

**Short Title:**

**Statistical Analysis Plan**

**ILH297-P003 /**

**NCT02691741**

**Full Title:**

**Statistical Analysis Plan**

**ILH297-P003**

**Protocol Title:** Clinical Investigation of Visual Function After Bilateral  
Implantation of Two Presbyopia-Correcting Trifocal IOLs

**Project Number:** A02622

**Protocol TDOC Number:** TDOC-0051465

**Author:**

[REDACTED]

[REDACTED]

**Template Version:** Version 4.0, approved 16MAR2015

**Approvals:** See last page for electronic approvals.

**Job Notes:**

This is the original (Version 1.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 of the study protocol.

## **Executive Summary:**

### **Key Objectives:**

The key objective is to demonstrate non-inferiority of the TFNT00 IOL to the 839MP IOL in mean photopic binocular uncorrected intermediate (60 cm) visual acuity (UCIVA) at Visit 4A (120-180 days post 2<sup>nd</sup> eye implantation).

### **Decision Criteria for Study Success:**

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

A two-sided 90% confidence interval using repeated measures analysis of variance will be generated for the difference in mean photopic binocular uncorrected intermediate (60 cm) visual acuity of TFNT00 IOL group minus 839MP IOL group based on least squares means. Non-inferiority of the TNFT00 IOL will be concluded if the upper bound of the interval is less than the margin, 0.1 logMAR.



4.6 Subgroup Analyses and Effect of Baseline Factors..... 18

4.7 Interim Analysis for Effectiveness ..... 19

5 Safety Analysis Strategy ..... 19

5.1 Safety Assessments ..... 19

5.2 Safety Hypotheses ..... 19

5.3 Statistical Methods for Safety Analyses ..... 20

5.3.1 Adverse Events ..... 20

5.3.2 Device Deficiencies ..... 21

5.3.3 Surgical Problems ..... 21

5.3.4 Intraocular Pressure ..... 21

5.3.5 Slit Lamp Examination ..... 22

5.3.6 IOL Observations ..... 22

5.3.7 IOL Position Change ..... 22

5.3.8 Subjective Posterior Capsule Opacification ..... 22

5.3.9 Posterior Capsulotomy ..... 22

5.3.10 Fundus Visualization ..... 22

5.3.11 Dilated Fundus Examination ..... 23

5.4 Interim Analysis for Safety ..... 23

6 Analysis Strategy for Other Endpoints ..... 23

7 Sample Size and Power Calculations ..... 23

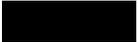
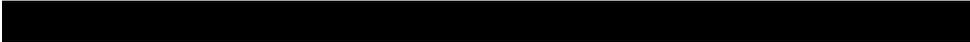
8 References ..... 24

9 Revision History ..... 24

█ [REDACTED] 24

11 Appendix ..... 25

### List of Tables

		15
Table .4-2	Summary of Analysis Strategy for All Effectiveness Endpoints .....	16
Table .11-1	Schedule of Visits .....	25

### List of Figures

Figure .1-1	Study Design .....	7
Figure .4-1	Multiple Testing Strategy .....	18

# 1 Study Objectives and Design

## 1.1 Study Objectives

### *Primary Objective:*

To demonstrate **non-inferiority** of ACRYSOF IQ PanOptix presbyopia-correcting IOL Model TFNT00 to the AT Lisa tri IOL Model 839MP in mean photopic binocular uncorrected **intermediate** (60 cm) visual acuity at Visit 4A

### *Secondary Objectives:*

1. To demonstrate **superiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **intermediate** (60 cm) visual acuity at Visit 4A
2. To demonstrate **non-inferiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **distance** (4 m) visual acuity at Visit 4A
3. To demonstrate **non-inferiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **near** (40 cm) visual acuity at Visit 4A
4. To demonstrate **superiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **near** (40 cm) visual acuity at Visit 4A
5. To demonstrate **superiority** of ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP in mean photopic binocular uncorrected **distance** (4 m) visual acuity at Visit 4A
6. To **characterize** the binocular defocus curve profiles, contrast sensitivity and patient satisfaction with ACRYSOF IQ PanOptix IOL versus the AT LISA tri IOL Model 839MP at Visit 4A

