Short Title:

Statistical Analysis Plan ILX369-P001

Full Title:

Statistical Analysis Plan ILX369-P001/ NCT03579433

Protocol Title:	Postmarket Study of ORA with VerifEye+ and Barrett Toric Calculator used for the Implantation of AcrySof Toric
Project Number:	A03319
Protocol TDOC Number:	TDOC-0055329
Author:	[redacted]
	Principal Statistician
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 5.0 of the study protocol.

Executive Summary:

Key Objectives:

To evaluate the percentage of eyes with BCDVA of 20/20 or better in eyes implanted with AcrySof Toric selected by ORA with VerifEye + and Barrett Toric Calculator

Decision Criteria for Study Success:

Not applicable.

Table of Contents

List of Tables

1 Study Objectives and Design

1.1 Study Objectives

Primary Effectiveness Objective:

To evaluate the percentage of eyes with best corrected distance visual acuity (BCDVA) of 20/20 or better in eyes implanted with AcrySof Toric selected by ORA with VerifEye + and Barrett Toric Calculator

[redacted]

Safety Objectives:

To evaluate adverse events including secondary surgical interventions related to the investigational device

1.2 Study Description

This is a prospective, randomized, contralateral, multicenter, postmarket study. A total of 115 subjects will be enrolled to achieve 90 evaluable subjects. Treatments will be randomized between eyes and the eye with more visually significant cataract as measured by BCDVA will undergo surgery first. If the BCDVA is equal between eyes, the right eye will undergo surgery first.

The IOL power will be determined using any IOL power calculator. Sites that have LenSx will use it for primary and secondary incisions, capsulorhexis, and phacofragmentation consistently in both eyes for all subjects. Sites that don't have LenSx will use standard manual procedures.

For the eyes in the ORA with VerifEye + study group, the IOL toric power and axis and axis mark alignment will be provided by ORA. For eyes in the Barrett Toric study group, the IOL toric selection and axis will be provided by the Barrett Toric Calculator and axis alignment will be done manually (ie, without ORA guidance).

The study will be conducted at up to 10 sites in the US. Surgery will be done on each eye on different days 7 to14 days apart. Total follow-up duration is 6 months. There will be 10 visits in total. The study flow chart is available in Figure 7-1 of the protocol, and schedule of study procedures and assessments are available in Table 3-1 of the protocol.

1.3 Randomization

Subjects will be randomized in a 1:1 ratio to receive treatment with ORA System with VerifEye+ or the Barrett Toric Calculator in the first treated eye. Since this is a contralateral study, each subject should have one eye treated with each technique.

Only after signing the ICF, a subject will be assigned a subject number by the electronic data capture system.

A randomization list will be generated using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Subjects will be assigned treatment according to the randomization list uploaded in the IRT system. The randomization list will be generated and maintained by the Study Sponsor. The randomization will be stratified by study site.

At Visit 0, all eligible subjects will be randomized via the IRT system. The Investigator or delegate will access the IRT system after confirming that the subject meets all the eligibility criteria. A randomization number will be automatically assigned to the subject according to the subject randomization list. The IRT system will inform the site user of the treatment assignment to be used for the subject.

1.4 Masking

All members associated with the study (at the site and the Study Sponsor) are unmasked to the assigned treatment.

1.5 Interim Analysis

There will be an interim analysis performed using the 1-month follow up data. This will be performed after the last subject has completed the 1-month follow up visit. There are no expected design adaptations planned using the results of this analysis.

2 Analysis Sets

2.1 Effectiveness Analysis Sets

There will be two effectiveness analysis sets. The All implanted set (AAS) includes all eyes with successful IOL implantation, T3-T6 and recommended by ORA. The Per Protocol Analysis Set (PPS) includes all eyes with successful IOL implantation, T3-T6 and recommended by ORA and with no major protocol deviations. The primary analysis set for effectiveness is the PPS.

2.2 Safety Analysis Set

Safety Analysis Set (SS) will include all eyes with attempted implantation with any IOL (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, ethnicity), listing of treatment assignments by site, and a summary of screen failures by reason. 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. Tables will be presented by treatment. Subject characteristics and study conduct summaries will be presented for the AAS and the safety analysis set.

4 Effectiveness Analysis Strategy

4.1 Effectiveness Endpoints

Primary Effectiveness Endpoint:

Percentage of eyes with BCDVA of 20/20 or better at 6 months

[redacted]

4.2 Effectiveness Hypotheses

Not Applicable.

