<div align="center">

Short Title:

Statistical Analysis Plan

ILI875-C001

Full Title:

Statistical Analysis Plan
ILI875-C001 / NCT03010254

</div>

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

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Protocol TDOC Number: TDOC-0050634

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Principal Statistician

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.

Executive Summary:

Key Objectives:

The key objective is to demonstrate superiority of the ACRYSOF IQ EDF IOL to ACRYSOF IQ Monofocal IOL in mean monocular photopic distance-corrected intermediate visual acuity (DCIVA) (at 66 cm from spectacle plane) at Month 3/Visit 4A.
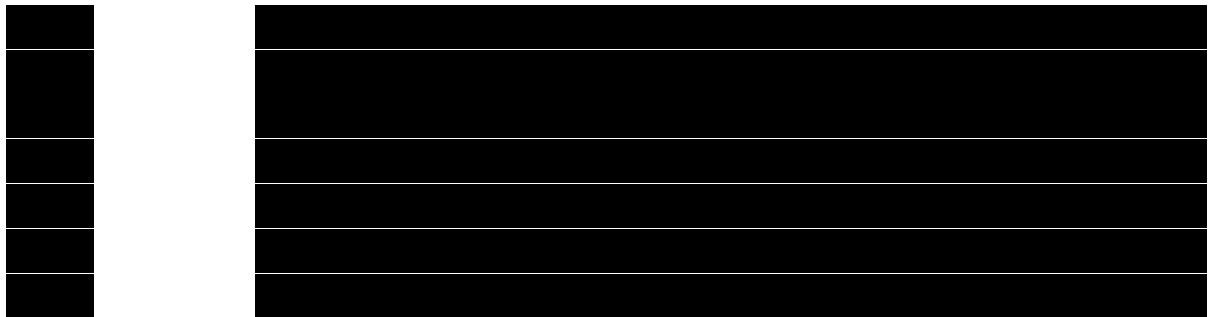
Decision Criteria for Study Success:

The study will be considered a success if, at least, the primary objective is met.

A two-sample t-test comparing the IOL groups for photopic DCIVA at 66 cm will be performed. The primary objective will be demonstrated if the one-sided p-value is less than 0.025.

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

Table of Contents

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

List of Tables

List of Figures

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

1   Study Objectives and Design

1.1   Study Objectives

Primary Objective:

To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic distance-corrected intermediate visual acuity (DCIVA) (at 66 cm from spectacle plane) at Month 3/Visit 4A.

Secondary Objectives:

To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular photopic best corrected distance visual acuity (BCDVA) at Month 3/Visit 4A.

To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL in mean monocular photopic distance corrected near visual acuity (DCNVA) (at 40 cm from spectacle plane) at Month 3/Visit 4A.

To demonstrate that mean monocular defocus curve for ACRYSOF IQ Extended Depth of Focus IOL has a range of defocus at least 0.50 D greater negative range than ACRYSOF IQ Monofocal IOL at 0.20 logMAR (20/32 line) at Month 3/Visit 4A.

To demonstrate that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL in mean monocular mesopic contrast sensitivity with and without glare at Month 6/Visit 5A respectively.

To demonstrate that ACRYSOF IQ EDF IOL is superior to ACRYSOF IQ Monofocal IOL with respect to proportion of subjects who respond "Never" to Q1 and Q3 of the spectacle use questionnaire at Month 6/Visit 5A respectively.

Primary Safety Objective:

To demonstrate that the adverse event rates of ACRYSOF IQ EDF IOL are not worse than Safety Performance Endpoint (SPE) rates as defined in IS EN ISO 11979-7:2014 at Month 3/Visit 4A.

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

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

enrollment into this study. Subjects will be randomly assigned in a 5:4 ratio to receive either Model DFT015 (test article) or Model SN60WF (control article) in both eyes. The first surgical eye is defined as the eye with the worse BCDVA. If the BCDVA is the same in both eyes, the right eye (OD) is identified as the first surgical eye. The second eye implant must occur within 28 days of the first eye implant.

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

The schedule of visits is included as Table 10–1 in the appendix.

