Short Title:

Statistical Analysis Plan ILI875-C002

Full Title:

Statistical Analysis Plan ILI875-C002

Protocol Title: A Prospective, Randomized, Controlled, Multi-Center Clinical Study of the ACRYSOF® IQ Extended Depth of Focus IOL

[redacted] [redacted]

Protocol TDOC Number: TDOC-0053387

Author: [redacted]

[redacted]

Approvals: See last page for electronic approvals.

Job Notes:

This is Version 3.0 of Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 4.0 of the study protocol TDOC-0053387. See Section 8, Revision History, for a summary of revisions.

Executive Summary:

Key Objectives:

Below are listed the study's co-primary objectives. Each objective is assessed at Visit 4A (120-180d postoperative).

1. To demonstrate ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic DCIVA
2. To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular photopic BCDVA
3. To demonstrate that the monocular mean defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.5 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.2 logMAR
4. To demonstrate that ACRYSOF IQ EDF IOL has at least 50% of eyes achieving DCIVA of 0.2 logMAR or better

Decision Criteria for Study Success:

A successful outcome on the co-primary effectiveness endpoints is indicated by successful outcomes on all 4 of these endpoints.

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1 Study Objectives and Design

1.1 Study Objectives

Co-Primary Objectives:

Below are listed the study's co-primary objectives. Each objective is assessed at Visit 4A (120-180d postoperative).

1. To demonstrate that ACRYSOF IQ Extended Depth of Focus IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic DCIVA

2. To demonstrate that ACRYSOF IQ Extended Depth of Focus IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular photopic BCDVA

3. To demonstrate that the monocular mean defocus curve for ACRYSOF IQ Extended Depth of Focus IOL has a range of defocus at least 0.5 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.2 logMAR

4. To demonstrate that ACRYSOF IQ Extended Depth of Focus IOL has at least 50% of eyes achieving DCIVA of 0.2 logMAR or better

Secondary Objectives:

Below are listed the study's secondary objectives. Each objective is assessed at Visit 4A (120-180d postoperative).

1. To demonstrate that ACRYSOF IQ Extended Depth of Focus IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic DCNVA

   In addition, the following performance targets will also be assessed to demonstrate clinical significance:

   - Demonstrate at least 50% of eyes with ACRYSOF IQ EDF IOL achieve a monocular DCNVA of 0.3 logMAR or better

   - Percentage of eyes achieving monocular DCNVA of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group is at least 25 percentage points higher than in ACRYSOF IQ Monofocal IOL group

2. To demonstrate that ACRYSOF IQ Extended Depth of Focus IOL is superior to AcrySof IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?)

3. To describe mean monocular photopic UCIVA outcomes

4. To describe mean monocular photopic UCDVA outcomes

Co-Primary Safety Objectives:

Below are listed the study's co-primary safety objectives. Each objective is assessed at Visit 4A (120-180d postoperative).

1. To demonstrate that ACRYSOF IQ EDF IOL adverse event rates are not worse than the historical control SPE rates, as defined in IS EN ISO 11979-7:2014
2. To describe monocular mesopic contrast sensitivity test (with and without glare) outcomes

Secondary Safety Objective:

To estimate rates of severe and most bothersome (separately) visual disturbances as reported by subjects using a questionnaire at Visit 4A (120-180d postoperative)

1.2 Study Description

This is a prospective, multi-center, randomized, parallel group, controlled, assessor and subject masked study. Both eyes of a subject must require cataract surgery to qualify for enrollment into this study. Subjects will be randomly assigned in a 1:1 ratio to receive either model DFT015 (test article) or model SN60WF (control article) in both eyes. To further reduce bias, all subjects and site assessors will be masked to subject treatment assignment until the end of the study.

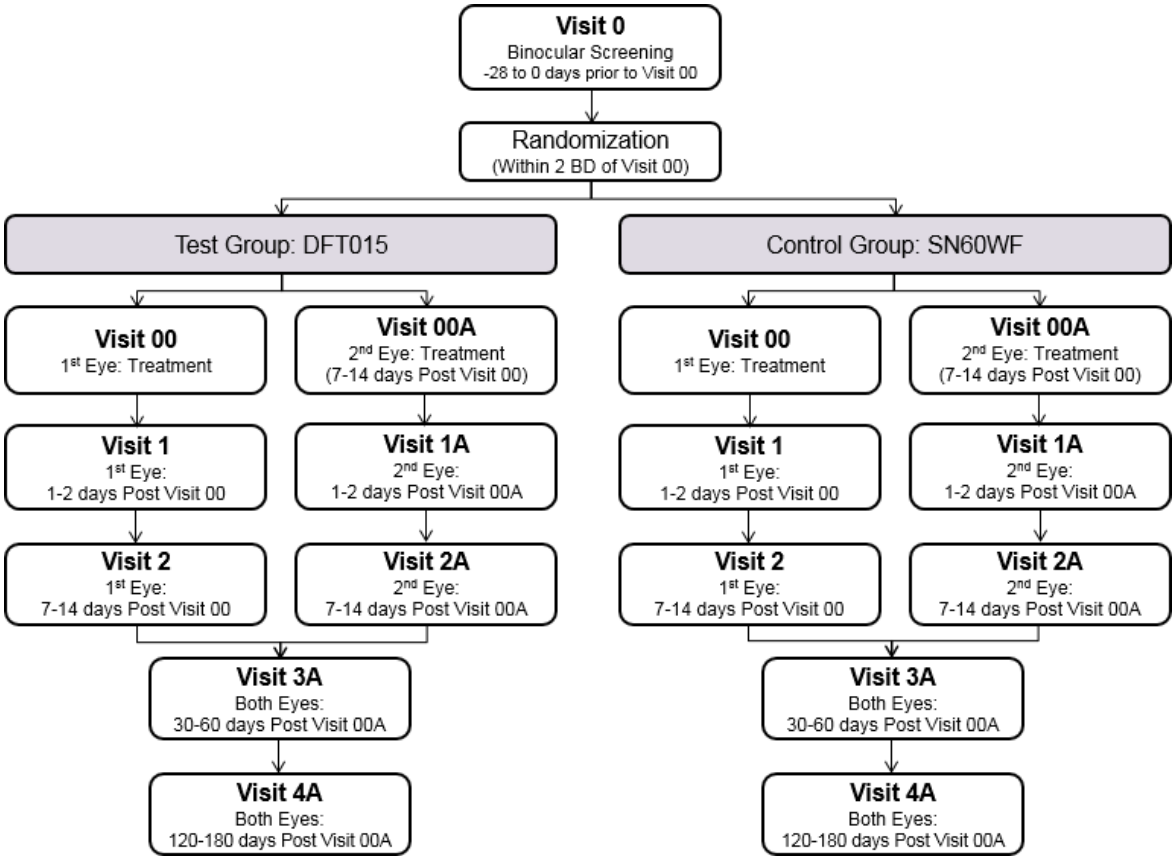
The first operative eye is defined as the eye with the worse BCDVA. If the BCDVA is the same in both eyes, identify the right eye (OD) as the first operative eye. The second eye implant must occur within 14 days of the 1st eye implant.

