Short Title:

Statistical Analysis Plan

ILV814-P001

Full Title:

Statistical Analysis Plan ILV814-P001/NCT03350503

Protocol Title: AcrySof IQ Toric A-code post-market clinical study

[redacted] [redacted]

Protocol TDOC Number: TDOC-0054060

[redacted] [redacted]

Biostatistician, Clinical Biometrics, CDMA & Regulatory Affairs, Japan

[redacted] [redacted]

Approvals: See last page for electronic approvals.

Job Notes:

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.

Executive Summary:

Key Objectives:

The objective of this study is to describe safety and effectiveness for patients who are implanted with AcrySof IQ Toric (A-code).

Primary effectiveness variable is the absolute value of IOL rotation at Visit 4 from Visit 00, and it will be compared with ISO grid for IOL performance [1] below for reference.

- Percentage of eyes with rotation of less than 10 degrees in 90% of cases at Visit 4 from Visit 00
- Percentage of eyes with rotation of less than 20 degrees in 95% of cases at Visit 4 from Visit 00
- Percentage of eyes with rotation of less than 30 degrees in 99% of cases at Visit 4 from Visit 00

Table of Contents

List of Tables

List of Figures

1 Study Objectives and Design

1.1 Study Objectives

The objective of this study is to describe safety and effectiveness for patients who are implanted with AcrySof IQ Toric (A-code). All analysis in this study will be performed for the descriptive purpose.

1.2 Study Description

This is a prospective, single-arm, and multicenter study. The subject who has corneal astigmatism, will be judged by Alcon Toric IOL Calculator to be eligible implantation of SN6AT3, SN6AT4, SN6AT5 and will be implanted recommended IOL model will be enrolled. The subjects will be examined from pre-operative visit to 3 years post-operatively. One hundred and twenty subjects will be enrolled. One eligible eye will be selected as a target eye for effectiveness analysis. If both eyes are eligible, the eye in which IOL is implanted first will be selected as a target eye. Non-target eyes will be included in safety analysis if the eye is implanted with test article.

A total of 10 scheduled visits are planned including the Preoperative (Visit 0) and the Operative (Visit 00 and Visit 00-A).

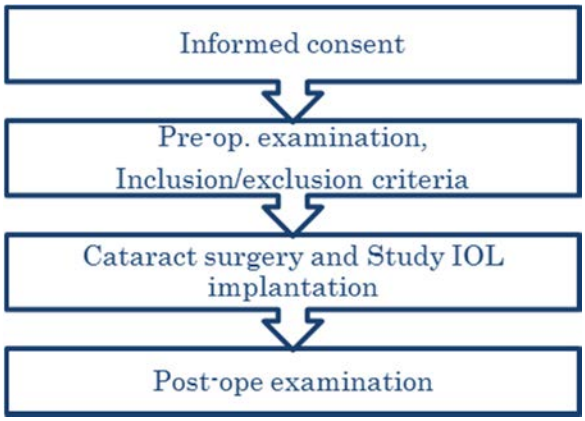

Figure 1-1 Outline of this study

Scheduled postoperative visits must occur at the following intervals: 1-2 days, 7-14 days, 30-60 days, 120-180 days, 330-420 days, 630-780 days and 990-1140 days. See Table 1-1 Schedule of Study Visits.

Table 1-1 Schedule of Study Visits

Time from Implantation	Study Visit
Preoperative	Visit 0
Operative (Day 0)	Visit 00 / 00-A
1-2 days	Visit 1
7-14 days	Visit 2
30-60 days	Visit 3
120-180 days	Visit 4
330-420 days	Visit 5
630-780 days	Visit 6
990-1140 days	Visit 7

1.3 Randomization

This is a single-arm study. All subjects will be implanted with AcrySof IQ Toric A-code SN6AT3, SN6AT4 and SN6AT5.

1.4 Masking

This is an open label study.

1.5 Interim Analysis

Interim analysis will be conducted twice after all subjects complete Visit 4 (Day 120-180) and Visit 6 (Day 630 - 780) visits to evaluate safety and effectiveness of the test lens. The primary analysis will be conducted after all subjects complete Visit 4. The final analysis will be conducted after all subjects complete Visit 7 (Day 990-1140). Interim analyses are not intended to stop the study early. Also, the interim analysis will be performed in the same way of the final analysis at Visit 7.

