Short Title:

Statistical Analysis Plan ILV814-P001/NCT03350503

Full Title:

Statistical Analysis Plan ILV814-P001

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

[redacted] [redacted]

Protocol TDOC Number: TDOC-0054060

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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, [redacted]

- ≠ Percentage of eyes with rotation of less than 10 degrees in [redacted]
- ≠ Percentage of eyes with rotation of less than 20 degrees [redacted]
- ≠ Percentage of eyes with rotation of less than 30 degrees [redacted]

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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. [redacted]

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

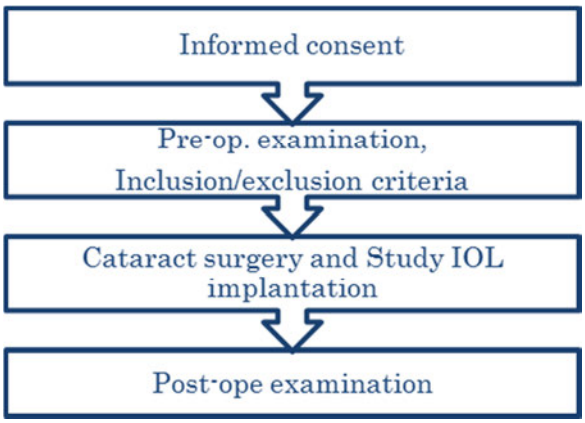


Figure 1-1 Outline of this study

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

[redacted] 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). [redacted]

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. [redacted]

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

Key exploratory variables are as follows.

- [redacted] IOL rotation [redacted]

[redacted]

IOL rotation: IOL axis difference between study visits

[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
[redacted]										
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

Other exploratory variables are as follows.

- Uncorrected distance visual acuity

≠ Best corrected distance visual acuity

≠ [redacted]

≠ SSNG densitometry

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

[redacted]

4.3.2 Key Exploratory Analysis

Key exploratory analyses are as follows. For key exploratory variables, descriptive statistics, N and percentage will be provided, and confidence intervals and p-values will be calculated as needed. However, all p-values will be provided for descriptive purpose, not as formal statistical tests.

4.3.2.1 [redacted] IOL rotation [redacted]

Descriptive statistics (mean, SD, N, median, min and max) will be provided for variables below.

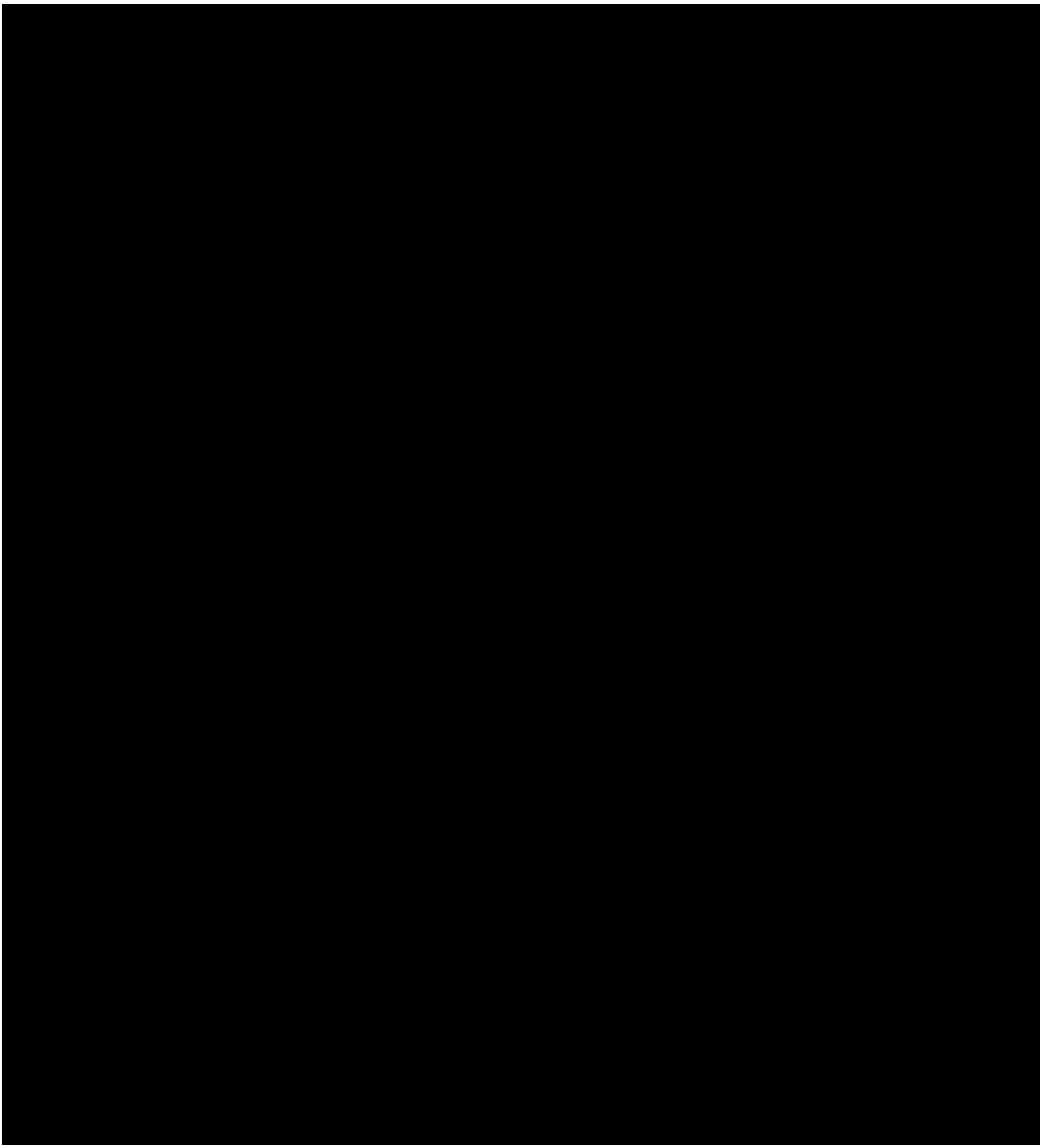
- [redacted]
- Absolute value of IOL rotation from Visit 00 axis at each study visit
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