An overview of the study design is depicted in Figure 1-1.

The schedule of visits is included as Table 9-1 in the appendix.

The purpose of the study is to demonstrate the safety and performance of ACRYSOF IQ EDF IOL at Month 6/Visit 4A. After all subjects complete Month 6/Visit 4A, the study database will be locked to conduct planned analyses. Results from these analyses will be used in a clinical study report for submission.

Figure 1-1 Study Design Diagram



A total of 9 scheduled visits are planned and subject participation is expected to last 7-8 months. The visits include a Screening visit (Visit 0), two Operative Visits (Visit 00 and Visit 00A), and 6 postoperative visits at the following intervals: Day 1-2 (Visit 1/1A), Day 7-14 (Visit2/2A), Day 30-60 (Visit 3A), and Day 120-180 (Visit 4A). See Figure 9-1 Study Design. Primary endpoint data will be collected at the Month 6/ Visit 4A (120-180 day post 2nd eye implantation).

Note: Visit 4A may be completed over 2 days within a 2 week period. Both days must fall within the specified visit window.

1.3 Randomization

Subjects will be randomized in a 1:1 ratio to receive either ACRYSOF IQ EDF IOL or ACRYSOF IQ Monofocal IOL. Randomization will be stratified by site. Only after signing the informed consent form (ICF), a subject will be assigned a subject number by the electronic data capture (EDC) system. The Investigator (or delegate) at Operative Visit / Visit 00 will initiate randomization in EDC after confirming the subject is eligible for randomization. Randomization must be completed no more than two business days prior to the first eye operative visit (Visit 00), and post lens power calculation and IOL power selection of both test and control IOLs, unless there is a valid reason to randomize earlier. After randomization is initiated, all eligible subjects will be randomized to one of two treatment arms.

1.4 Masking

The assessor and subject will be masked in this study. Subjects will be masked to their treatment assignment for the entire duration of the study.

Site personnel performing the manifest refraction, all VA assessments (including defocus curve testing) and all contrast sensitivity assessments will remain masked with regard to treatment assignment until after the final database lock. Alcon and site personnel will not reveal the treatment assignment to study subjects at any time during the study. Should a subject safety concern arise, refer to Section 13.10 of the protocol (Unmasking of the Study Treatment).

1.5 Interim Analysis

Not Applicable.

2 Analysis Sets

2.1 Efficacy Analysis Sets

The all-implanted analysis set (AAS) includes all randomized eyes with successful IOL implantation.

The best-case analysis set (BAS). BAS includes all eyes successfully implanted that had:

- at least 1 postoperative visit~~;~~
- no preoperative ocular pathology
- no macular degeneration detected at any time

- no previous surgery for the correction of refractive errors
- no major protocol violation

The primary analysis set for effectiveness analyses will be the AAS. Additional supportive analyses will be performed using the BAS.

All effectiveness analyses will be conducted according to actual test or control article implanted.

2.2 Safety Analysis Set

The Safety Analysis Set will include all eyes with attempted IOL implantation (successful or aborted after contact with the eye).

The Safety Analysis Set will be used for analysis of safety endpoints.

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. For treatment-emergent safety analyses, eyes will be categorized under the actual test or control article implanted (or attempted to implant).

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, summary of screen failures by reason and listing of subjects excluded from key analysis sets including reasons. 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 and overall.

Subject characteristics and study conduct summaries will be presented for the AAS and the safety analysis set. Subject characteristics and study conduct summaries for the best-case analysis set will be presented if the number of subjects excluded exceeds 10%.

4 Effectiveness Analysis Strategy

A success on co-primary effectiveness endpoints would be indicated by successful outcomes on all 4 of these endpoints (2 hypothesis tests and 2 performance targets). A total of four

hypothesis tests will be conducted to address the primary and secondary objectives of the study. Overall Type I error will be maintained at the 0.05 level using a sequential testing approach described in Section 4.4.

Hypothesis tests on secondary effectiveness endpoints will be conducted only after successful outcomes on all 4 co-primary effectiveness endpoints are demonstrated.

Analyses on performance targets are based on point estimates.

Only the first eye of each subject will be included in the primary statistical analysis (as described in IS EN ISO 11979-7:2014).

4.1 Effectiveness Endpoints

4.1.1 Co-Primary Effectiveness

- Monocular distance corrected intermediate visual acuity (DCIVA) at 66 cm
- Monocular best corrected distance visual acuity (BCDVA)
- Monocular depth of focus assessed by the mean defocus curve evaluation
- Percentage of eyes achieving monocular distance corrected intermediate visual acuity (DCIVA) of 0.2 logMAR or better at 66 cm

4.1.2 Secondary Effectiveness

- Monocular distance corrected near visual acuity (DCNVA) at 40 cm
    - Percentage of eyes with monocular DCNVA of 0.3 logMAR or better
- Proportion of subjects who respond “Never” to Q1 of the IOLSAT questionnaire: “Overall, in the past 7 days, how often did you need to wear eyeglasses to see?”
- Monocular uncorrected intermediate visual acuity at 66 cm
- Monocular uncorrected distance visual acuity

[redacted]

4.2 Effectiveness Hypotheses

4.2.1 Co-Primary Effectiveness Hypotheses

The null and alternative hypotheses for the co-primary effectiveness objectives are:

ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic distance corrected intermediate visual acuity (66 cm from spectacle plane) at Visit 4A (120-180d postoperative)

The null and alternative hypotheses for the first co-primary analysis are:

$$H_0: \mu_{DFT015VA} \geq \mu_{SN60WFVA}$$
$$H_A: \mu_{DFT015VA} < \mu_{SN60WFVA}$$

where $\mu_{DFT015VA}$ and $\mu_{SN60WFVA}$ refer to the mean monocular photopic DCIVA at 66 cm for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

ACRYSOF IQ EDF IOL is non-inferior compared to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic best corrected distance visual acuity at Visit 4A (120-180d postoperative). The non-inferiority margin will be 0.1 logMAR.

The null and alternative hypotheses for the second co-primary endpoint are:

$$H_0: \mu_{DFT015VA} - \mu_{SN60WFVA} \geq \Delta$$
$$H_A: \mu_{DFT015VA} - \mu_{SN60WFVA} < \Delta$$

where Δ refers to the non-inferiority margin, set at 0.1 logMAR, and $\mu_{DFT015VA}$ and $\mu_{SN60WFVA}$ refer to the mean monocular photopic BCDVA for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

Two performance targets in support of the primary effectiveness objectives are:

Monocular mean defocus curve for ACRYSOF IQ EDF IOL has a range of defocus at least 0.5 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.2 logMAR at Visit 4A (120-180d postoperative).

