Post Approval Study of the AcrySof® IQ ReSTOR® Toric IOLs

STUDY ID

ILR431b-P001

STATISTICAL ANALYSIS PLAN v3

November 22, 2022

NCT03733730

Short Title:
Statistical Analysis Plan
ILR431b-P001

Full Title:
Statistical Analysis Plan
ILR431b-P001

Protocol Title:	Post Approval Study of the AcrySof® IQ ReSTOR® Toric IOLs
[redacted]	[redacted]
Protocol Document ID Number:	V-CLN-0001270
[redacted]	[redacted]
	[redacted]
Approvals:	See last page for electronic approvals.

Job Notes:

This is the second revision (Version 3.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 10.0 of the study protocol.

Executive Summary:

Key Objectives:

The primary objective of this study is to report the rate of post-surgical intraocular inflammation (based upon a specified case definition) reported within a 180-day post-surgical period following attempted implantation of an ACRYSOF IQ ReSTOR Toric IOL or ACRYSOF IQ ReSTOR IOL in the US.

Table of Contents

List of Tables

List of Figures

1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

The primary objective is to report the rate of post-surgical intraocular inflammation (based upon a specified case definition) reported within a 180-day post-surgical period following attempted implantation of an ACRYSOF IQ RESTOR Toric IOL or ACRYSOF IQ RESTOR IOL in the US.

1.2 Study Description

This is a prospective, multi-center, active surveillance post-approval study designed to estimate the incidence of post-surgical intraocular inflammation (based upon a specific case definition) in approximately 3,300 eyes that have been implanted with an ACRYSOF IQ RESTOR Toric IOL or ACRYSOF IQ RESTOR multifocal IOL in the US (Cohort 2) for up to 180 days. Active surveillance will be conducted through systematic collection, analysis, and interpretation of all reported cases of post-surgical intraocular inflammation over 4 visits ranging from 1 to 180 days post implantation of the ACRYSOF IQ RESTOR Toric or ACRYSOF IQ RESTOR IOL. The ACRYSOF IQ RESTOR Toric IOL and ACRYSOF IQ

RESTOR IOL are commercially available in the United States. This study will include adults (≥ 22 years of age) with preoperative cataract in the study eye(s). Potential subjects will be screened for enrollment into the study. Those qualifying will be considered enrolled in the study at the time the informed consent form is signed and attend a total of up to 11 scheduled visits. The subject will be considered exposed to treatment at the time of surgery when the investigational product touches the eye.

The study includes two groups of subjects (Cohort 1 and Cohort 2).

Cohort 1: Subjects implanted from November 2018 through July 2020 with ACRYSOF IQ RESTOR +3.0 D Multifocal Toric IOL (Models SND1T3, SND1T4, SND1T5 or SND1T6) or an ACRYSOF IQ RESTOR +2.5 D Multifocal Toric IOLs (Models SV25T3, SV25T4, SV25T5, and SV25T6) in at least one eye.

Note: At time of Protocol Amendment 7, Cohort 1 enrollment is complete.

Cohort 2: Subjects implanted after July 2020 with ACRYSOF IQ RESTOR +3.0 D Multifocal Toric IOL (Models SND1T3, SND1T4, SND1T5 or SND1T6) or an ACRYSOF IQ RESTOR +2.5 D IOL (Model SV25T0) in at least one eye.

Note: This Cohort will include subjects enrolled under Amendment 7 and later.

An overview of the study design is depicted in Figure 7-1 of the protocol, and the schedule of visits is presented in Table 12-1.

1.3 Randomization

Not applicable.

1.4 Masking

Not applicable.

1.5 Interim Analysis

Interim reports pertaining to the progress of the post-approval study will be submitted to the FDA for review every six months up to the first two years, or as requested, starting from the date of FDA approval of the ReSTOR +3.0 D Toric intraocular lens, and will continue to be submitted annually thereafter until study completion.