## 1.2 Study Description

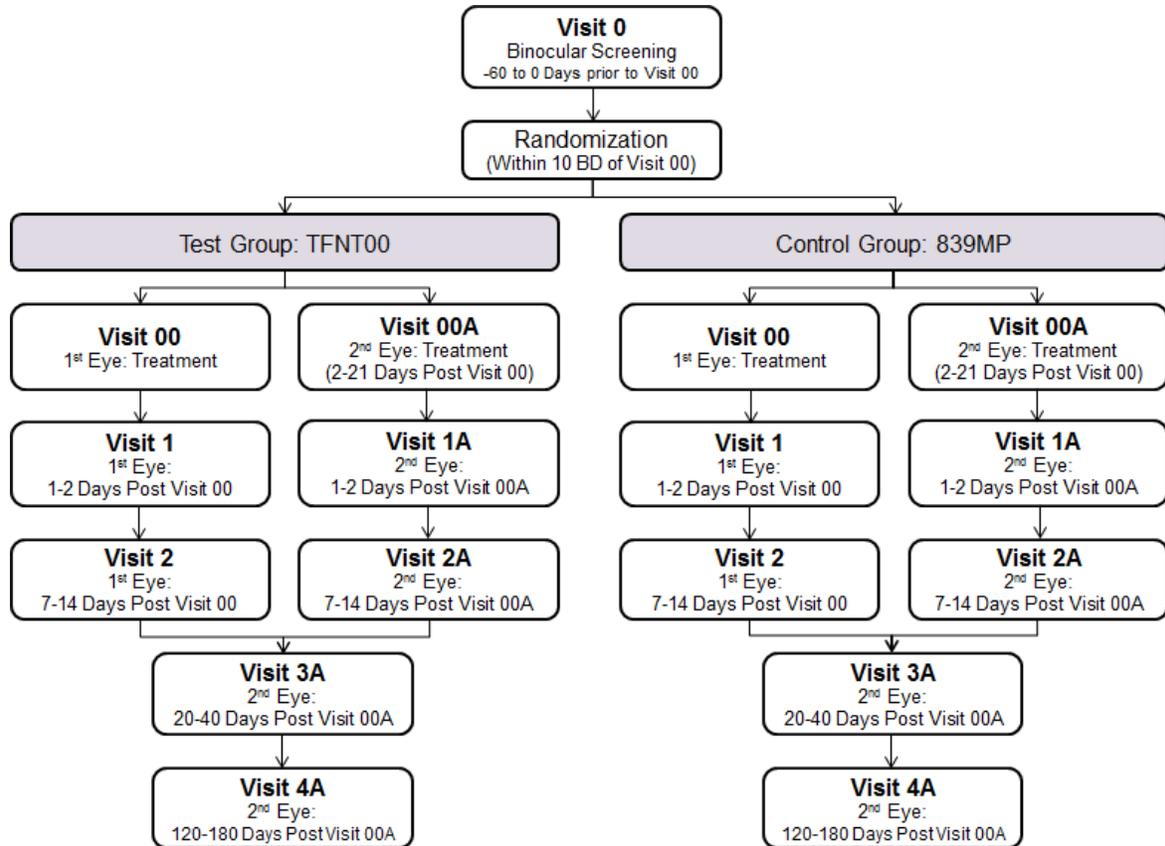
This study is a prospective, multi-center, postmarket trial comparing the visual function of 2 presbyopia-correcting trifocal IOLs following bilateral implantation. Both trifocal IOLs are

commercially available in the countries where the study is being conducted. Enrolled subjects will attend a total of 9 visits (6 postoperative) approximately over a 7 month period.

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

The schedule of visits is included as Table 11-1 in the appendix.