ACRYSOF IQ EDF IOL has at least 50% of eyes achieving monocular photopic distance corrected intermediate vision of 0.2 logMAR or better at Visit 4A (120-180d postoperative).

Primary analysis for each of the performance targets will be for the first implanted eye. Second implanted eye analysis will be supportive.

4.2.2 Secondary Effectiveness Hypotheses

The statistical hypothesis in support of the first secondary effectiveness objective is:

ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to mean monocular photopic distance corrected near visual acuity (40 cm from spectacle plane) at Visit 4A (120-180d postoperative)

The null and alternative hypotheses for the first secondary analysis are:

$$H_0: \mu_{DFT015VA} \geq \mu_{SN60WFVA}$$
$$H_A: \mu_{DFT015VA} < \mu_{SN60WFVA}$$

where $\mu_{DFT015VA}$ and $\mu_{SN60WFVA}$ refer to the mean monocular photopic DCNVA at 40 cm for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

Two performance targets in support of the first secondary effectiveness objective are:

- At least 50% of eyes with ACRYSOF IQ EDF IOL achieve a monocular DCNVA of 0.3 logMAR or better.

- The percentage of eyes with DCNVA of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group is at least 25 percentage points higher than in ACRYSOF IQ Monofocal IOL group.

Primary analysis for each of the performance targets will be for the first implanted eye. Second implanted eye analysis will be supportive.

The statistical hypothesis in support of the second secondary effectiveness objective is:

ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 of the IOLSAT questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?) at Visit 4A (120-180d postoperative).

The null and alternative hypotheses for the second secondary analysis are:

$$H_0: \pi_{DFT015Q1} \leq \pi_{SN60WFQ1}$$
$$H_A: \pi_{DFT015Q1} > \pi_{SN60WFQ1}$$

where $\pi_{DFT015Q1}$ and $\pi_{SN60WFQ1}$ refer to the proportion of subjects who responded "Never" for the test and control lenses.

There are no hypothesis tests or performance targets associated with the third and the fourth secondary effectiveness endpoints (UCIVA and UCDVA, respectively).

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

4.3.1.1 Monocular Distance Corrected Intermediate Visual Acuity at 66 centimeters

Analysis of the first primary effectiveness endpoint (DCIVA) will be based on a two-sample t-test, with a type I error rate of 2.5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

The following SAS pseudocode will be used for the primary analysis:

```
proc glm data=visual_acuity;
   where IMPLANT_EYE = 'First';
   class LENS_MODEL;
   model DCIVA6 = LENS_MODEL;
   estimate 'Trt_Eff' LENS_MODEL 1 -1;
   lsmeans LENS_MODEL / pdiff cl;
run;
```

Poolability of primary outcomes across sites will be assessed using a fixed effects model including main effects of treatment and site along with a treatment by site interaction effect. Subjects across sites will be considered poolable if the interaction effect is not significant at type I error of 0.15. If the interaction effect is significant, a mixed effects model will be used to estimate treatment effect. The following mixed effect models will be used and compared using Bayesian information criterion (BIC).

1. A fixed effect for treatment and random effects for site and site by treatment interaction

2. A fixed effect for treatment and random effect for site

The model with smaller BIC will be selected as the final model to estimate treatment effect (Littell 2006). The SAS pseudocode for each of the above models are provided below.

Fixed effects model for assessing poolability:

```
proc mixed data=visual_acuity;
  where IMPLANT_EYE = 'First';
  class LENS_MODEL SITE;
  model DCIVA4 = LENS_MODEL | SITE /DDFM = satterth;
  lsmeans LENS_MODEL / pdiff cl;
 ods output Diffs= DIFF LSMeans= LSMEAN;
run;
```

Mixed effects model(s) for obtaining estimate of treatment effect in the presence of random site effect or random site and site by treatment interaction effects:

```
proc mixed data=visual_acuity;
  where IMPLANT_EYE = 'First';
  class LENS_MODEL SITE;
  model DCIVA4 = LENS_MODEL /DDFM = satterth;
  random SITE SITE*LENS_MODEL; *[OR] random SITE;
  lsmeans LENS_MODEL / pdiff cl;
 ods output Diffs= DIFF LSMeans= LSMEAN;
run;
```

ISO requires that only the first eye of each subject is included in the primary analysis - Section 6.6 of ISO 11979-7:2014. An analysis with a mixed-effect model analysis of variance (ANOVA) accounting for correlation between the first and the second eye will be performed as a sensitivity analyses. The following SAS pseudocode will be used:

```
proc mixed data=visual_acuity;
  class SUBJECT_ID LENS_MODEL;
  model DCIVA4 = LENS_MODEL /DDFM = satterth;
  random SUBJECT_ID;
    lsmeans LENS_MODEL / pdiff cl;
 ods output Diffs= DIFF LSMeans= LSMEAN;
run;
```

4.3.1.2 Monocular Best Corrected Distance Visual Acuity

Analysis of the second primary effectiveness endpoint (BCDVA) will be based on a two-sample t-test, with a type I error rate of 5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated one-sided 95% upper confidence limit will be presented.

Data poolability will be analyzed by testing a treatment by site interaction effect as described in 4.3.1.1. A sensitivity analysis with a mixed-effect model analysis of variance (ANOVA) accounting for correlation between the first and the second eye will be performed as a sensitivity analyses as described in 4.3.1.1.

4.3.1.3 Monocular Depth of Focus

For the first performance target (depth of focus), the line plot of the average visual acuity at each defocus level (ie, defocus curve) will be used to estimate the negative lens induced depth of focus at 0.2 logMAR. The depth of focus will be estimated as the dioptric range between zero defocus and the first point on the negative lens induced defocus curve that crosses the 0.2 logMAR using a linear interpolation. The difference in the depth of focus between ACRYSOF IQ EDF IOL and ACRYSOF IQ Monofocal IOL will be presented.

If the defocus value for the ACRYSOF IQ EDF IOL is at least 0.50 D greater than the value for the ACRYSOF IQ Monofocal IOL at 0.20 logMAR for the first implanted eye, then the performance target will be met.

The following sensitivity analyses will be performed on the depth of focus endpoint:

Exclude extreme outliers (individual depth of focus values less than Q1 – 3*IQR or greater than Q3 + 3*IQR)

Exclude mild outliers (individual depth of focus values less than Q1 – 1.5*IQR or greater than Q3 + 1.5*IQR), where Q1 = 25th percentile, Q3= 75th percentile, and IQR = Q3 – Q1.

The depth of focus data (including defocus curves) will be presented by IOL group, 3 photopic pupil size ranges [<3.0 mm (small), ≥3.0 mm to ≤4.0 mm (medium), and >4.0 mm (large)] and three axial length ranges [<21.0 mm (short), ≥21.0 mm to ≤26.0 mm (medium), and >26.0 mm (long)]. Descriptive summary statistics (number of eyes, mean, median, standard deviation, minimum, and maximum) on individual depth of focus value will be presented by IOL group.

