Short Title:

Statistical Analysis Plan
ILH297-P004 /
NCT03268746

Full Title:

Statistical Analysis Plan
ILH297-P004

Protocol Title:	Clinical Investigation of the Visual Outcomes and Safety after Bilateral Implantation of a Trifocal Presbyopia Correcting IOL in A Korean Population
Project Number:	A03226
Protocol TDOC Number:	TDOC-0054099
Author:	[redacted] Ph.D.
	[redacted]
Template Version:	Version 4.0, approved 16MAR2015
Approvals:	See last page for electronic approvals.
Job Notes:	

This is Version 2 of 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 main objective of this investigation is to describe visual outcomes and assess safety at 3 months (90-120 days) post bilateral implantation of the ACRYSOF IQ PanOptix Presbyopia Correcting IOL in a Korean population.

Decision Criteria for Study Success:

Not applicable.

Table of Contents

List of Tables

List of Figures

1 Study Objectives and Design

1.1 Study Objectives

1.1.1 Primary Objective

Describe visual outcomes (binocular defocus curve) at 3 months (90-120 days) post bilateral implantation of the ACRYSOF IQ PanOptix Presbyopia Correcting intraocular lens (IOL), Model TFNT00 in Korea population

1.1.2 Secondary Objectives

- Describe binocular defocus curve at 1 month (30-60 days) post bilateral implantation.
- Describe best corrected distance visual acuity (BCDVA) 4m at 1 and 3 months (Visit 3A and Visit 4A) post bilateral implantation.
- Describe uncorrected visual acuity (UCVA) at 1 and 3 months (Visit 3A and Visit 4A) post bilateral implantation.
- Describe contrast sensitivity at 3 months (Visit 4A) post bilateral implantation.
- Describe subjective symptom at 3 months (Visit 4A) post bilateral implantation.

[redacted]

1.1.4 Safety Objective

Assess safety during the study up to 3 months (90-120 days) post bilateral implantation of the ACRYSOF IQ PanOptix Presbyopia Correcting IOL, Model TFNT00 in Korea population.

1.2 Study Description

This is a prospective, single arm, unmasked, non-randomized, multi-center study of ACRYSOF IQ PanOptix Presbyopia Correcting IOL in a Korean population.

The diagram of planned visits is shown in Figure 1 in the appendix. The study plan is included as Table 2 in the appendix.

1.3 Randomization

Not applicable. This is a single-arm study.

1.4 Masking

This is a single arm study. Treatment is known to the investigators, subjects or Alcon personnel involved with the planning and execution of the study.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

2.1 Efficacy Analysis Sets

Full analysis set (FAS) is defined as all subjects with successful bilateral IOL implantation. All-implanted analysis set (AAS) is defined as all eyes with successful implantation of the test product.

All effectiveness analyses of binocular assessments will be based on the full analysis set (FAS). All-implanted analyses set (AAS) will be used for effectiveness analyses of monocular assessments.

2.2 Safety Analysis Set

The safety analysis set will include all patients with attempted IOL implantation (successful or aborted after contact with the eye).

2.3 Pharmacokinetic Analysis Set

Not Applicable.

3 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries include the following tables and listings: a subject disposition table, demographics table (including age, gender, race, ethnicity, height, arm length) and listing, baseline characteristics table (including [redacted] BCDVA, [redacted]), prior medications listing, medical history listing, summary of screen failures by reason, listing of subjects excluded from key analysis sets. All descriptive summary statistics will be displayed with n and % for categorical data, and with mean, standard deviation, median, minimum, and maximum for

continuous data. Monocular data will be presented separately for the first and second operative eye and overall.

Subject characteristics and study conduct summaries will be presented for FAS, AAS and the safety analysis set.

4 Effectiveness Analysis Strategy

4.1 Effectiveness Endpoints

Primary Endpoint

- Binocular defocus curve at 3 months post-implantation (Visit 4A)

Secondary Endpoints

- Binocular defocus curve at 1 months post-implantation (Visit 3A)
- Best corrected binocular visual acuity at distance (4m) (Visit 3A, 4A)
- Monocular uncorrected visual acuity at week 1, month 1 and month 3 post-implantation (Visit 2, 2A, 3A, 4A) at 40cm, 60cm and 4m
- Binocular uncorrected visual acuity at month 1 and month 3 post-implantation (Visit 3A, 4A) at 40cm, 60cm and 4m
- Photopic best corrected binocular contrast sensitivity with & without glare at 3 months post-implantation (Visit 4A)
- Subjective symptom questions at pre-operatively and post-operatively: 3 months post implantation (Visit 4A)

4.2 Effectiveness Hypotheses

No hypothesis testing is planned for any endpoints. The outcomes will be summarized descriptively.