The purpose of the study is to demonstrate the safety and performance of the ACRYSOF IQ EDF IOL at Month 3/Visit 4A. After all subjects complete Month 3/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. The study will be continued until all subjects complete Month 6/Visit 5A, at which time the study database will be locked to report longer term safety and performance results.

Figure 1–1   **Study Design**

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective
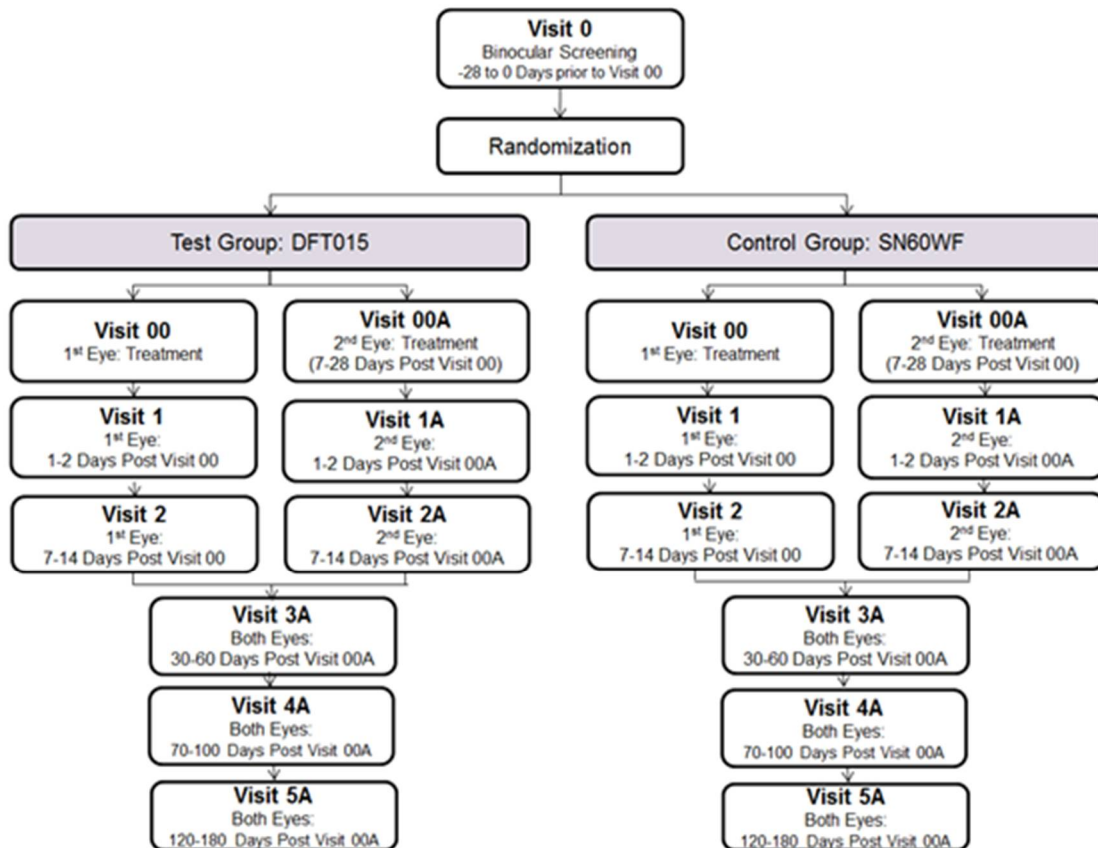
1.3   Randomization

Subjects will be randomized in a 5:4 ratio to receive either ACRYSOF IQ EDF IOL or ACRYSOF IQ Monofocal IOL, respectively.

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 that the subject meets all the eligibility criteria and confirming the subject is eligible for randomization. Randomization must be completed no more than two business days prior to the first operative visit, 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 and all visual acuity testing, which will include best corrected distance visual acuity (BCDVA), ███████████████████████████ distance corrected intermediate visual acuity (DCIVA), ██████████████████████████████, distance corrected near visual acuity (DCNVA), ████████████████████████████ defocus curve testing, and contrast sensitivity will remain masked with regard to treatment assignment until after the final database lock (Month 6/Visit 5A). Alcon and site personnel will not reveal the treatment assignment to study subjects at any time during the study.