4.3.1.4 Monocular Distance Corrected Intermediate Visual Acuity of 0.2 logMAR or Better at 66 centimeters

For the second performance target (DCIVA), the percentage of eyes achieving distance corrected intermediate visual acuity of 0.2 logMAR or better in each IOL group will be presented and compared against the performance target of 50%.

4.3.2 Secondary Effectiveness Analyses

A success on the first secondary effectiveness endpoint will be indicated by successful outcomes on the hypothesis test and two performance targets. A hypothesis test on the second secondary effectiveness endpoint will be conducted only after successful outcomes on the first secondary endpoint are demonstrated.

4.3.2.1 Monocular Distance Corrected Near Visual Acuity at 40 centimeters

Analysis of first secondary effectiveness endpoint (DCNVA) will be based on a two-sample t-test, with a type I error rate of 2.5%, 1-sided. The difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

Two performance targets in support of the first secondary effectiveness objective are:

At least 50% of eyes with ACRYSOF IQ EDF IOL achieve a monocular DCNVA of 0.3 logMAR or better

The percentage of eyes achieving monocular DCNVA of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group is at least 25 percentage points higher than in ACRYSOF IQ Monofocal IOL group.

For the first performance target, the percentage of eyes achieving distance corrected near visual acuity of 0.3 logMAR or better in ACRYSOF IQ EDF IOL group will be presented and compared against the performance target of 50%. For the second performance target, the percentage of eyes achieving distance corrected near visual acuity of 0.3 logMAR or better in each IOL group will be presented and the difference between the IOL groups (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) will be compared against the performance target of 25%.

4.3.2.2 Proportion of Subjects Who Respond "Never" to Q1 of the IOLSAT Questionnaire

A two-sided 95% confidence interval for the difference in proportions (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) will be calculated using the Miettinen-Nurminen method (1985), and ACRYSOF IQ EDF IOL will be determined to be superior to ACRYSOF IQ Monofocal IOL if the lower boundary of the confidence interval is greater than zero. This is equivalent to using a type I error rate of 2.5%, 1-sided.

The following SAS pseudocode will be used to estimate the difference in proportions and the corresponding two-sided 95% confidence interval.

```
proc freq data=IOLSAT;
  tables IOL*IOLSATQ1 /riskdiff(CL= MN) alpha = 0.05;
  * MN = Miettinen and Nurminen inverted score test;
  ods output PdiffCLs=CI_by_MN;
run;
```

If IOLSAT questionnaire generates scores, the cumulative distribution curves showing the percentage of subjects with a given change in their score compared to baseline by IOL group will be presented to help determine whether any observed differences are meaningful.

In addition, the frequencies of responses to each item in IOLSAT will be summarized by IOL group and visit with counts and percentages.

4.3.2.3 Monocular Uncorrected Intermediate Visual Acuity at 66 centimeters

For the third secondary effectiveness endpoint (UCIVA), the following descriptive statistics will be provided for each IOL 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

- 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

Descriptive statistics including mean, median, standard deviation, number of eyes, minimum, maximum and two-sided 95% confidence interval will be presented for overall, by preoperative corneal cylinder (≤ 0.5 D vs. > 0.5 D), and by residual cylinder (≤ 0.5 D vs. > 0.5 D) at Visit 4A (120-180d postoperative).

In addition, the difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided 95% confidence interval will be presented.

First implanted eyes and second implanted eyes assessments will be in separate tables.

4.3.2.4 Monocular Uncorrected Distance Visual Acuity

The analysis for the fourth secondary effectiveness endpoint will be same as described in section 4.3.2.3.

[redacted]

4.3.3.1 Visual Acuity Endpoints

In general, for visual acuity endpoints, the following descriptive statistics will be provided for each IOL 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

- 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

Descriptive statistics including sample size, mean, median, standard deviation, number of eyes, minimum, maximum and the confidence interval will be presented.

In addition, the difference in means (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated confidence interval will be presented.

First implanted eyes, second implanted eyes and binocular assessments will be in separate tables.

[redacted]

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4.3.3.3 Manifest Refraction

The following endpoints will be used to summarize the outcome from manifest refraction:

MRSE (Manifest Refraction Spherical Equivalent) = sphere + ½ cylinder

Predicted TRRE (Target Residual Refractive Error)

Prediction Error at 6 months = MRSE at 6 months – Predicted TRRE

The number, percent and cumulative percent of eyes will be presented for MRSE, TRRE and Prediction Error by IOL group in the following categories: within 0.25 D, within 0.50 D, within 1.0 D and >1.0 D.

In addition, descriptive statistics (sample size, mean, median, standard deviation, number of eyes, minimum, maximum, and two-sided 95% confidence interval) will be provided by IOL group.

First implanted eyes and second implanted eyes will be in separate tables.

[redacted]

Table 4-1 summarizes the key effectiveness analyses.

Table 4–1 Summary of Analysis Strategy for Key Effectiveness Endpoints

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method	Analysis Set	Missing Data Approach
Primary				
Mean Monocular DCIVA for superiority (1st Eye)	M	Two-sample t-test	AAS	Observed data only
Mean Monocular DCIVA for superiority (1st Eye)	S	Fixed effect model with treatment, site, and treatment by site	AAS	Observed data only

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method	Analysis Set	Missing Data Approach
		interaction		
Mean Monocular DCIVA for superiority (1st Eye)	S	Mixed effect model poolability[b]	AAS	Observed data only
Mean Monocular DCIVA for superiority (1st Eye)	S	Mixed effect model poolability[c]	AAS	Observed data only
Mean Monocular DCIVA for superiority (1st Eye)	S	Fully Conditional Specification	AAS	Multiple Imputation
Mean Monocular DCIVA for superiority (1st Eye)	S	Control-based pattern imputation	AAS	Multiple Imputation
Mean Monocular DCIVA for superiority (1st Eye)	S	Two-sample t-test	BAS	Observed data only
Mean Monocular DCIVA for superiority (2nd Eye)	S	Two-sample t-test	AAS	Observed data only
Mean Monocular DCIVA for superiority (Both Eyes)	S	Mixed effect model with a random subject effect	AAS	Observed data only
Mean Monocular BCDVA for non-inferiority (1st Eye)	M	Two-sample t-test[d]	AAS	Observed data only
Mean Monocular BCDVA for non-inferiority (1st Eye)	S	Fixed effect model with treatment, site, and treatment by site interaction[d]	AAS	Observed data only
Mean Monocular BCDVA for non-inferiority (1st Eye)	S	Mixed effect model poolability[b,d]	AAS	Observed data only
Mean Monocular BCDVA for non-inferiority (1st Eye)	S	Mixed effect model poolability[c,d]	AAS	Observed data only
Mean Monocular BCDVA for non-inferiority (1st Eye)	S	Fully Conditional Specification[d]	AAS	Multiple Imputation
Mean Monocular BCDVA for non-inferiority (1st Eye)	S	Control-based pattern imputation[d]	AAS	Multiple Imputation
Mean Monocular	S	Two-sample t-test[d]	BAS	Observed data