**Figure .1-1 Study Design**



### 1.3 Randomization

Post consent, the EDC system will assign the subject number. Within 10 business days of surgery, qualified subjects will be randomized, in a 1:1 ratio, to either the TFNT00 or 839MP IOL.

Randomization will be stratified by study site to ensure a balance of study treatment allocations within each investigational site.

## 1.4 Masking

In order to reduce bias, the observer (ie, study technician assessing primary and secondary endpoint data) and the subject will be masked to the treatment assignment for the duration of his/her trial participation, and will be provided with his/her permanent implant card upon study exit.

In addition, all Alcon personnel involved with planning, execution and analysis of the study will be masked with regard to treatment assignment while the study is in progress. The exception will be the Brand Lead who will receive unmasked interim analysis results.

## 1.5 Interim Analysis

An interim analysis of the data will be performed when all subjects complete Visit 3A (20-40 days post 2<sup>nd</sup> eye implantation) in order to support the study publication plan of the test articles for near, intermediate and distance visual acuity, contrast sensitivity, defocus curves and adverse events. The interim analysis results will be distributed to a limited audience to limit potential bias in Visit 4A assessments. The clinical trial team with the exception of the Brand Lead will be masked to interim analysis results.

## 2 Analysis Sets

### 2.1 Effectiveness Analysis Sets

The all-implanted analysis set (AAS) will include all eyes with successful test or control article bilateral implantation.

The best-case analysis set (BAS) will include all eyes successfully implanted with the test or control article that had at least one postoperative visit, and with no macular degeneration at any time, and no major protocol deviations. Subjects who become pregnant at any time during the study will also be excluded from the BAS.

The primary analysis set for performance analyses will be the AAS for all performance endpoints, except for binocular defocus and contrast sensitivity for which it will be considered supportive. The BAS will be the primary set for binocular defocus and contrast sensitivity. Additional supportive analyses may be conducted using the BAS or AAS.

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

## **2.2 Safety Analysis Set**

All eyes with attempted test or control article implantation (successful or aborted after contact with the eye) will be considered evaluable for the Safety Set (SS).

The SS will be used for analysis of safety endpoints.

Safety analyses will be conducted using the SS 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 assignment by investigator, 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 primary effectiveness analysis set and the safety analysis set. Subject characteristics and study conduct summaries for the BAS analysis set will be presented if the number of subjects excluded exceeds 10%.

## **4 Effectiveness Analysis Strategy**

A total of six hypothesis tests will be conducted to address the primary and secondary objectives of the study.

The primary (Gate 1 in Figure .4-1) will be a test of non-inferiority, tested at an alpha of 0.05.

The first and second secondary (Gate 2 in Figure .4-1) will be two tests, one of superiority and one of non-inferiority, each tested at an alpha of 0.025 for a family-wise Type I error rate controlled at 0.05. The third secondary will be a test of non-inferiority and the fourth and fifth secondary (Gates 3, 4 and 5 in Figure .4-1) will be tests of superiority at an alpha of 0.05 if both of the first and second secondary null hypotheses are rejected and at an alpha of 0.025

if only one of them is rejected. The sixth secondary objective endpoints [REDACTED] will be summarized descriptively.

## 4.1 Effectiveness Endpoints

### Primary Effectiveness

- Mean binocular uncorrected intermediate VA (60 cm) (For non-inferiority testing)

### Secondary Effectiveness

- Mean binocular uncorrected intermediate VA (60 cm) (For superiority testing)
- Mean binocular uncorrected distance VA (4 m)
- Mean binocular uncorrected near VA (40 cm)
- Mean photopic binocular defocus curve
- Mean photopic without glare binocular distance contrast sensitivity
- Mean photopic with glare binocular distance contrast sensitivity
- Mean mesopic without glare binocular distance contrast sensitivity
- Mean mesopic with glare binocular distance contrast sensitivity
- Subject satisfaction

## 4.2 Effectiveness Hypotheses

### 4.2.1 Primary Effectiveness Hypotheses

The primary objective is to demonstrate non-inferiority of the TFNT00 IOL to the 839MP IOL in mean photopic binocular uncorrected intermediate (60 cm) visual acuity (UCIVA) at Visit 4A.