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) includes all eyes successfully implanted that had:

- at least 1 postoperative visit;

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

- no macular degeneration at any time; and

- no major protocol violation.

The primary analysis set for effectiveness analyses will be the all-implanted analysis set (AAS) except for Defocus Curve testing which will use the best-case analysis set (BAS) as the primary analysis set.

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).

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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%.

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

4   Effectiveness Analysis Strategy

Overall Type I error will be maintained at the 0.05 level (two-sided) using a sequential testing approach described in Section 4.4.

4.1   Effectiveness Endpoints

Primary Effectiveness

- Monocular photopic DCIVA at 66 cm

Secondary Effectiveness

- Monocular BCDVA at 4 m

- Monocular DCNVA at 40 cm

- Monocular depth of focus assessed by the mean defocus curve

- Monocular mesopic contrast sensitivity at 12 cycles per degree with and without glare respectively

- Proportion of subjects who respond "Never" to Q1 and Q3 of the spectacle use questionnaire respectively

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4.2   Effectiveness Hypotheses

4.2.1   Primary Effectiveness Hypotheses

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{DFT015} \geq \mu_{SN60WF}$$

$$H_A: \mu_{DFT015} < \mu_{SN60WF}$$

where μ_{DFT015} and μ_{SN60WF} refer to the mean monocular photopic distance-corrected intermediate visual acuity (at 66 cm from spectacle plane) for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

4.2.2   Secondary Effectiveness Hypotheses

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

$$H_0: \mu_{DFT015} - \mu_{SN60WF} \geq \Delta$$

$$H_A: \mu_{DFT015} - \mu_{SN60WF} < \Delta$$

where Δ refers to the non-inferiority margin, set at 0.1 logMAR, and μ_{DFT015} and μ_{SN60WF} refer to the mean monocular photopic best-corrected distance visual acuity for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

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

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

$$H_0: \mu_{DFT015} \geq \mu_{SN60WF}$$

$$H_A: \mu_{DFT015} < \mu_{SN60WF}$$

where μ_{DFT015} and μ_{SN60WF} refer to the mean monocular photopic distance-corrected near visual acuity (at 40 cm from spectacle plane) for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

There is no hypothesis test for the third secondary objective (defocus curve).

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

$$H_0: \mu_{DFT015CS} - \mu_{SN60WFCS} \leq \Delta$$

$$H_A: \mu_{DFT015CS} - \mu_{SN60WFCS} > \Delta$$

where Δ refers to the non-inferiority margin set at -0.15 log unit, and $\mu_{DFT015CS}$ and $\mu_{SN60WFCS}$ refer to the mean monocular mesopic contrast sensitivity score (log unit) for the test and control lenses, respectively, in the first implanted eye. Second implanted eye analysis will be supportive.

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

$$H_0: \pi_{DFT015} \leq \pi_{SN60WF}$$
$$H_A: \pi_{DFT015} > \pi_{SN60WF}$$

where π_{DFT015} and π_{SN60WF} refer to the proportion of subjects who responded "Never" for the test and control lenses.

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

For the primary effectiveness analysis, treatment group comparison for photopic distance-corrected intermediate visual acuity will be made and the primary objective will be demonstrated if (one-sided) $P < 0.025$ from a two-sample t-test at Month 3/Visit 4A. The difference in means (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) and the

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

associated two-sided 95% confidence interval will be presented.

The following SAS pseudo code will be used for the primary analysis:

```
proc glm data=visual_acuity;
   where IMPLANT_EYE = 'First';
   class LENS_MODEL;
   model DCIVA4 = 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[1]. The SAS pseudo code 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 site by treatment interaction:

```
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;
```

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

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 pseudo code 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;
```

4.3.2   Secondary Effectiveness Analyses

4.3.2.1   Best Corrected Distance Visual Acuity at 4 m

The statistical model associated with the hypotheses for the first secondary effectiveness analysis will be tested by generating a one-sided 97.5% upper confidence limit based on the difference (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) in means using a two-sample t-test at Month 3/Visit 4A. The upper bound of the one-sided 97.5% confidence limit will be compared to the margin, 0.10 logMAR. If the upper bound is less than the margin, the null hypothesis will be rejected and it will be concluded that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL for best corrected distance visual acuity at 4 m. The SAS pseudo code is identical to that of the primary analysis.