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method	Analysis Set	Missing Data Approach
BCDVA for non-inferiority (1st Eye)				only
Mean Monocular BCDVA for non-inferiority (2nd Eye)	S	Two-sample t-test[d]	AAS	Observed data only
Mean Monocular BCDVA for non-inferiority (Both Eyes)	S	Mixed effect model with a random subject effect	AAS	Observed data only
Monocular Depth of Focus (1st Eye)	M	Performance target: difference vs monofocal ≥ 0.5 D; descriptive statistics	AAS	Observed data only
Monocular Depth of Focus (1st Eye)	S	Performance target: difference vs monofocal ≥ 0.5 D; descriptive statistics	BAS	Observed data only
Monocular Depth of Focus (2nd Eye)	S	Performance target: difference vs monofocal ≥ 0.5 D; descriptive statistics	AAS	Observed data only
Monocular Depth of Focus (1st Eye)	S	Performance target: difference vs monofocal ≥ 0.5 D; descriptive statistics	AAS	Exclude extreme outliers
Monocular Depth of Focus (1st Eye)	S	Performance target: difference vs monofocal ≥ 0.5 D; descriptive statistics	AAS	Exclude mild outliers
% Monocular DCIVA of 0.2 logMAR or better (1st Eye)	M	Performance target: ≥ 50%; descriptive statistics	AAS	Observed data only
% Monocular DCIVA of 0.2 logMAR or better (1st Eye)	S	Performance target: ≥ 50%; descriptive statistics	BAS	Observed data only
% Monocular DCIVA of 0.2 logMAR or better (2nd Eye)	S	Performance target: ≥ 50%; descriptive statistics	AAS	Observed data only
Secondary				
Mean Monocular	M	Two-sample t-test	AAS	Observed data

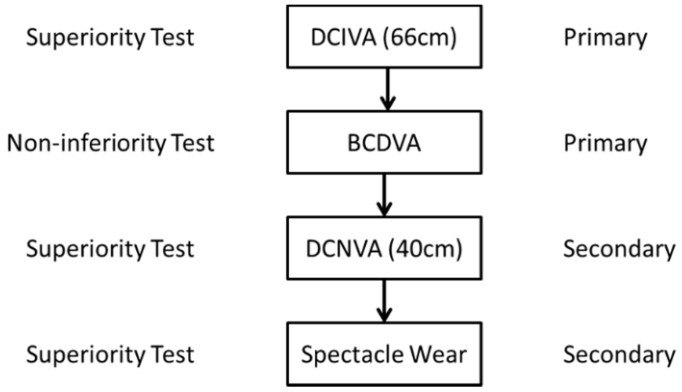
Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method	Analysis Set	Missing Data Approach
DCNVA for superiority (1st Eye)				only
Mean Monocular DCNVA for superiority (1st Eye)	S	Fixed effect model with treatment, site, and treatment by site interaction	AAS	Observed data only
Mean Monocular DCNVA for superiority (1st Eye)	S	Mixed effect model poolability[b]	AAS	Observed data only
Mean Monocular DCNVA for superiority (1st Eye)	S	Mixed effect model poolability[c]	AAS	Observed data only
Mean Monocular DCNVA for superiority (1st Eye)	S	Fully Conditional Specification	AAS	Multiple Imputation
Mean Monocular DCNVA for superiority (1st Eye)	S	Control-based pattern imputation	AAS	Multiple Imputation
Mean Monocular DCNVA for superiority (1st Eye)	S	Two-sample t-test[d]	BAS	Observed data only
Mean Monocular DCNVA for superiority (2nd Eye)	S	Two-sample t-test[d]	AAS	Observed data only
Mean Monocular DCNVA for superiority (Both Eyes)	S	Mixed effect model with a random subject effect	AAS	Observed data only
% Monocular DCNVA of 0.3 logMAR or better (1st Eye)	M	Performance target: ≥ 50%; Descriptive statistics	AAS	Observed data only
% Monocular DCNVA of 0.3 logMAR or better (1st Eye)	S	Performance target: ≥ 50%; Descriptive statistics	BAS	Observed data only
% Monocular DCNVA of 0.3 logMAR or better (2nd Eye)	S	Performance target: ≥ 50%; Descriptive statistics	AAS	Observed data only
% Monocular DCNVA of 0.3 logMAR or better (1st	M	Performance target: difference vs monofocal ≥ 25%;	AAS	Observed data only

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method	Analysis Set	Missing Data Approach
Eye)		Descriptive statistics		
% Monocular DCNVA of 0.3 logMAR or better (1st Eye)	S	Performance target: difference vs monofocal ≥ 25%; Descriptive statistics	BAS	Observed data only
% Monocular DCNVA of 0.3 logMAR or better (2nd Eye)	S	Performance target: difference vs monofocal ≥ 25%; Descriptive statistics	AAS	Observed data only
IOLSAT Q1 for superiority	M	Miettinen-Nurminen method	AAS	Observed data only
IOLSAT Q1 for superiority	S	Miettinen-Nurminen method	BAS	Observed data only

[a]M=Main analysis approach; S=Sensitivity or supportive analysis approach
[b]Fixed effect for treatment and random effects for site and site by treatment interaction
[c]Fixed effect for treatment and random effect for site
[d]Non-inferiority margin of 0.10

4.4 Multiplicity Strategy

Overall type I error will be maintained at 0.05 level using the sequential testing approach summarized in the figure below.



If any null hypothesis is not rejected, no further hypothesis testing will be performed.

4.5 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of the first two co-primary endpoints (monocular DCIVA (66cm) and monocular BCDVA (4 m)) and the first secondary (monocular DCNVA (40 cm)) visual acuity

endpoints will be conducted to assess the consistency of treatment effect across various subgroups if appropriate.

The consistency of the treatment effect for the first two co-primary and the first secondary visual acuity endpoints will be assessed for first eye and second eye using descriptive statistics by category of the following subgroup factors:

- Age category (<65 vs. ≥65 years)
- Investigative site
- Adverse event (study eyes with ocular adverse events vs. study eyes without ocular adverse events) and
- Preoperative ocular pathology (study eyes with vs. study eyes without)

Descriptive statistics provided will be sample size, mean, median, standard deviation, number of eyes, minimum, maximum, and the confidence interval. Listings of monocular DCIVA (66cm), monocular BCDVA (4 m) and monocular DCNVA (40 cm) at every visit for each eye will also be provided.

These subgroup analyses will be performed for the AAS.

4.6 Handling of Missing Data

The AAS and BAS do not include any imputed values. Although the influence of missing data is expected to be minimal, the following sensitivity analyses will be conducted to assess the impact of missing data on the conclusions for the first two co-primary effectiveness endpoints and first secondary effectiveness endpoint. Examples are shown for DCIVA.

1. Multiple imputation (with a fully conditional specification) method will be used to impute and estimate the treatment effect.