4.3 Statistical Methods for Effectiveness Analyses

For effectiveness analyses, the 90% confidence interval (CI) of the mean will be two-sided and based on the t statistic. The percentage of categorical variables will be based on the number of observations in a category and total number of non-missing observations. Monocular results will be presented separately for the first and second operative eye.

Besides the descriptive summary tables, individual listings will also be presented for each effectiveness endpoint.

4.3.1 Primary Effectiveness Endpoint

The visual acuity data in logMAR for binocular defocus curve at Month 3 (Visit 4A) will be summarized with the number of observations, mean, standard deviation, median, minimum and maximum, 90% CI of the mean. A plot will be generated for the defocus curve with amount of defocus along x-axis and logMAR visual acuity (mean and two-sided 90% CI of mean) at each defocus along the y-axis.

4.3.2 Secondary Effectiveness Endpoints

4.3.2.1 Binocular defocus curve at 1 months post-implantation (Visit 3A)

The visual acuity data in logMAR for binocular defocus curve data at Month 1 will be summarized with the number of observations, mean, standard deviation, median, minimum and maximum, 90% CI of the mean. A plot will be generated for the defocus curve with amount of defocus along x-axis and logMAR visual acuity (mean and two-sided 90% CI of mean) at each defocus along the y-axis.

4.3.2.2 Best corrected binocular visual acuity at distance (Visit 3A, 4A)

Best corrected binocular visual acuity at distance (Visit 3A, 4A) will be summarized by visit with the number of observations, mean, median, standard deviation, minimum, maximum and 90% CI of the mean.

BCDVA will also be summarized as categorical variables, by visit, with number of non-missing observations, cumulative frequency and percentage (count and percentage of observations smaller than a given logMAR value) in the following categories:

- 20/20 or better ($\leqslant$ 0.00 logMAR)

- 20/25 or better (≤ 0.10 logMAR)
- 20/32 or better (≤ 0.20 logMAR)
- 20/40 or better (≤ 0.30 logMAR)

4.3.2.3 Uncorrected monocular & binocular visual acuity at 1 & 3 months post-implantation (Visit 3A, 4A) at 40cm, 60cm and 4m

Uncorrected monocular visual acuity will be summarized in the same way as BCDVA as specified in section 4.3.2.2.

For the uncorrected monocular visual acuity at 40cm, 60cm and 4m, descriptive summaries will be made for the following visits: Visit 2, Visit 2A, Visit 3A and Visit 4A by operative eye.

For the uncorrected binocular visual acuity at 40cm, 60cm and 4m, descriptive summaries will be made for the following visits: Visit 3A and Visit 4A.

[redacted]

4.3.2.5 Subjective symptom questions at pre-operatively and post-operatively: 3 months post implantation (Visit 4A)

Subjective symptom questions will be summarized by visit (Visit 0, Visit 4A) per question with total number of observations, count in the category, and percent in the category.

[redacted]

[redacted]

4.4 Multiplicity Strategy

Not applicable.

[redacted]

4.6 Interim Analysis for Efficacy

Not Applicable. No interim analysis is planned for this study.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events including secondary surgical interventions (SSIs) related to the optical properties of the IOL.
- Device deficiencies
- Posterior capsule opacification
- Posterior capsulotomy
- IOL position change
- Intraocular pressure
- Surgical problems

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 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 the test product.

5.3.1 Adverse Events (Including Secondary Surgical Interventions Related to the Optical Properties of the IOL)

The definition of an Adverse Event (AE) and an Adverse Device Effect is as set forth in section 1 of the study protocol.

Counts and percentage of eyes with ocular adverse events, including the SSI will be presented by first, second operative eyes and overall. Counts and percentages of subjects with non-ocular adverse events will be presented by subject. Incidence by visit and cumulative incidence will be presented.