4.3.2.2   Distance Corrected Near Visual Acuity at 40 cm

For the second secondary effectiveness analysis, IOL group comparison for photopic distance corrected near visual acuity will be made and the objective will be demonstrated if (one-sided) $P < 0.025$ from a two-sample t-test at Month 3/Visit 4A. The SAS pseudo code is identical to that of the primary analysis.

4.3.2.3   Depth of Focus

For the third secondary effectiveness analysis (depth of focus), a line plot of the average visual acuity at each defocus level (i.e., defocus curve) will be used to estimate the negative lens induced depth of focus at 0.2 logMAR (20/32 line) at Month 3/Visit 4A. 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 depth of focus between ACRYSOF IQ EDF IOL and ACRYSOF IQ

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

Monofocal IOL will be presented, separately for first implanted eye, second implanted eye and binocular assessments.

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 (20/32 line)-for the first implanted eye, then the third secondary objective will be met.

The depth of focus data (including defocus curves) will be presented by IOL group, three 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.

4.3.2.4   Mesopic Contrast Sensitivity With and Without Glare

The hypotheses for the fourth secondary effectiveness analysis will be tested by generating a one-sided 97.5% lower confidence limit based on the difference in means (ACRYSOF IQ EDF IOL – ACRYSOF IQ Monofocal IOL) using a two-sample t-test. The lower bound of the one-sided 97.5% confidence limit will be compared to the margin, -0.15 log unit. If the lower bound is greater than the margin, the null hypothesis will be rejected and it will be concluded that ACRYSOF IQ EDF IOL is non-inferior to ACRYSOF IQ Monofocal IOL for monocular mesopic contrast sensitivity. Monocular mesopic contrast sensitivity without glare at 12 cycles per degree will be tested followed by monocular mesopic contrast sensitivity with glare at 12 cycles per degree.

Scoring methods for log contrast sensitivity values are described in details in Section 5.3.3.

To assess the quantitative extent of bias resulting from subjects who cannot identify the sample patch, a censored regression model (which is a generalization of the standard Tobit model) [6, 7] will be used to estimate the difference in means and the corresponding interval of the log contrast sensitivity values while accounting for censored observations. The following SAS pseudo codes are shown, as an example, for mesopic contrast sensitivity without glare at 12 CPD measured in the 1st implanted eyes.

```
data mcsdata;
  set mcsdata;
  if      cpd12= -1 then logCS = 0.609999;
  else if cpd12=  0 then logCS = 0.61;
  else if cpd12=  1 then logCS = 0.91;
  else if cpd12=  2 then logCS = 1.08;
  else if cpd12=  3 then logCS = 1.25;
```

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

```
        else if cpd12=  4 then logCS = 1.40;
        else if cpd12=  5 then logCS = 1.54;
        else if cpd12=  6 then logCS = 1.69;
        else if cpd12=  7 then logCS = 1.84;
        else if cpd12=  8 then logCS = 1.99;

        if lens='SN60WF' then IOL = 0;
        else if lens = 'DFT015' then IOL = 1;
    run;

    proc qlim data=csdata(where=(lens='SN60WF' or lens='DFT015'));
        where glare = 'without Glare' and sureye = '1st';
        model logCS = IOL / censored(lb=0.609999);
        ods output ParameterEstimates = param2;
    run;
```

4.3.2.5   Proportion of Subjects Who Respond "Never" to Q1 and Q3 of the Spectacle Use Questionnaire

For the fifth secondary effectiveness endpoint, 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 [5], 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. Response to Q3 of spectacle use questionnaire will be tested followed by response to Q1 of spectacle use questionnaire.