2. The sensitivity of inferences to departures from the MAR assumption will be examined using a pattern-mixture model approach (with a control-based pattern imputation). (Ratitch 2011)

Sensitivity Analysis 1:

A fully conditional specification (FCS) method will be used to impute missing values at all visits in a data set with an arbitrary missing pattern. The FCS method uses a separate conditional distribution for each imputed variable.

The following SAS pseudocode with the PROC MI procedure will be used to impute missing values using FCS method:

```
/* multiple imputation w/ MAR assumption         */
/* DCIVA1-DCIVA4 should be in parallel structure */
proc mi data=mi_in seed=1001 nimpute=10 mu0=.3 .2 .1 .0 out=mi_out1;
   fcs nbiter=20 reg; *reg(/details);
   var DCIVA1 DCIVA2 DCIVA3 DCIVA4;
run;

/* run glm on each iteration of mi */
proc glm data=mi_out1;
   by _Imputation_;
   class LENS_MODEL;
   model DCIVA4 = LENS_MODEL;
   estimate 'Trt_Eff' LENS_MODEL 1 -1;
   ods output Estimates = glm_out1;
run;

/* no need to sort if there is only one parameter being estimated */
proc sort data=glm_out1;
   by _imputation_;
run;

/* generate estimates and CIs from multiple imputation */
proc mianalyze data=glm_out1;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates = Param_out1;
run;
```

Sensitivity Analysis 2:

The sensitivity of inferences to departures from the MAR assumption will be examined using a pattern-mixture model approach with a control-based pattern imputation.

The following SAS pseudocode with the PROC MI procedure will be used to implement the control-based pattern imputation:

```
/* multiple imputation w/ MNAR assumption            */
/* DCIVA1-DCIVA4 should be in parallel structure     */
proc mi data=mi_in seed=1001 nimpute=10 mu0=.3 .2 .1 .0 out=mi_out2;
   class LENS_MODEL;
   fcs nbiter=20 reg; *reg(/details);
   mnar model( DCIVA1 DCIVA2 DCIVA3 DCIVA4/modelobs=(LENS_MODEL='SN60WF'));
```

```
   var DCIVA1 DCIVA2 DCIVA3 DCIVA4;
run;

/* run glm on each iteration of mi */
proc glm data=mi_out2;
   by _Imputation_;
   class LENS_MODEL;
   model DCIVA4 = LENS_MODEL;
   estimate 'Trt_Eff' LENS_MODEL 1 -1;
   ods output Estimates = glm_out2;
run;

/* no need to sort if there is only one parameter being estimated */
proc sort data=glm_out2;
   by _imputation_;
run;

/* generate estimates and CIs from multiple imputation */
proc mianalyze data=glm_out2;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates = Param_out2;
run;
```

4.7 Interim Analysis for Efficacy

Not Applicable.

5 Safety Analysis Strategy

5.1 Safety Endpoints

5.1.1 Co-primary Safety Endpoints

- Adverse events including Secondary Surgical Interventions (SSIs)
- Mesopic contrast sensitivity (with and without glare)

5.1.2 Secondary Safety Endpoints

- Rates of severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire

5.1.3 Supportive Safety Endpoints

- Intraocular pressure
- Slit-lamp findings including IOL observations
- Dilated fundus findings including fundus visualization
- IOL tilt/decentration

- Subjective posterior capsular opacification (PCO) assessment
- Posterior capsulotomy
- Intraoperative surgical problems
- Other procedures at surgery (combined and/or additional)
- Device deficiencies

5.2 Safety Hypotheses

Cumulative and persistent AEs listed in IS EN ISO 11979-7:2014 will be compared with the historical control SPE rates. 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

Except otherwise stated, the analysis set for all 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 investigational product, except otherwise stated.

5.3.1 Primary Safety Analyses

5.3.1.1 Adverse Events

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) for either eye, will be tabulated by preferred term with a breakdown by treatment, separately for first and second eyes. An eye with multiple ocular AEs of the same preferred term is 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, separately for first and second implanted eyes.

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, descriptive summaries (counts and percentages) for specific AEs will be presented by IOL group. The one-sided exact 95% lower confidence limit of incidence rates (proportion of eyes with events) observed for each IOL group will be compared to the cumulative and persistent adverse event safety and performance endpoint (SPE) rates. In addition to SPE rates predefined in IS EN ISO 11979-7, the rate of adverse events that may be specifically related to ACRYSOF IQ EDF IOL design features; and any other significant events will be provided. These rates will be accompanied by two-sided exact 95% confidence intervals.

Table 5–1 Adverse Event Safety and Performance Endpoint Rates

Adverse Event	SPE Rate (%)
Cumulative	
Cystoid Macular Oedema	3.0
Hypopyon	0.3
Endophthalmitis[a]	0.1
Lens dislocated from posterior chamber	0.1
Pupillary block	0.1
Retinal detachment	0.3
Secondary surgical intervention[b]	0.8
Persistent	
Corneal stroma oedema	0.3
Cystoid macular oedema	0.5
Iritis	0.3
Raised IOP requiring treatment	0.4

[a]Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.
[b]Excludes posterior capsulotomies.
SPE = Safety and Performance Endpoint
SPE rates are from Table B.2 – Posterior Chamber IOL Adverse Event Rates in IS EN ISO11979-7:2014.

The number and percentage of secondary surgical interventions will be presented with a breakdown by IOL group and implanted eye. In addition, the number and percentage of secondary IOL interventions will be presented with a breakdown by IOL group and implanted eye in each of the following categories:

1) Related to IOL - due to optical properties
2) Related to IOL - not due to optical properties

A listing of secondary IOL interventions and secondary surgical interventions unrelated to IOL will also be presented, respectively.

5.3.1.2 Mesopic Contrast Sensitivity (With and Without Glare)

Contrast sensitivity testing is conducted at 1.5, 3.0, 6.0 and 12.0 CPD for mesopic testing. At each CPD, the presentations consist of a sample grating (represented as 'S' in Table 5–2) followed by 8 gratings of decreasing contrast levels for testing (represented by numbers 1 to 8 in Table 5–2). A subject's performance at each CPD is either an 'S', if only the sample grating is identified, or numbers 1 to 8 (with 8 corresponding to the lowest level of contrast that can be identified). Scores of 'S' are recorded as 0 in the scoring form. If a subject is unable to identify the sample grating at a particular CPD, the data for that CPD is considered missing and will be recorded as a -1 in the scoring form.

The following table presents the manufacturer's recommended log contrast sensitivity norms corresponding to the recorded scores of -1, 0, or 1-8.