For each interim report, the number of eyes enrolled, the number of eyes with an attempted implantation and the number of eyes with successful implantation of the ACRYSOF IQ RESTOR study IOLs will be reported. In addition, the rates for post-surgical intraocular inflammation, Toxic Anterior Segment Syndrome (TASS), acute postoperative endophthalmitis, chronic postoperative endophthalmitis, and uncategorized cases of post-surgical intraocular inflammation (based upon the specified case definition) will be reported, and a listing of all such events will be provided. A listing of all ocular serious adverse events will also be provided.

2 ANALYSIS SETS

Subject evaluability will be determined prior to locking the database for each cohort, accordingly, based upon the Deviation and Evaluability Plan (DEP).

In the case that the integrity, quality, and accuracy of the data are suspect for a site or parameter an evaluation of the findings will be done and appropriate statistical analysis conducted to mitigate bias in the results will be determined, including possible exclusion of site or parameter from the analysis.

2.1 Efficacy Analysis Sets

Not applicable.

2.2 Safety Analysis Set

The safety set includes all eyes with attempted test article implantation (successful or aborted after contact with the eye). The safety set will be the primary analysis set for all safety analyses. Modified safety set includes all eyes with successful test article implantation. The modified safety set will be used for a sensitivity analysis of the primary safety endpoint.

Second eye surgery within 6 months of the occurrence of first cataract surgery will be included in the primary analysis. Second eye surgeries after 6 months of the first surgery are also included. If both eyes of a subject are enrolled in this study, full follow-up information from both eyes will be used in the primary analysis. The above definition applies to both Cohort 1 and Cohort 2.

Unless otherwise specified, analyses described below will be reported only for Cohort 2.

2.3 Pharmacokinetic Analysis Set

Not applicable.

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Summary statistics will be provided for demographic characteristics. Number and percentage will be presented for categorical variables and descriptive statistics including mean, standard deviation, median, minimum and maximum will be presented for continuous variables.

4 EFFICACY ANALYSIS STRATEGY

Not applicable. This is a post-approval safety study of the ACRYSOF IQ RESTOR Toric IOL.

5 SAFETY ANALYSIS STRATEGY

5.1 Safety Endpoints

The primary safety endpoint is the rate (per 1,000 IOL implants) of post-surgical intraocular inflammation (based upon the specified case definition) reported within a 180-day post-surgical period following attempted implantation of study IOLs for Cohort 2.

The secondary safety endpoints are the rates (per 1,000 IOL implants) of Toxic Anterior Segment Syndrome (TASS), acute postoperative endophthalmitis, chronic postoperative endophthalmitis, and uncategorized cases of post-surgical intraocular inflammation (based

upon the specified case definition), respectively, reported within a 180-day post-surgical period following attempted implantation of study IOLs for Cohort 2.

[redacted]

Other safety endpoints for Cohort 2 are:

- Adverse events
- Device deficiencies
- Problems during surgery
- Other surgical procedures during surgery
- Best Corrected Distance Visual Acuity (BCDVA)
- Intraocular Pressure (IOP)
- Slit lamp observations that include, but not limited to:
    - Hypopyon
    - Corneal precipitates granulomatous
    - Corneal precipitates non-granulomatous
    - Fibrin in the anterior chamber, on the surface of the iris or on the IOL
- Fundus observations
- Slit lamp examinations
    - Aqueous cell
    - Aqueous flare
    - Eyelid edema
    - Conjunctival hyperemia
    - Ciliary flush
- Corneal Assessment
    - Corneal edema

- Corneal haze

- Evaluation of vitreous cells
- Evaluation of vitreous haze
- Culture of ocular media
- Subject Reported Symptoms

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 all safety endpoints stated in Section 5.1.

5.3 Statistical Methods for Safety Analyses

Except otherwise stated, the primary analysis set for all safety analyses is the safety analysis set as defined in Section 2.2. The modified safety set will be used for a sensitivity analysis of the primary and secondary safety endpoints. Baseline will be defined as the last measurement prior to exposure to investigational product, except otherwise stated.