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{\text{TFNT00VA}} - \mu_{\text{839MPVA}} \geq \Delta$$

$$H_A: \mu_{\text{TFNT00VA}} - \mu_{\text{839MPVA}} < \Delta$$

where,  $\Delta$  refers to the non-inferiority margin, set at 0.1 logMAR, and  $\mu_{\text{TFNT00VA}}$ ,  $\mu_{\text{839MPVA}}$ , refer to the mean binocular high contrast UCIVA for the test and control lenses, respectively.

#### 4.2.2 Secondary Effectiveness Hypotheses

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

$$H_0: \mu_{\text{TFNT00VA}} \geq \mu_{\text{839MPVA}}$$

$$H_A: \mu_{\text{TFNT00VA}} < \mu_{\text{839MPVA}}$$

where  $\mu_{\text{TFNT00VA}}$ ,  $\mu_{\text{839MPVA}}$ , refer to the mean binocular high contrast UCIVA, UCNVA or UCDVA for the test and control lenses, respectively.

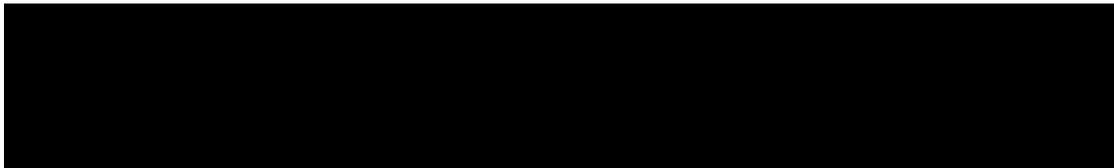
The null and alternative hypotheses for the second and third secondary analysis are:

$$H_0: \mu_{\text{TFNT00VA}} - \mu_{\text{839MPVA}} \geq \Delta$$

$$H_A: \mu_{\text{TFNT00VA}} - \mu_{\text{839MPVA}} < \Delta$$

where  $\Delta$  refers to the non-inferiority margin, set at 0.1 logMAR, and  $\mu_{\text{TFNT00VA}}$ ,  $\mu_{\text{839MPVA}}$ , refer to the mean binocular high contrast UCDVA or UCNVA for the test and control lenses, respectively.

Descriptive statistics will be generated for the sixth secondary objective endpoints. No hypothesis tests will be performed.



## 4.3 Statistical Methods for Effectiveness Analyses

### 4.3.1 Primary Effectiveness Analyses

The primary hypothesis will be tested by generating a two-sided 90% confidence interval based on least squares means using a repeated measures analysis of variance model. The variable 'visit' will be entered as a classification variable to avoid assumptions on the shape of the response. Two-sided 90% confidence intervals for the difference between treatment groups at each visit will be reported with Visit 4A prospectively identified as the primary time point of interest. The upper bound of the two-sided 90% confidence interval will be compared to the margin, 0.1. If the upper bound is less than the margin, the null hypothesis will be rejected and the TFNT00 IOL will be concluded to be non-inferior to the 839MP IOL for UCIVA. SAS pseudo-code for this model follows:

```
proc mixed data=uci_va order=internal noclprint;
class treatment visit subject;
model uci_va = treatment|visit / solution ddfm=kenwardroger;
repeated / type=un sub=subject(treatment);
lsmeans treatment / cl diff alpha=0.1;
run;
```

