greater than 99% assuming the mean BCDVA is 0.0 logMAR (SD = 0.18 for All-Implanted Analysis Set).

Similarly, with a sample size of 300 evaluable eyes, the probability to demonstrate that at least 285 (95%) of evaluable eyes implanted with Clareon IOL having monocular best corrected distance visual acuity (BCDVA) of 0.3 logMAR or better at 12 months postoperative (Visit 5) is greater than 97% assuming the mean BCDVA is 0.0 logMAR (SD = 0.16 for Best-Case Analysis Set).

For any event where zero incidence is observed in 300 eyes with Clareon IOL, the one-sided exact 95% upper confidence is less than 1%. Thus, with 95% confidence, the true adverse event rate is less than 1%.

Approximately 350 subjects will be unilaterally implanted with the Clareon IOL in order to ensure at least 300 evaluable subjects complete the study.

8   References

1. Retzlaff JA, Sanders DR, Kraff MC. Development of SRK/T IOL Implant Power Calculation Formula. J. Cataract Refract Surg. V16, 333-340, erratum, p. 528 (1990).

2. Simpson MJ, Charman WN. The effect of testing distance on intraocular lens power calculation. J Refract Surg. V30, 726, p.726 (2014).

9   Revision History

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

Section 1.1,

Alcon – Business Use Only Statistical Analysis Plan   **Effective Date:** 01-Mar-2018
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Alcon – Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

Alcon - Business Use Only Statistical Analysis Plan
Document: TDOC-0053637   **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

10   Appendix

Table 10–1   **Schedule of Visits**

Activity	Visit 0 Day -30 to 0 Preoperative	Visit 00 Day 0 Operative Visit	Visit 1 1-2 Days Postoperative	Visit 2 7-14 Days Postoperative	Visit 3 30-45 Days Postoperative	Visit 4 120-180 Days Postoperative	Visit 5[8] 330-420 Days Postoperative\ Early Exit
Informed Consent	X						
Demographics	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X	X	X
Urine Pregnancy Test[1]	X						
Inclusion/Exclusion	X	X					
Keratometry	X						
▮▮▮▮▮▮▮	X						
Operative Eye		X					
Surgery/Treatment		X					
Surgical Report ▮▮▮▮▮▮ • ▮▮▮ • Incision size • Implant success • Intended axis of placement ▮▮▮▮▮▮		▮					
▮▮▮▮▮▮		X					
▮▮▮▮▮▮		X					
▮▮▮▮▮▮	▮		▮	▮	▮	▮	▮
Monocular BCDVA	X			X	X	X	X
▮▮	X		X	X	X	X	X
Slit Lamp Exam	X		X	X	X	X	X
▮▮▮▮▮			X	X	X	X	X
▮▮▮▮▮			X	X	X	X	X

Activity	Visit 0 Day -30 to 0 Preoperative	Visit 00 Day 0 Operative Visit	Visit 1 1-2 Days Postoperative	Visit 2 7-14 Days Postoperative	Visit 3 30-45 Days Postoperative	Visit 4 120-180 Days Postoperative	Visit 5[8] 330-420 Days Postoperative\ Early Exit
Slit lamp photography, if applicable[5]			X	X	X	X	X
IOL Axis of Orientation Slit Lamp Imaging[6]		X			X	X	
███████ ██	X						X
Adverse Events (Including SSIs)	X	X	X	X	X	X	X
████████		X	X	X	X	X	X

[1] Required for women of child-bearing potential

████████████████████████
███████████████████
███████████████████████

[5] See MOP for Slit lamp Photography requirements; dilation required for assessment
[6] Sites participating in rotational stability sub-study; dilation required for assessment

██████████████████████████

[8] If possible, perform Visit 5 procedures for an early exiting subject

Alcon – Business Use Only Statistical Analysis Plan
Document: TDOC-0053637 **Version:** 2.0; Effective; CURRENT
Status: Effective

Effective Date: 01-Mar-2018

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
███████████	███████████ ███	████████
███████████	██████████ ███	██████████
███████████	██████████ ███	██████████
██████████	██████████ ███	███████