AEs will be summarized using the following tables:

- All Adverse Events (Serious and Non-Serious Combined)
  - Ocular
  - Non-Ocular
- All Adverse Device Effects (including Serious Adverse Device Effects)
  - Ocular
  - Non-Ocular
- All Serious Adverse Events (including Serious Adverse Device Effects)
  - Ocular
  - Non-Ocular
- Subject listings
  - Ocular Serious Adverse Events
  - Non-Ocular Serious Adverse Events
  - Ocular Non-serious Adverse Events
  - Non-Ocular Non-serious Adverse Events
  - Adverse events resulting in study discontinuation
  - Adverse events resulting in death

Additionally, any adverse event experienced by a subject during the screening period will be presented separately in a listing.

5.3.2 Secondary Surgical Interventions Related to the Optical Properties of the IOL

Number and percentage of eyes with a secondary surgical intervention related to the optical properties of the IOL will be presented by scheduled and unscheduled visit and by operative eye. A listing will be presented for subjects with a secondary surgical intervention. The listing will include the following variables: investigator, subject, visit, operative eye, reason of the SSI related to the optical properties of the IOL (or reason of SSI related/ unrelated to the IOL as recorded on the eCRF).

5.3.3 Device Deficiencies

Number and percentage of device deficiencies (including IOL damage) will be tabulated, separately for the first and second operative eye. In addition, a listing all device deficiencies, as recorded on the Device Deficiency Form will be provided.

5.3.4 Posterior Capsule Opacification

Number and percentage of eyes in each category of posterior capsule opacification will be presented by visit and by operative eye. A list of eyes with posterior capsule opacification will be presented. The listing will include the following variables: investigator, subject, age, sex, operative eye, visit, category of posterior capsule opacification.

5.3.5 Posterior Capsulotomy

The number and percentage of eyes with posterior capsulotomy will be tabulated by operative eye. A list of eyes with posterior capsule will be presented, including the following variables: investigator, subject, age, sex, operative eye, visit, date of the posterior capsulotomy, diameter of the posterior capsulotomy (mm).

5.3.6 IOL Position Change

Number and percentage of eyes with a change in IOL position category (Tilted, Decentered) will be presented by visit and by operative eye. In addition, a listing of subjects with IOL position change will be provided. The listing will include the following variables: investigator, subject, age, sex, visit, operative eye and amount of tilting (degrees) or decentration (mm).

5.3.7 Intraocular Pressure

Intraocular pressure (mmHg) will be summarized with number of observations, mean, standard deviation, median, minimum, maximum by scheduled and unscheduled visits. The summery will be made by operative eye. In addition, a listing of intraocular pressure will be presented. The listing will include the following variables: investigator, subject, age, sex, operative eye, visit, baseline IOP, IOP, IOP change from baseline. Baseline IOP is the last IOP measurement prior to the cataract surgery.

5.3.8 Surgical Problems

Numbers and percentages of eyes with surgical problems will be presented. In addition, a listing of subjects with surgical problems will be provided. The listing will include the

following variables: investigator, subject, age, sex, operative eye and description of surgical problem.

5.3.9 Others

Results of slit lamp exams, IOL observations, fundus exams, other procedures at surgery, surgical report (including lens information) will be listed. The listings will include the following variables as applicable: investigator, subject, age, sex, eye, visit and the description of the results as collected in the eCRF.

5.4 Interim Analysis for Safety

Not applicable.

6 Pharmacokinetic Analysis Strategy

Not Applicable.

7 Analysis Strategy for Other Endpoints

Not Applicable.