2 Analysis Sets

2.1 Efficacy Analysis Sets

All Implanted Analysis Set (AAS):

All-Implanted Analysis Set (AAS) will include all eyes with successful test article implantation.

Best Case Analysis Set (BAS):

Best-Case Analysis Set (BAS) will include all eyes with successful test article implantation that had

- at least 1 postoperative visit; and
- no major protocol violation

The AAS and BAS will be used for primary effectiveness analysis in the study, with priority given to AAS results. The AAS will be used for exploratory analysis in the study.

2.2 Safety Analysis Set

The pre-treatment safety analysis set will be used to summarize occurrence of adverse experiences prior to exposure to the test article. The treatment-emergent safety analysis set will be used for safety analysis after implantation of test article. Non-target eyes will be included in safety analysis if the eye is implanted with test article.

2.3 Pharmacokinetic Analysis Set

Not Applicable.

3 Subject Characteristics and Study Conduct Summaries

For all datasets (Safety Analysis Set, AAS, BAS), demographic factors (sex, age, axial length, planned IOL angle, astigmatism type, IOL model, pre-operative astigmatism), descriptive statistics will be provided. For sex, age (<60, 60-69, 70-79, ≥ 80), axial length (<22, 22-26.9, ≥27 mm), planned IOL angle (0-45° or 135-180°, 46-134°), astigmatism type (with-the rule, against-the rule, oblique), IOL model (SN6AT3, SN6AT4, SN6AT5), the N and percentage will be provided. For age, axial length and pre-operative astigmatism, arithmetic mean, standard deviation, N, median, min and max will be provided.

4 Efficacy Analysis Strategy

4.1 Efficacy Endpoints

Primary effectiveness variable is the absolute value of IOL rotation at Visit 4 from Visit 00 [1], and it will be categorized as follows.

- Absolute value of IOL rotation of less than 10 degrees
- Absolute value of IOL rotation of less than 20 degrees
- Absolute value of IOL rotation of less than 30 degrees

[redacted]

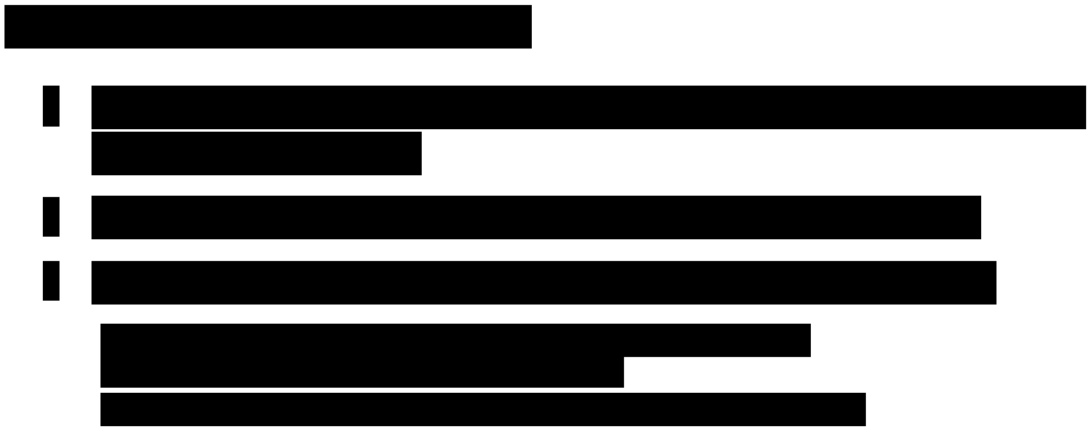

Table 4-1 Definition of Axis Difference

	Intended axis	Visit 00	Visit 00-A	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Intended axis		Axis placement error	Misalignment (Axis placement error + Rotation)	Misalignment	Misalignment	Misalignment	Misalignment	Misalignment	Misalignment	Misalignment
Visit 00			Rotation	Rotation	Rotation	Rotation	Rotation	Rotation	Rotation	Rotation
Visit 00-A				Rotation	Rotation	Rotation	Rotation	Rotation	Rotation	Rotation
Visit 1					Rotation	Rotation	Rotation	Rotation	Rotation	Rotation
Visit 2						Rotation	Rotation	Rotation	Rotation	Rotation
Visit 3							Rotation	Rotation	Rotation	Rotation
Visit 4								Rotation	Rotation	Rotation
Visit 5									Rotation	Rotation
Visit 6										Rotation
Visit 7										

Difference = Column - Row

[redacted]

[redacted]

4.2 Efficacy Hypotheses

No confirmatory hypothesis testing will be conducted for primary analysis.