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;
```

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

4.3.3.2   Defocus Curve Evaluation

Descriptive statistics (mean, median, standard deviation, number of eyes/subjects, minimum, maximum, and two-sided 95% confidence intervals) will be provided for the logMAR VA measured on the ETDRS chart at each defocus value (-2.50 D to -0.50 D in 0.50 D increments, -0.25 D to +0.25 D in 0.25 D increments, +0.50 D to +1.50 D in 0.50 D increments) for all eyes/subjects. The mean logMAR VA measured on the ETDRS chart at each defocus value will be displayed graphically for all eyes/subjects, separately for first implanted eye, second implanted eye and binocular assessments. Mean logMAR visual acuity will be plotted versus defocus value, including two-sided 95% confidence intervals and standard deviations, with the amount of defocus along the x-axis and logMAR VA at each defocus point along the y-axis. The defocus tables and plots will be generated overall and by site at Month 3/Visit 4A and Month 6/Visit 5A.

In addition, monocular defocus curves for the first implanted eye and second implanted eye will be presented, by IOL group, for the following three photopic pupil size ranges [<3.0 mm (small), ≥3.0 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)] at Month 3/Visit 4A and Month 6/Visit 5A.

4.3.3.8 Spectacle Use Questionnaire

Response to each question in spectacle use questionnaire will be summarized with descriptive statistics (number and percentages) by IOL group.

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

4.4   Multiplicity Strategy

Overall type I error will be maintained at 0.05 level for the Month 3/Visit 4A (70-100 day post 2nd eye implantation) analyses using the sequential testing approach summarized in the figure below.

Superiority Test	DCIVA (66cm)	Primary
Non-inferiority Test	BCDVA (4m)	Secondary
Superiority Test	DCNVA (40cm)	Secondary
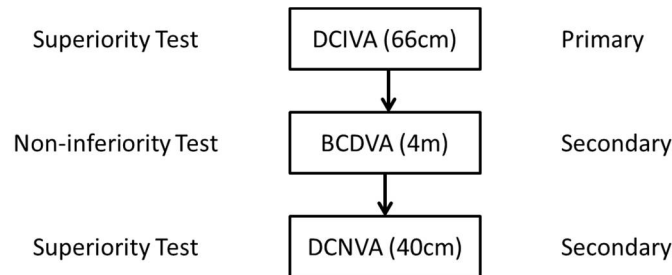
The following primary and secondary effectiveness analyses will be performed on the Month 6/Visit 5A (120-180 day post 2nd eye implantation) data using the sequential testing approach summarized in the figure below if the primary and both secondary null hypotheses are rejected for the Month 3/Visit 4A (70-100 day post 2nd eye implantation) analysis. If any null hypothesis is not rejected, no further hypothesis testing will be performed.

Superiority Test	DCIVA (66cm)	Primary
Non-inferiority Test	BCDVA (4m)	Secondary
Superiority Test	DCNVA (40cm)	Secondary
Non-inferiority Test	Mesopic CS	Secondary
Superiority Test	Spectacle Use	Secondary
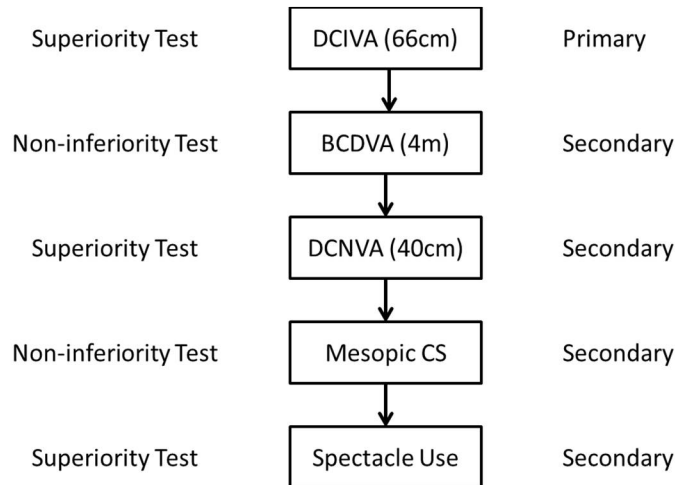
4.5   Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of the primary and secondary visual acuity endpoints will be conducted to assess the consistency of treatment effect across various subgroups.

The consistency of the treatment effect for monocular DCIVA, monocular BCDVA and monocular DCNVA will be assessed descriptively using summary statistics by category of the following subgroup factors:

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

- Age category (<65 vs. ≥65 years)
- 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)

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 from the primary endpoint analysis.

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[4]).

Sensitivity Analysis 1:

A fully conditional specification (FCS) method will be used to impute missing DCIVA 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 pseudo-code with the PROC MI procedure will be used to impute missing DCIVA 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 parameter _imputation_;
run;

/* generate estimates and CIs from multiple imputation */
proc mianalyze data=glm_out1;
  by parameter;
  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 pseudo-code 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 parameter _imputation_;
run;

/* generate estimates and CIs from multiple imputation */
proc mianalyze data=glm_out2;
  by parameter;
  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

The safety assessments are:

- Adverse Events

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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

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   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.   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

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 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.

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5.3.3   Contrast Sensitivity

Contrast sensitivity testing is conducted at ███████████████
███████████████████████   12.0 CPD for mesopic testing. ██████████
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The following table presents the manufacturer's recommended log contrast sensitivity norms corresponding to the recorded scores of -1, 0, or 1-8.

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

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										
12.0	0.31	0.61	0.91	1.08	1.25	1.40	1.54	1.69	1.84	1.99

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

Analyses of log contrast sensitivity will be performed ████████████████████ ██████████ 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 unable to see a targeted spatial frequency at any available contrast, including that of the reference patch (i.e., score of -1 in EDC), are assigned values corresponding to score of -1 in Table 5-2 following manufacturer's recommendation.

Descriptive statistics (mean, median, standard deviation, number of subjects, minimum, maximum, and 95% confidence intervals) will be provided.

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To assess the quantitative extent of bias resulting from subjects who cannot identify the sample patch (score of -1 in EDC), a censored regression model (which is a generalization of the standard Tobit model) [6, 7] will be used to estimate the mean and the standard deviation of the log contrast sensitivity values while accounting for censored observations (i.e., score of -1 in EDC). The following SAS pseudo codes are shown, as an example, for mesopic contrast sensitivity without glare at 12 CPD measured in the 1st implanted eyes.