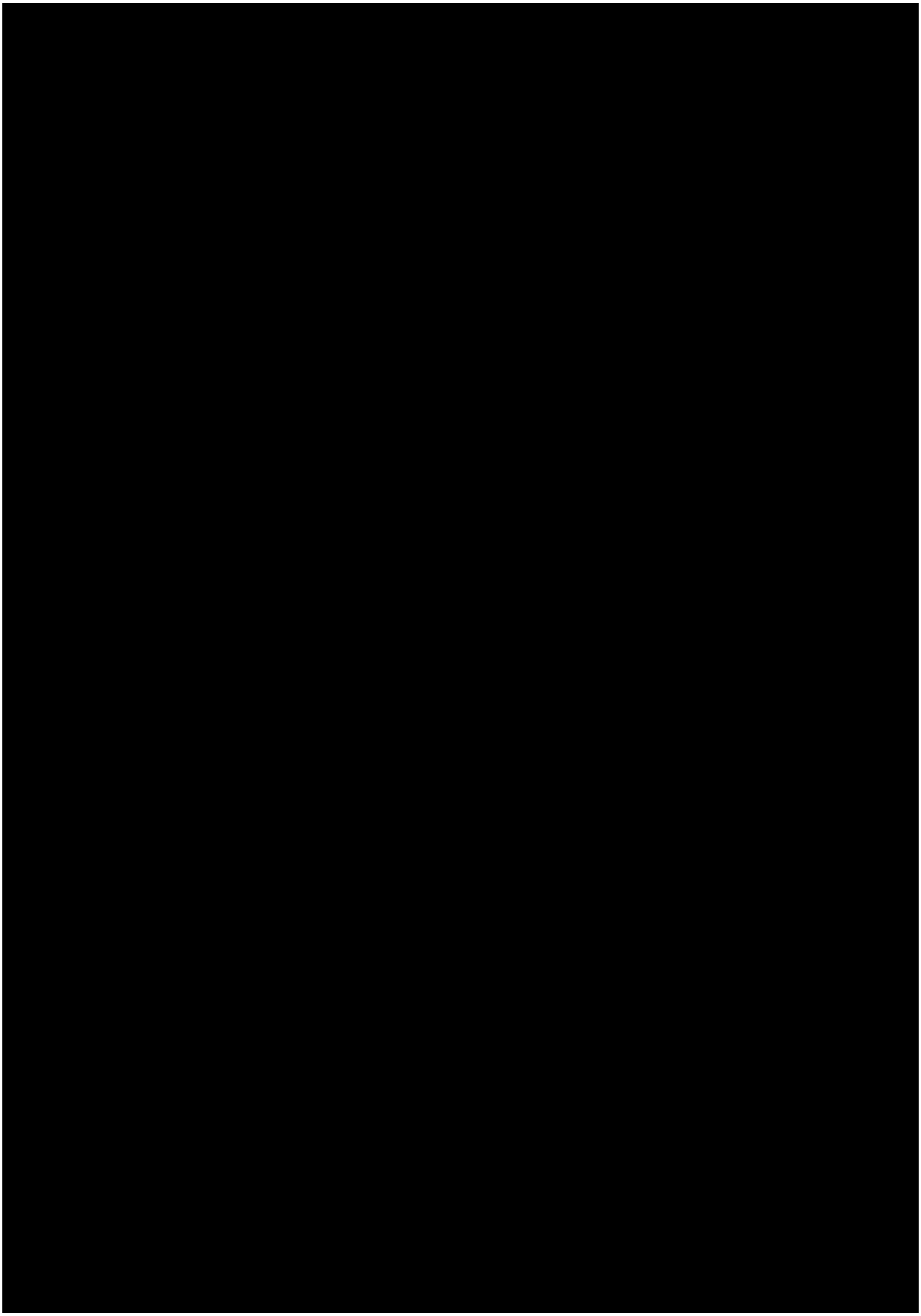
8 Sample Size and Power Calculations

Assuming a standard deviation of 0.17 logMAR for defocus visual outcomes, a sample size of 40 subjects will ensure more than 99% probability to observe the half width of 90% two-sided confidence interval to be not larger than 0.06 logMAR at a defocus point. The precision of estimates are within ±3 letters with visual outcomes.

Assume a dropout rate of 10% at month 3, an approximate total of 44 subjects with intended bilateral IOL implantation are planned to be enrolled in the study to achieve 40 subjects with complete data at month 3.

9 References

None.



[redacted]