5.3.1 Post-Surgical Intraocular Inflammation

For the primary safety endpoint, the rate (per 1,000 IOL implants) of post-surgical intraocular inflammation (based upon the specified case definition) reported within a 180-day post-surgical period following attempted implantation of study IOLs (Cohort 2) in the United States will be estimated along with the exact two-sided 95% confidence interval. The event rate (per 1,000 IOL implants) is calculated as:

Total # of reported events/Total # of attempted implants x 1,000

An eye with multiple reports of inflammation is only counted once toward the total of the inflammation cases and the one related to device will take precedence. The inflammations related to the device will also be summarized. Event rates will be presented by first eye, second eye, and overall eyes, respectively. A subgroup analysis on the primary safety endpoint will be performed by age groups (22-64 years vs. 65 years or older). If both eyes of a subject are enrolled in this study, full follow-up information for both eyes will be used in the primary analysis.

As sensitivity analyses, cumulative event rates of post-surgical intraocular inflammation (based upon the specified case definition) at 180 days will be provided using Kaplan-Meier estimator for first eyes, second eyes, and overall eyes. The corresponding two-sided 95%

confidence interval of the rates will also be provided. Graphical presentations of the Kaplan-Meier post-surgical intraocular inflammation curves for overall eyes will be included. Kaplan-Meier estimators will be calculated using two different censoring rules as follows:

1. Full follow-up information for both eyes is used. If an eye does not have inflammation, then follow-up is censored at the time (days) from each surgery to the last known date in the study for each eye;
2. If a subject has a second cataract surgery within 180 days of the occurrence of the first cataract surgery, the follow-up for the first eye will be censored at the time of second surgery, in the case of no inflammation before the second surgery, for calculating rates for first eyes.

For secondary safety, the rates of Toxic Anterior Segment Syndrome, acute postoperative endophthalmitis, chronic postoperative endophthalmitis, and uncategorized cases of postsurgical intraocular inflammation (based upon the specified case definition) reported within a 180-day post-surgical period following attempted implantation of study IOLs (Cohort 2) in the United States will be estimated for first eyes, second eyes, and overall eyes along with the exact two-sided 95% confidence intervals. An eye with multiple same type of inflammation is only counted once toward the total of that type of inflammation and the one related to device will take precedence. An eye with multiple different types of inflammation is only counted once; the inflammation related to device will take precedence, otherwise the precedence will follow the sequence of TASS, acute postoperative endophthalmitis, chronic postoperative endophthalmitis, and uncategorized cases. Inflammations related to the device will also be reported. Cumulative event rates at 180 days will be provided using Kaplan-Meier estimator as described above for first eyes, second eyes, and overall eyes for the secondary safety endpoints as a sensitivity analysis.

A listing of eyes with all such primary and/or secondary events will be provided, where all multiple inflammations that occurred in one eye will be listed.

A listing of eyes with post-surgical intraocular inflammation and with a corneal edema grade greater than the lowest level (Grade 0 – no stromal or epithelial edema) will be provided.

Summary statistics for the rate (per 1,000 IOL implants) of post-surgical inflammation will be provided by presence of corneal edema for overall, first eyes, and second eyes.

5.3.2 Adverse Events

The applicable definition of an Adverse Event (AE) is in the study protocol. All AEs occurring from when a subject signs informed consent to when a subject exits the study will

be accounted for in the reporting. A treatment-emergent AE is an event not present prior to exposure to treatment or any pre-existing event that worsens following exposure to treatment. All information obtained on adverse events will be displayed by subject and eye.

The number and percentage of all ocular adverse events and the associated two-sided exact 95% confidence interval, including secondary surgical interventions (SSIs) for either eye, will be tabulated for any event and by preferred term with a breakdown by overall, first eyes, and second eyes. An eye with multiple ocular adverse events of the same preferred term is only counted once toward the total of this preferred term. Adverse events related to the study IOL are referred to as adverse device effects.