```
data mcsdata;
  set mcsdata;
  if      cpd12= -1 then logCS = 0.609999;
  else if cpd12=  0 then logCS = 0.61;
  else if cpd12=  1 then logCS = 0.91;
  else if cpd12=  2 then logCS = 1.08;
  else if cpd12=  3 then logCS = 1.25;
  else if cpd12=  4 then logCS = 1.40;
```

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

```
      else if cpd12=  5 then logCS = 1.54;
      else if cpd12=  6 then logCS = 1.69;
      else if cpd12=  7 then logCS = 1.84;
      else if cpd12=  8 then logCS = 1.99;
   run;

   proc qlim data=mcsdata(where=(lens='SN60WF' or lens='DFT015'));
      where glare = 'without Glare' and sureye = '1st';
      by lens;
      model logCS = / censored(lb=0.609999);
      ods output ParameterEstimates = param;
   run;
```

Alcon - Business Use Only Statistical Analysis Plan

Document: TDOC-0053439

Version: 3.0; Most-Recent; Effective; CURRENT

Effective Date: 25-Jun-2018

Printed By:

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Page 29

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5.4   Interim Analysis for Safety

Not Applicable.

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7   Sample Size and Power Calculations

<u>Effectiveness</u>

The proposed sample size (N = 234; 130 Bilateral EDF IOL and 104 Bilateral Monofocal IOL) provides >99% power for the superiority hypothesis test on mean monocular DCIVA (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 provides 74% power for the non-inferiority hypothesis test with respect to mean monocular BCDVA (4 m) when tested at the 0.025 level of significance (one-sided) with a non-inferiority margin of 0.10 logMAR assuming:

- Difference in BCDVA (4 m) [logMAR]: Mean (SD) = 0.04 (0.16)

The proposed sample size provides >99% power for the superiority hypothesis test on mean monocular DCNVA (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 provides 74% power for the non-inferiority hypothesis test with respect to mean monocular mesopic contrast sensitivity value when tested at the 0.025 level of significance (one-sided) with a non-inferiority margin of -0.15 log unit assuming:

- Difference in contrast sensitivity [log unit]: Mean (SD) = -0.02 (0.38)

The expected sample size (N = 131) will provide 84% power, with α=0.025, 1-sided, to detect a difference of 25% in proportion of subjects who respond "Never" to Q1 and Q3 of the spectacles use questionnaire, respectively, assuming

- Proportion of subjects who respond "Never" is 50% in the ACRYSOF IQ EDF IOL group.

Approximately 260 subjects will be randomized to achieve 234 subjects who complete the study, assuming a 10% drop-out rate. It is expected that approximately 131 subjects will respond to spectacle use questionnaire in this study.

<u>Adverse Events</u>

For any event where zero incidence is observed in 130 operative eyes with ACRYSOF IQ EDF IOL, the one-sided exact 95% upper confidence limit is less than 2.3%. Thus, with 95% confidence the true adverse event rate is less than 2.3%.

8   References

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4. Ratitch B, O'Kelly, M. Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures. *Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group)*, SP04, Nashville (2011).