11 Appendix

Figure 1. Diagram of scheduled visits

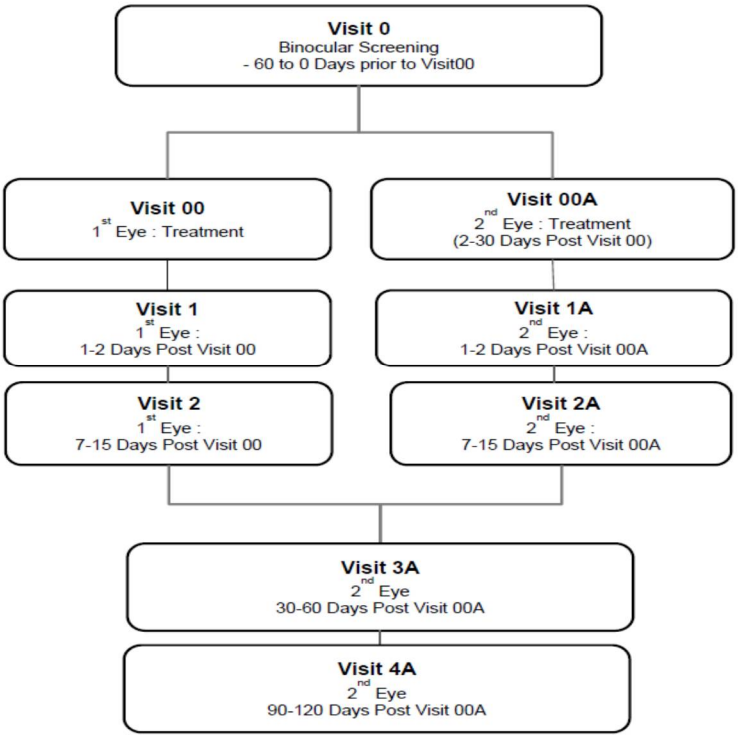


Table 2. Study Plan

		1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -60-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-15 Post Visit 00	**Visit 00A** [2] 2-30 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-15 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A** [3] 90-120 Days Post Visit 00A	**Unscheduled Visit**
General Assessments and Procedures										
Informed Consent	X									
Demographics	X									
Medical History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[4]	X									
Inclusion/Exclusion	X	X			X					
Administer Treatment(s)		X			X					
Ophthalmic Assessments										
[redacted]										
Distance VA at 4 m										
• Monocular Uncorrected				X[10]			X[11]	X[6]	X[6]	
• Binocular Uncorrected								X	X	
• Binocular Best Corrected	X							X	X	
Intermediate VA at 60 cm										
• Monocular Uncorrected				X[10]			X[11]	X[6]	X[6]	
• Binocular Uncorrected								X	X	
Near VA at 40 cm										
• Monocular Uncorrected				X[10]			X[11]	X[6]	X[6]	
• Binocular Uncorrected								X	X	
Lighting measurements	X			X			X	X	X	
Binocular Defocus Curve								X	X	
[redacted]										

		1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -60-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-15 Post Visit 00	**Visit 00A** [2] 2-30 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-15 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A** [3] 90-120 Days Post Visit 00A	**Unscheduled Visit**
[redacted]										
Photopic Best Corrected Contrast Sensitivity with & without Glare									X	
Subject symptoms	X								X	
Slit Lamp Examination	X		X	X		X	X	X	X	X
IOL Observations			X	X		X	X	X	X	X
Lens decentration and tilt (IOL Position Change)			X	X		X	X	X	X	X
Subjective PCO			X	X		X	X	X	X	X
Posterior Capsulotomy			X	X		X	X	X	X	X
Dilated Fundus Examination	X							X	X	X
Fundus Visualization								X	X	
Intraocular Pressure	X		X	X		X	X	X	X	X
Surgical Procedure & Assessments										
Surgical report (including implanting surgeon, lens power, implant success, intended axis of placement, OVD and target refractive error[5])		X			X					
Operative eye		X			X					
Surgical problems		X			X					
Lens Information		X			X					
Final Incision Size[7,8]		X			X					
IOL damage		X			X					
Other Surgical Procedures		X			X					
Adverse Events & Device Deficiencies										
Adverse Events[9]	X	X	X	X	X	X	X	X	X	X
Secondary Surgical Interventions		X	X	X	X	X	X	X	X	X

		1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -60-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-15 Post Visit 00	**Visit 00A**[2] 2-30 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-15 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A**[3] 90-120 Days Post Visit 00A	**Unscheduled Visit**
Device Deficiencies		X	X	X	X	X	X	X	X	X

1. Visit 00 (1st eye surgery) must occur within 60 calendar days from Preoperative Visit (Visit 0).
2. Visit 00A (2nd eye surgery) must occur after a minimum of 2 calendar days and a maximum of 30 calendar days after Visit 00.
3. If necessary, Visit 4A may be completed over 2 days within a two-week period. Both days must fall within the specified visit window.
4. In women of child bearing potential only.
5. Data is reported in EDC at the surgical visit, but may be collected at a previous visit.
6. Testing is conducted monocular bilaterally.
7. Capture in source (not captured in EDC).
8. Only measure in cases with surgical complications.
9. Collected from time of consent onward.
10. 1st operative eye
11. 2nd operative eye

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
08/25/2018 01:14:26	[redacted]	[redacted]
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08/27/2018 17:25:19	[redacted]	[redacted]
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08/27/2018 22:02:23	[redacted]	[redacted]