Adverse events will be summarized in tables with the following:

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
    e. Pre-Treatment Adverse Events
    f. Ocular Adverse Events from Non-Study Eyes
    g. Secondary Surgical Interventions

5.3.3 Device Deficiencies

The number and percentage of all device deficiencies will be tabulated by overall, first eyes, and second eyes. In addition, a listing of device deficiencies will also be provided.

5.3.4 Problems During Surgery

The number and percentage of eyes with problems during surgery will be tabulated by overall, first eyes, and second eyes. In addition, a listing of subjects with problems during surgery will be provided.

5.3.5 Other Surgical Procedures During Surgery

The number and percentage of eyes with other surgical procedures during surgery will be tabulated by overall, first eyes, and second eyes. A listing of all other surgical procedures during surgery will be provided.

5.3.6 Monocular Best Corrected Visual Acuity (BCDVA)

The number and percentage of eyes with visual acuity of

1. 20/20 Snellen or better
2. 20/25 Snellen or better
3. 20/32 Snellen or better
4. 20/40 Snellen or better
5. Worse than 20/40 Snellen

will be presented at each study visit, separately for overall, first eyes, and second eyes. A listing of all monocular BCDVA results, as well as a listing of eyes with any postoperative BCDVA worse than 20/40 will be provided.

5.3.7 Intraocular Pressure

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

A summary table with number and percentages of eyes in each category of IOP change from baseline to last IOP assessment and to any scheduled 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 (no change), 6 to 10 mmHg decrease, 11 to 20 mmHg decrease, 21 to 30 mmHg decrease, and >30 mmHg decrease, separately for overall, first eyes, and second eyes. For change to any scheduled visit, an eye will be counted only once in the category that represents maximum change from baseline across all postoperative 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.

5.3.8 Slit Lamp Observations

For each slit-lamp parameter, number and percentages of eyes that experience an abnormality will be presented by overall, first eyes, and second eyes by scheduled visit. A listing will be provided which presents all eyes with an abnormality in any slit-lamp parameter at any postoperative visit.

5.3.9 Fundus Observations

For each fundus observation parameter, number and percentages of eyes that experience an abnormality will be presented by overall, first eyes, and second eyes by scheduled visit. A listing will be provided which presents all eyes with an abnormality in any fundus parameter at any postoperative visit.

5.3.10 Slit Lamp Examination

The number and percentage of “worst case” grading for aqueous cell, aqueous flare, eyelid edema, conjunctival hyperemia, and ciliary flush at any postoperative visit will be presented by overall, first eyes, and second eyes. A listing of eyes with a grade for aqueous cells greater than the lowest level, or with a grade for the other type of examination greater than the second lowest level at any postoperative visit will be provided.

5.3.11 Corneal Assessment

5.3.11.1 Corneal Edema

Summary statistics for postoperative corneal edema will be presented using number and percentages for each location along with the corresponding grading. Prior to 15 November 2021 grading of corneal edema was only reported at the location of worst inflammation (“worst case”). After this date grading was reported at each location (“all case”) of the cornea. A combined table will be used to present both “worst case” and “all case”

assessments of corneal edema by scheduled postoperative visit. The statistics will be presented by overall, first eyes, and second eyes. A listing of eyes with a grade greater than the lowest level (Grade 0 – no stromal or epithelial edema) at any visit will be provided along with the location of corneal edema.

A listing of eyes with reported post-surgical inflammation and with a grade greater than the lowest level (Grade 0 – no stromal or epithelial edema) of corneal edema at any postoperative visit will be provided. A summary for the rate of post-surgical inflammation will be provided by presence of corneal edema for overall, first eyes, and second eyes.

5.3.11.2 Corneal Haze

The number and percentage of "worst case" by grading for corneal haze at scheduled postoperative visits will be presented by overall, first eyes, and second eyes. A listing of eyes with a rating greater than the lowest level (Rating 0 – clear cornea) at any visit will be provided.