4.3.3 Other Exploratory Analysis

Other exploratory variables are as follows.

- ≠ Uncorrected distance visual acuity
- ≠ Best corrected distance visual acuity
- [redacted]
- ≠ SSNG densitometry

For other exploratory variables, descriptive statistics (mean, standard deviation, N, median, min and max) will be provided for actual value and change from appropriate baseline at each visit for continuous variables. For categorical variables, N and percent will be provided for each category at each visit. Each descriptive statistics will be presented overall and by IOL

model (SN6AT3, SN6AT4, SN6AT5). [redacted]

[redacted]

4.4 Multiplicity Strategy

No confirmatory hypothesis tests are planned.

[redacted]

[redacted]

4.6 Interim Analysis for Efficacy

[redacted] 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). [redacted]

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

≠ Glistening grade,

≠ YAG laser treatment rate for post capsular opacification,

≠ Adverse Events, and

≠ Device Deficiencies.

In addition to the above mentioned, incidence of subjective posterior capsule opacification and abnormal ocular condition will be summarized.

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 analysis set for all safety analyses is defined in Section 2.2. Safety variables after exposure to the test article are listed in Section 5.1. Each safety variable will be summarized descriptively. Also, safety variables will be analyzed by IOL model (SN6AT3, SN6AT4, SN6AT5) as needed.

5.3.1 Glistening Grade

The categories of grading scale for glistenings include Grade 0 (No glistenings), Grade 1 (Mild: 50/mm^3), Grade 2 (Moderate: 100/mm^3), and Grade 3 (Severe: 200/mm^3). Descriptive categorical statistics including number and percent of eyes with glistening grading scale will be tabulated at scheduled visit and/or unscheduled visit. Also, number and percentage of the eyes with worst glistening grade through the postoperative visits will be tabulated.

5.3.2 YAG Laser Treatment Rate for Post Capsular Opacification

YAG laser treatment will be recorded as whether Nd:YAG laser capsulotomy was performed or not (none/yes). Number and percentage of eyes which were performed YAG laser treatment will be summarized at scheduled and/or unscheduled visit and through the postoperative visits.

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 [redacted] A listing of all device deficiencies will also be provided.

5.3.5 Posterior Capsule Opacification

The number and percentage of eyes with posterior capsule opacification in each category (None, Clinically not-significant, Clinically significant, and Clinically significant requiring a YAG) will be tabulated by scheduled visit and/or unscheduled visit. The number and

percentage of eyes with posterior capsule opacification through postoperative visits will also be summarized.

[redacted]

5.4 Interim Analysis for Safety

[redacted] 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). [redacted]

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.

[redacted]