Table 5–2 Contrast Sensitivity Values for the CSV-1000E in Log Units

VV		**S**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
EDC	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
CPD										
1.5	0.30	0.60	0.90	1.07	1.22	1.37	1.52	1.67	1.82	1.97
3.0	0.40	0.70	1.00	1.17	1.34	1.49	1.63	1.78	1.93	2.08
6.0	0.61	0.91	1.21	1.38	1.55	1.70	1.84	1.99	2.14	2.29
12.0	0.31	0.61	0.91	1.08	1.25	1.40	1.54	1.69	1.84	1.99
18.0	0.01	0.17	0.47	0.64	0.81	0.96	1.10	1.25	1.40	1.55

Based on scoring instructions from http://www.vectorvision.com/csv1000-norms/ accessed on 15MAY2017
VV = Vector Vision Scoring
EDC = Electronic Data Capture

Analyses of log contrast sensitivity will be performed for each testing condition and spatial frequency. Prior to averaging or any other statistical calculations, contrast threshold values corresponding to 0 - 8 will be converted to log contrast sensitivity values using Table 5–2.

Subjects who score a (-1) i.e. are unable to see a targeted spatial frequency at any available contrast, including that of the reference patch, are assigned the lowest measurable value (corresponding to score of 0 in Table 5–2). The resulting mean will be preceded by the appropriate inequality symbol (<) to indicate that the actual contrast sensitivity is less than the calculated value. Similarly, the resulting standard deviations and any other variability statistics calculated from the data sets containing unmeasurable values (-1) will be preceded by the appropriate inequality symbol (>). The number and percentage of subjects who cannot see any contrast (i.e. scores of -1) will be recorded and tabulated for each spatial frequency to provide a qualitative extent of the bias. Descriptive statistics will include number of eyes, mean, standard deviation, median, minimum, maximum, and additional percentiles (10th, 25th, 75th, and 90th percentiles). Descriptive tables will include a note that the corresponding mean values are biased upward and variability values are biased downward (using < and > symbols).

The 5th percentile of log contrast sensitivity values will be calculated for the control group, then the percentage of eyes in the test group that achieved a log contrast sensitivity lower than this value will be presented.

In addition, for mesopic contrast sensitivity, descriptive summary statistics will be presented by IOL group and 3 mesopic pupil size ranges: [<3.0 mm (small), ≥3.0 mm to ≤4.0 mm (medium), and >4.0 mm (large)].

5.3.2 Secondary Safety Analyses

5.3.2.1 Visual Disturbances Using the QUVID Questionnaire

For the secondary safety endpoint, descriptive summaries (counts and percentages) for the severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire will be presented by IOL group and visit. These rates will be accompanied by two-sided exact 95% confidence intervals.

If QUVID questionnaire generates scores, the cumulative distribution curves showing the percentage of subjects with a given change in their score compared to baseline by IOL group will be presented to help determine whether any observed differences are meaningful.

Counts and percentages of subjects who did not have a given visual disturbance at baseline but developed and present at Visit 4A (120-180d postoperative) will be presented.

5.3.3 Supportive Safety Analyses

5.3.3.1 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole mmHg.

Descriptive summaries (N, mean, median, standard deviation, standard error, minimum and maximum) of observed values and change from baseline values will be presented at each study visit by IOL group, separately for first and second implanted eyes.

A summary table with number and percentages of eyes in each category of IOP change from baseline to last on-treatment IOP assessment and to any 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, 6 to 10 mmHg decrease, 11 to 20 mmHg decrease, 21 to 30 mmHg decrease, and >30 mmHg decrease, separately for first and second implanted eyes. For change to any visit, an eye will be counted only in the category that represents maximum change from baseline across all post-baseline 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.

5.3.3.2 Slit-Lamp Examination

The number and percentage of all abnormal slit lamp examination findings and “worst case” grading for aqueous cells and flare will be tabulated by IOL group and implanted eye.

A listing will be provided which presents all eyes with an abnormality in any slit-lamp parameter at any postoperative visit.

5.3.3.3 Dilated Fundus Examination

The number and percentage of all dilated fundus examination findings or visualization difficulty will be tabulated by IOL group and implanted eye.
A listing will be provided which presents all eyes with abnormality or visualization difficulty in any fundus parameter at any postoperative visit.

5.3.3.4 IOL Observations

IOL observations will be summarized by lens model using descriptive statistics, including frequency (N) and percent of eyes, separately for first and second implanted eyes, at each

scheduled and unscheduled visit where the data were collected. “Other” IOL observations will be summarized and sorted by subject identification (site number, subject number), treatment, and by visit, separately for first and second implanted eyes.

5.3.3.5 IOL Position Change

Descriptive statistics (number and percentages) on eyes with a change from baseline in IOL position category (Tilted, Decentered) will be presented by IOL group, separately for first and second implanted eyes. In addition, a listing of eyes with IOL position change will be provided.

5.3.3.6 Subjective Posterior Capsule Opacification

A frequency and incidence table of the “worst case” posterior capsule opacification (including capsulotomy) will be presented by IOL group, separately for first and second implanted eyes. In addition, the difference in the rate (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided exact 95% confidence interval will be presented.

A listing of eyes with clinically significant posterior capsule opacification, clinically significant posterior capsule opacification requiring YAG or posterior capsulotomy will be presented which includes the posterior capsule opacification or capsulotomy values at all visits.

5.3.3.7 Posterior Capsulotomy

The number and percentage of eyes with posterior capsulotomy will be tabulated with a breakdown by IOL group, separately for first and second implanted eyes. In addition, the difference in the rate (ACRYSOF IQ EDF IOL minus ACRYSOF IQ Monofocal IOL) and the associated two-sided exact 95% confidence interval will be presented.

5.3.3.8 Surgical Problems

Descriptive statistics (number and percentages) on eyes with surgical problems will be presented by IOL group, separately for first and second implanted eyes. In addition, a listing of subjects with surgical problems will be provided.

5.3.3.9 Other Procedures at Surgery

A listing of all other procedures at surgery will be provided.

5.3.3.10 Device Deficiencies

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

5.4 Interim Analysis for Safety

Not Applicable.

6 Sample Size and Power Calculations

Approximately 220 subjects will be randomized to achieve 200 subjects who complete the study.

Effectiveness

The proposed sample size (N = 200; 100 for each IOL group) provides >99% power for the superiority hypothesis test on mean monocular photopic distance corrected intermediate visual acuity (66 cm) when tested at the 0.025 level of significance (one-sided). This assessment assumes:

Difference in DCIVA (66 cm) [logMAR]: Mean (SD) = -0.12 (0.18)

The proposed sample size will provide 84% power for the non-inferiority hypothesis with respect to mean photopic monocular best corrected distance visual acuity when tested at the 0.05 level of significance (one-sided) with a non-inferiority margin of 0.1 logMAR assuming:

Difference in BCDVA [logMAR]: Mean (SD) = 0.04 (0.16)

The proposed sample size provides >99% power for the superiority hypothesis test on mean photopic monocular distance corrected near visual acuity (40 cm) when tested at the 0.025 level of significance (one-sided). This assessment assumes:

Difference in DCNVA (40 cm) [logMAR]: Mean (SD) = -0.12 (0.18)

The proposed sample size will provide 94% power, with α=0.025, 1-sided, to detect a difference of 25% in proportion of subjects who respond “Never” to Q1 of the IOLSAT questionnaire (Overall, in the past 7 days, how often did you need to wear eyeglasses to see?), assuming a 50% rate in the ACRYSOF IQ EDF IOL group.