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

4.3.1.1 Best Corrected Distance Visual Acuity

For BCDVA, the following descriptive statistics will be provided by treatment group:

- 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
    - 0.4 logMAR or better: ≤0.40 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
- 20/50 Snellen or better: ≤0.44 logMAR

- Mean, median, standard deviation, number of eyes, minimum, maximum and two-sided 95% confidence interval

[redacted]

[redacted]

[redacted]

4.4 Multiplicity Strategy

Not Applicable.

4.5 Subgroup Analyses and Effect of Baseline Factors

Not applicable.

4.6 Interm Analysis for Effectiveness

The interim analysis will be conducted to summarize the following endpoints:

- Percentage of eyes with BCDVA of 20/20 or better at 1 month
- [redacted]

There will be an interim database lock and the interim analysis will be conducted after the last subject has completed the 1-month follow up visit. The objective of the interim analysis is to assess the effectiveness and safety of each treatment group when all subjects complete Visit 3A (30-60 days post Visit 00A).

5 Safety Analysis Strategy

There are no safety hypotheses planned in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters.

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events including SSIs

- Device deficiencies

[redacted]

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

5.3.1 Advserse Events including SSIs

All information obtained on adverse events (AEs) will be displayed by treatment and subject. The number and percentage of all ocular adverse events, including secondary surgical interventions (SSIs) will be tabulated by preferred term with a breakdown by treatment. An eye with multiple ocular AEs of the same preferred term will be only counted once toward the total of this preferred term.

The number and percentage of all adverse events will also be tabulated with a breakdown by treatment.

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

In addition, the number and percentage of secondary surgical interventions will be presented

5.3.2 Device Deficiencies

The number and percentage of all device deficiencies will be tabulated with a breakdown by treatment group. A listing of all device deficiencies, as recorded on the Device Deficiency Form, will also be provided.

5.4 Interim Analysis for Safety

Safety summaries will include adverse events and SSIs as outlined in section 5.3.1.

6 Pharmacokinetic Analysis Strategy

Not Applicable.

7 Analysis Strategy for Other Endpoints

Not Applicable

8 Sample Size and Power Calculations

In order to estimate the percent of eyes with BCDVA of 20/20 or better (i.e., ≤ 0.04 logMAR) at 6 months postop, the 95% confidence interval of the percent of eyes with BCDVA of 20/20 or better at 6 months postop will be calculated based on the binomial distribution. With a sample size of 90 eyes, per the binomial distribution, the width of the 95% confidence interval ranges from 4.0% to 21.5%. As an example, for an observed outcome of 70%, the 95% confidence interval per binomial distribution is (59.4%, 79.2%) with a width of 19.8%.

For different number of available eyes at 6 months (70, 75, 80, 85, 90, 95, and 100) and different observed percent of eyes with BCDVA of 20/20 or better at 6 months (70%, 75%, and 80%), the table below summarizes the corresponding confidence intervals and the width of the confidence intervals. With a sample size of at least 70 eyes at 6 months postoperatively, the width of confidence interval is less than 23% if the observed rate is ≥ 70%.

Table .8–1 95% Confidence Interval and Width per Binomial Distribution

Number of Eyes at 6 Months	Observed Percent of Eyes with BCDVA of 20/20 or Better		
	70%	75%	80%
70	(57.9%, 80.4%) 22.5%	(64.0%, 85.2%) 21.2%	(68.7%, 88.6%) 19.9%
75	(59.0%, 80.6%) 21.6%	(63.3%, 84.0%) 20.7%	(69.2%, 88.4%) 19.2%
80	(58.7%, 79.7%) 21.0%	(64.1%, 84.0%) 19.9%	(69.6%, 88.1%) 18.6%
85	(59.7%, 80.0%) 20.3%	(64.7%, 84.0%) 19.3%	(69.9%, 87.9%) 18.0%
90	(59.4%, 79.2%) 19.8%	(65.4%, 84.0%) 18.6%	(70.2%, 87.7%) 17.4%

95	(60.3%, 79.4%) 19.2%	(64.8%, 83.1%) 18.3%	(70.5%, 87.5%) 17.0%
100	(60.0%, 78.8%) 18.7%	(65.3%, 83.1%) 17.8%	(70.8%, 87.3%) 16.5%

9 References

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10 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 5.0 of the study protocol.

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