5.3.12 Vitreous Cells

For eyes with inflammation, the number and percentage of "worst case" evaluation category for vitreous cells at any postoperative visit will be presented by overall, first eyes, and second eyes. A listing of eyes with an evaluation category greater than the lowest level (0 – none; no cells) at any postoperative visit will be provided along with the location and descriptions of vitreous cells.

5.3.13 Vitreous Haze

For eyes with inflammation, the number and percentage of "worst case" evaluation category for vitreous haze at postoperative visits will be presented by overall, first eyes, and second eyes. A listing of eyes with an evaluation category greater than the lowest level (0) at any postoperative visit will be provided.

5.3.14 Culture of Ocular Media

For eyes with inflammation, the number and percentage of test results (negative/positive) from culture of ocular media will be presented by overall, first eyes, and second eyes. A listing of eyes with a positive test result will be provided.

5.3.15 Subject Reported Symptoms

The number and percentage of subject reported symptoms at each scheduled visit will be presented by overall, first eyes, and second eyes. A listing of subject reported symptoms will be provided for the subset of eyes with post-surgical intraocular inflammation.

6 PHARMACOKINETIC ANALYSIS STRATEGY

Not applicable.

7 ANALYSIS STRATEGY FOR OTHER ENDPOINTS

Not applicable.

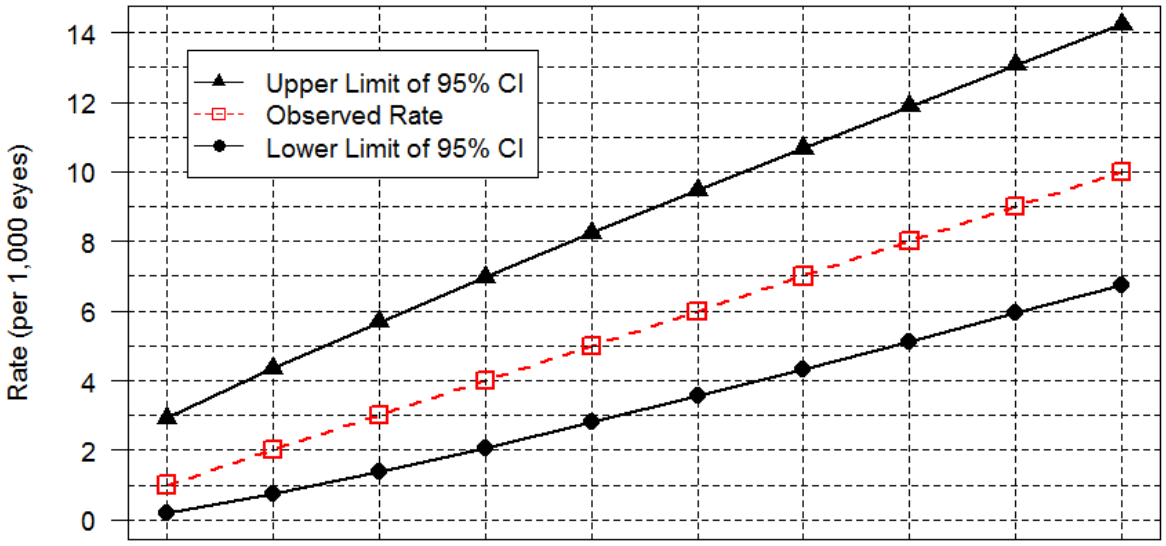
[redacted]

9 SAMPLE SIZE AND POWER CALCULATIONS

The precision of the estimated rate can be assessed using the width of an exact two-sided 95% confidence interval. In Figure 9-1, the exact two-sided 95% confidence intervals with a sample size (N) of 3,000 are shown when the observed rate ranges from 1 to 10 (per 1,000).