Adverse Events

For any event where zero incidence is observed in 100 operative eyes with AcrySof® IQ EDF IOL, the one-sided exact 95% upper confidence limit is less than 3%. Thus, with 95% confidence the true adverse event rate is less than 3%.

7 References

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Miettinen OS and Nurminen M. (1985). Comparative analysis of two rates. *Statistics in Medicine*, 4:213-226.

Ratitch, B., & O'Kelly, M. (2011). Implementation of pattern-mixture models using standard SAS/STAT procedures. *Proceedings of PharmaSUG*.

Retzlaff, J. A., Sanders, D. R., & Kraff, M. C. (1990). Development of the SRK/T intraocular lens implant power calculation formula. *Journal of Cataract & Refractive Surgery*, *16*(3), 333-340.

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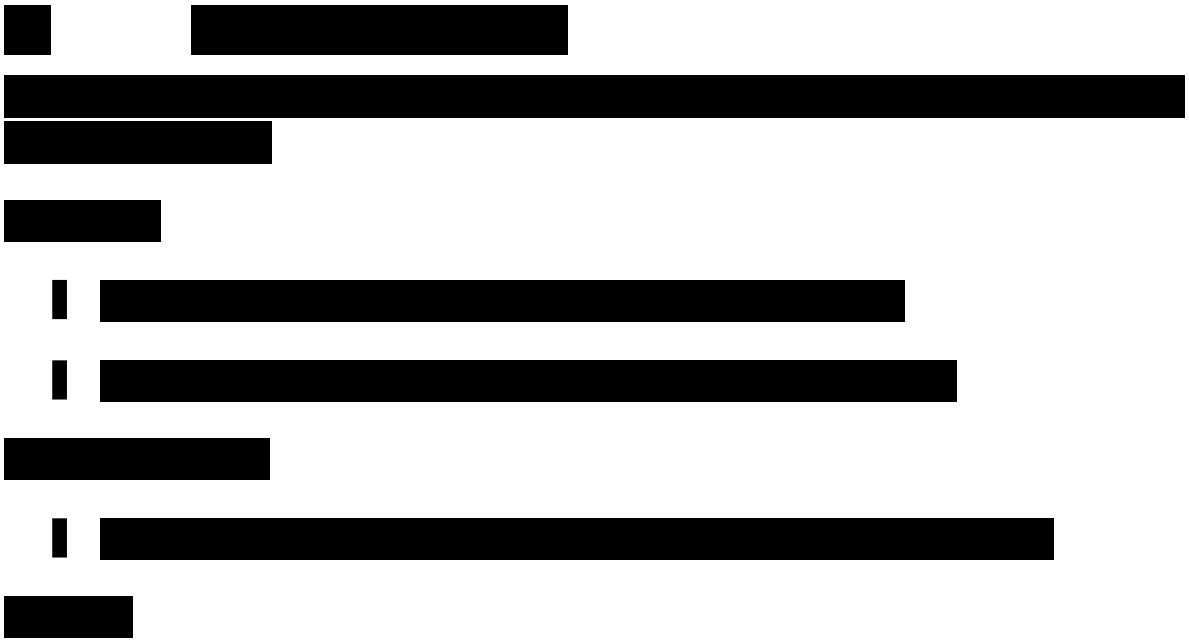
8 Revision History

This is Version 3.0 of Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 4.0 of the study protocol.



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[redacted]

[redacted]

[redacted]

[redacted]

9 Appendix

Table 9-1 Schedule of Visits

	Both Eyes	1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -28-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-14 Post Visit 00	**Visit 00A**[2] 7-14 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-14 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A**[3] 120-180 Days Post Visit 00A	**Early Exit**
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					
Ophthalmic Assessments										
QUVID questionnaire (for visual disturbance)	X							X	X	X
IOLSAT questionnaire (for spectacle need)	X							X	X	X
Anterior Chamber Depth	X									
Axial Length	X									
Keratometry	X									
Predicted Target Residual Refractive Error[5]	X									
Manifest Refraction (4 m)	X			X			X	X	X	X
Distance VA at 4 m										
• Photopic Uncorrected	X		X	X		X	X	X	X[6]	X
• Photopic Corrected	X			X			X	X	X[6]	X
[redacted]									[redacted]	
[redacted]									[redacted]	
Defocus Curve (4 m)									X[6]	
[redacted]	X								X	
Intermediate VA at 66 cm										

	Both Eyes	1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -28-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-14 Post Visit 00	**Visit 00A**[2] 7-14 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-14 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A**[3] 120-180 Days Post Visit 00A	**Early Exit**
• Photopic Uncorrected								X	X[6]	
• Photopic Distance Corrected								X	X[6]	
[redacted]									[redacted]	
[redacted]									[redacted]	
Near VA at 40 cm										
[redacted]								[redacted]	[redacted]	
• Photopic Distance Corrected								X	X[6]	
[redacted]									[redacted]	
[redacted]									[redacted]	
[redacted]									[redacted]	
Contrast Sensitivity										
• Mesopic without Glare									X	
• Mesopic with Glare									X	
Slit Lamp Examination	X		X	X		X	X	X	X	X
Aqueous Signs			X	X		X	X	X	X	X
IOL Observations			X	X		X	X	X	X	X
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
Intraocular Pressure	X		X	X		X	X	X	X	X
Dilated Fundus Exam	X							X	X	X
Fundus Visualization								X	X	X
Surgical Procedure & Assessments										
Cataract Surgery		X			X					
Lens Information		X			X					
Incision Location[7]		X			X					
Final Incision Size[7,8]		X			X					

	Both Eyes	1st Operative Eye			2nd Operative Eye			Both Eyes		
Visit	**Visit 0** Day -28-0 Preoperative	**Visit 00** [1] Day 0 Operative	**Visit 1** Day 1-2 Post Visit 00	**Visit 2** Day 7-14 Post Visit 00	**Visit 00A**[2] 7-14 Days Post Visit 00	**Visit 1A** Day 1-2 Post Visit 00A	**Visit 2A** 7-14 Days Post Visit 00A	**Visit 3A** 30-60 Days Post Visit 00A	**Visit 4A**[3] 120-180 Days Post Visit 00A	**Early Exit**
Problems during Surgery		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
Device Deficiencies		X	X	X	X	X	X	X	X	X

1. Visit 00 (1st eye surgery) must occur within 28 calendar days from Pre-Operative Visit (Visit 0).
2. Visit 00A (2nd eye surgery) must occur between 7 and 14 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) [redacted]
7. Capture in source (not captured in EDC).
8. Only measure in cases with surgical complications.
9. Collected from time of consent onward.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]	[redacted] KIMHY1K	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]