4.3 Statistical Methods for Efficacy Analyses

4.3.1 Primary Effectiveness Analysis

For the primary effectiveness analysis, number and percentage of subjects will be provided for each category of absolute value of IOL rotation at Visit 4 from Visit 00 for overall and by IOL model (SN6AT3, SN6AT4, SN6AT5).

- < 10 degrees / ≥10 degrees
- < 20 degrees / ≥20 degrees
- < 30 degrees / ≥30 degrees

Percentage of each category will be compared with ISO grid for IOL performance [1] below for reference.

- Percentage of eyes with rotation of less than 10 degrees in 90% of cases at Visit 4 from Visit 00
- Percentage of eyes with rotation of less than 20 degrees in 95% of cases at Visit 4 from Visit 00
- Percentage of eyes with rotation of less than 30 degrees in 99% of cases at Visit 4 from Visit 00

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

```
* Estimation of LSMEANS for absolute value of IOL rotation ;
```

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.4 Multiplicity Strategy

No confirmatory hypothesis tests are planned.

4.5 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of the primary endpoint will be conducted to assess the consistency of treatment effect across various subgroups.

The consistency of the treatment effect of the primary endpoints will be assessed descriptively using summary statistics by category of the following subgroup factors:

- Age category (<60, 60-69, 70-79, ≥80 years),
- Sex (Female, Male),
- Axial length (<22, 22-26.9, ≥27 mm),
- Planned IOL angle (0-45° or 135-180°, 46-134°),
- Astigmatism type (with-the rule, against-the rule, oblique), and
- IOL model (SN6AT3, SN6AT4, SN6AT5).

4.6 Interim Analysis for Efficacy

Interim analysis will be conducted twice after all subjects complete Visit 4 (Day 120-180) and Visit 6 (Day 630 - 780) visits to evaluate safety and effectiveness of the test lens. The primary analysis will be conducted after all subjects complete Visit 4. The final analysis will be conducted after all subjects complete Visit 7 (Day 990-1140). Interim analyses are not intended to stop the study early. Also, the interim analysis will be performed in the same way of the final analysis at Visit 7.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

[redacted]

[redacted]

- Adverse Events, and
- Device Deficiencies.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3.3 Adverse Events

A patient listing of adverse experiences prior to exposure to the test article will be provided. The number and percentage of eyes with ocular adverse events will be presented. Also, the number and percentage of subjects with non-ocular adverse events will be presented. An eye

with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term.

Adverse events will be summarized in the following tables:

- All Adverse Events (Serious and Non-Serious Combined)
  - Ocular
  - Non-Ocular
- All Adverse Device Effects
  - Ocular
  - Non-Ocular
- All Serious Adverse Events (including Serious Adverse Device Effects)
  - Ocular
  - Non-Ocular
- All Adverse Events Leading to Discontinuation (including Adverse Device Effects Leading to Discontinuation)
  - Ocular
  - Non-Ocular

Also, patient listings will be provided for adverse experiences occurred from informed consent to exposure to the test article with pre-treatment safety analysis set.

5.3.4 Device Deficiencies

The number and percentage of all device deficiencies with the eyes which is implanted in test article will be tabulated for overall and for separately study eye and non-study eye. A listing of all device deficiencies will also be provided.

[redacted]

[redacted]

5.4 Interim Analysis for Safety

Interim analysis will be conducted twice after all subjects complete Visit 4 (Day 120-180) and Visit 6 (Day 630 - 780) visits to evaluate safety and effectiveness of the test lens. The primary analysis will be conducted after all subjects complete Visit 4. The final analysis will be conducted after all subjects complete Visit 7 (Day 990-1140). Interim analyses are not intended to stop the study early. Also, the interim analysis will be performed in the same way of the final analysis at Visit 7.

6 Pharmacokinetic Analysis Strategy

Not Applicable.

7 Analysis Strategy for Other Endpoints

Not Applicable.

8 Sample Size and Power Calculations

According to ISO standards, at least 100 subjects should be enrolled to investigate IOL rotation. The 120 subjects will be enrolled assuming that dropout rate is around 16%.

9 Reference

[1] ISO 11979-7, "Ophthalmic implants -- Intraocular lenses -- Part 7: Clinical investigations," *6.2.2 Additional requirements for toric IOLs,* 2014.

10 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.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]