As an example, with N=3,000, the width of the exact two-sided 95% confidence interval will be 3.6 (per 1,000) when the observed rate is 2 (per 1,000).

Figure 9-1 **The exact two-sided 95% confidence intervals with N=3,000 when the observed rate ranges from 1 to 10 (per 1,000)**



10 REFERENCES

Not applicable.

[redacted]

12 APPENDIX

Table 12-1 Schedule of Study Procedures and Assessments

Procedure/ Assessment	Visit 0 (≤ 40 days pre-surgery 1st eye, ≤ 60 days pre-surgery 2nd eye)	Visit 00 & Visit 00A (surgery)	Visit 1 & Visit 1A (Day 1-2 post surgery)	Visit 2 & Visit 2A (Day 7-14 post surgery)	Visit 3 & Visit 3A (Day 30-60 post surgery)	Visit 4 & Visit 4A (Day 90 - 180 post surgery)	UNSV
Informed Consent	X						
Demographics	X						
Patient Medical History (Ocular and Nonocular)[3]	X						
Medications (use of medication prior to, during and post-surgery must be documented)[3]	X	X	X	X	X	X	X
Inclusion/ Exclusion	X	X					
Adverse Events (Volunteered and Elicited)	X	X	X	X	X	X	X
Device Deficiencies		X	X	X	X	X	X
Subject Reported Symptoms	X		X	X	X	X	X
Best Corrected Visual Acuity (BCVA)	X		X	X	X	X	X
Intraocular Pressure	X		X	X	X	X	X
Problems during surgery		X					
Other Surgical Procedures		X					
Aqueous cell	X		X	X	X	X	X
Aqueous flare	X		X	X	X	X	X
Corneal edema	X		X	X	X	X	X
Corneal haze	X		X	X	X	X	X

Fibrin in the anterior chamber, on the surface of the iris or on the intraocular lens (IOL)	X		X	X	X	X	X
Eyelid edema	X		X	X	X	X	X
Conjunctival hyperemia	X		X	X	X	X	X
Ciliary flush	X		X	X	X	X	X
Corneal precipitates	X		X	X	X	X	X
Hypopyon	X		X	X	X	X	X
Dilated fundus examination	X		X[1]	X[1]	X[1]	X[1]	X[1]
Vitreous cell	X		X[1]	X[1]	X[1]	X[1]	X[1]
Vitreous haze	X		X[1]	X[1]	X[1]	X[1]	X[1]
Photo documentation			X[2]	X[2]	X[2]	X[2]	X[2]
Culture of ocular media			X[2]	X[2]	X[2]	X[2]	X[2]

1 Required for cases of exacerbated post-surgical intraocular inflammation only.

2 Required at certain visits for cases of exacerbated post-surgical intraocular inflammation. See Manual of Procedures for details on requirements for which visit(s) testing is required.

3 Concomitant medications and medical history must be fully documented in the subject source documents. CRF data will be Targeted:

- Medical History: All ocular history, targeted systemic history
- Concomitant Medications: All ocular medications, targeted systemic medications

NOTE: Visits with an "A" refer to visits for the 2nd eye visits for cases where both eyes of a subject are enrolled. In the eCRF these visits will be noted with wording of "2nd Eye" instead of A. For example: Visit 1A will be shown as Visit 1-2nd Eye.

Signature Page for V-CLN-0002688 v3.0

Reason for signing: Approved	Name: Justin Webb Role: Approver Date of signature: 15-Nov-2022 04:42:35 GMT+0000

Reason for signing: Approved	Name: Kristi Rushin Role: Approver Date of signature: 18-Nov-2022 18:01:00 GMT+0000

Reason for signing: Approved	Name: Trina Patel Role: Approver Date of signature: 22-Nov-2022 18:43:58 GMT+0000

Reason for signing: Approved	Name: Suzanne Hackett Role: Author Date of signature: 22-Nov-2022 20:00:24 GMT+0000

Signature Page for V-CLN-0002688 v3.0