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9   Revision History

This is Version 2.0 of Statistical Analysis Plan for this study. ██████████████████

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Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

Alcon - Business Use Only Statistical Analysis Plan   **Effective Date:** 25-Jun-2018
Document: TDOC-0053439   **Version:** 3.0; Most-Recent; Effective; CURRENT
Status: Effective

10   Appendix

Table 10–1   Schedule of Procedures and Assessments

Visit	Visit 0 Pre-Op	Visit 00: OP[1]	Visit 1	Visit 2	Visit 00A: OP[2]	Visit 1A	Visit 2A	Visit 3A	Visit 4A[3]	Visit 5A[3]	Early Exit
Eye	Both Eyes	1st Eye	1st Eye	1st Eye	2nd Eye	2nd Eye	2nd Eye	Both Eyes	Both Eyes	Both Eyes	
Day Number	Day -28-0	Surgery	Day 1-2	Day 7-14	Surgery	Day 1-2	Day 7-14	Day 30-60	Day 70-100	Day 120-180	N/A
Informed Consent	X										
Demographics	X										
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X			X						
Urine Pregnancy Test[4]	X										
▮		▮									
▮		▮		▮			▮	▮	▮	▮	▮
▮											
Spectacle Use Questionnaire										X	X
Distance VA at 4 m											
• ▮		▮		▮	▮		▮	▮	▮	▮	▮
• Photopic corrected	X			X			X	X	X	X[5]	X
Intermediate VA at 66 cm											
• ▮								▮	▮	▮	
• Photopic Distance Corrected								X	X	X[5]	
Near VA at 40 cm											
• ▮									▮	▮	
• Photopic Distance Corrected									X	X[5]	
Defocus Curve (4 m)									X[5]	X[5]	
Contrast Sensitivity											
• Mesopic without Glare									X	X[5]	
• Mesopic with Glare									X	X[5]	
• ▮									▮	▮	
▮											
▮										▮	
▮											
▮									▮		
Target Residual Refractive Error[6]	X										
▮		▮	▮	▮		▮	▮	▮	▮		
▮								▮	▮		
▮		▮		▮	▮		▮	▮	▮	▮	
Operative Eye		X			X						

Visit	Visit 0 Pre-Op	Visit 00: OP[1]	Visit 1	Visit 2	Visit 00A: OP[2]	Visit 1A	Visit 2A	Visit 3A	Visit 4A[3]	Visit 5A[3]	Early Exit
Eye	Both Eyes	1st Eye	1st Eye	1st Eye	2nd Eye	2nd Eye	2nd Eye	Both Eyes	Both Eyes	Both Eyes	
Day Number	Day -28-0	Surgery	Day 1-2	Day 7-14	Surgery	Day 1-2	Day 7-14	Day 30-60	Day 70-100	Day 120-180	N/A
███████			█		█						
Incision Location[7]		X			X						
Final Incision Size[7]		X			X						
██████████		█			█						
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Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Secondary Surgical Interventions		X	X	X	X	X	X	X	X	X	X
Device Deficiencies		X	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 after a minimum of 7 calendar days and a maximum of 28 calendar days after Visit 00 (1st eye surgery).

[3] If necessary Visits 4A and 5A may be completed over 2 days within a two week period. All visits must be completed within the specified visit window.

[4] In women of child bearing potential only.

[5] Monocular (bilaterally) and binocular testing.

[6] Data is reported in EDC at the surgical visit, but may be collected at a previous visit.

[7] Captured in source. Not collected in EDC.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
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