### 4.3.2 Secondary Effectiveness Analyses

#### 4.3.2.1 Visual Acuity

For the superiority hypothesis tests, treatment group comparison for UCIVA will be made and the first secondary objective will be demonstrated if  $p < 0.025$  from a repeated measures analysis of variance. The variable 'visit' will be entered as a classification variable to avoid assumptions on the shape of the response. Tests will be conducted and two-sided 95% confidence intervals for the difference between treatment groups will be generated at each visit with Visit 4A prospectively identified as the primary time point of interest. For the fourth and fifth secondary objectives, superiority will be demonstrated if  $p < 0.05$  (or  $p < 0.025$ , depending on the gatekeeping) for UCNVA and UCDVA at Visit 4A, respectively. SAS pseudo-code for this model will be the same as for the primary effectiveness analysis with, for the first secondary objective, the change to  $\alpha = 0.05$  and for the fourth and fifth secondary objectives the change to  $\alpha = 0.05$  (if only one of the first or second secondary hypotheses is rejected) and  $\alpha = 0.1$  (if both the first and second secondary hypotheses are rejected). The multiple testing strategy is listed in more detail in Section 4.4.

For the non-inferiority hypothesis test of UCDVA, the second secondary objective, treatment group comparisons will be tested by generating a two-sided 95% confidence interval based on least squares means using a repeated measures analysis of variance model. The variable 'visit' will be entered as a classification variable to avoid assumptions on the shape of the response. Two-sided 95% confidence intervals for the difference between treatment groups at each visit will be reported with Visit 4A prospectively identified as the primary time point of interest. The upper bound of the two-sided 95% confidence interval will be compared to the margin, 0.1. If the upper bound is less than the margin, the null hypothesis will be rejected and the TFNT00 IOL will be concluded to be non-inferior to the 839MP IOL for UCDVA. SAS pseudo-code for this model will be the same as for the primary effectiveness analysis with the change to  $\alpha=0.05$ . The multiple testing strategy is listed in more detail in Section 4.4.

For the non-inferiority hypothesis test of UCNVA, the third secondary objective, treatment group comparisons will be tested by generating a two-sided 90% (or 95%) confidence interval based on least squares means using a repeated measures analysis of variance model. The variable 'visit' will be entered as a classification variable to avoid assumptions on the shape of the response. Two-sided 90% (or 95%) confidence intervals for the difference between treatment groups at each visit will be reported with Visit 4A prospectively identified as the primary time point of interest. The upper bound of the two-sided 90% (or 95%) confidence interval will be compared to the margin, 0.1. If the upper bound is less than the margin, the null hypothesis will be rejected and the TFNT00 IOL will be concluded non-inferior to the 839MP IOL for UCNVA. SAS pseudo-code for this model will be the same as for the primary effectiveness analysis with, for the third secondary objective, the change to  $\alpha=0.05$  (if only one of the first or second secondary hypotheses is rejected) and  $\alpha=0.1$  (if both the first and second secondary hypotheses are rejected). The multiple testing strategy is listed in more detail in Section 4.4.

For the decision of which alpha is appropriate in the SAS code for the third, fourth and fifth secondary objectives, use the following logic:

If the first secondary objective (UCIVA superiority) is met, but the second secondary objective (UCDVA non-inferiority) is not met, use  $\alpha=0.05$ .

If the first secondary objective (UCIVA superiority) is not met, but the second secondary objective (UCDVA non-inferiority) is met, use  $\alpha=0.05$ .

If the first secondary objective (UCIVA superiority) is met and the second secondary objective (UCDVA non-inferiority) is met, use  $\alpha=0.1$ .

If the first secondary objective (UCIVA superiority) is not met and the second secondary

objective (UCDVA non-inferiority) is not met, the other secondary objectives will not be tested.

Summaries of logMAR visual acuity will also include two-sided 90% confidence intervals. A composite visual acuity endpoint comprising binocular uncorrected visual acuity at Distance (4 m) and Near (40 cm), separately for Visits 3A and 4A, will be summarized as a categorical variable with the following categories: 20/20 or better ( $\leq 0.04$  logMAR), 20/25 or better ( $\leq 0.14$  logMAR), 20/32 or better ( $\leq 0.24$  logMAR) and 20/40 or better ( $\leq 0.34$  logMAR). Both binocular uncorrected visual acuities (distance and near) will have to meet the threshold to be counted in a category.

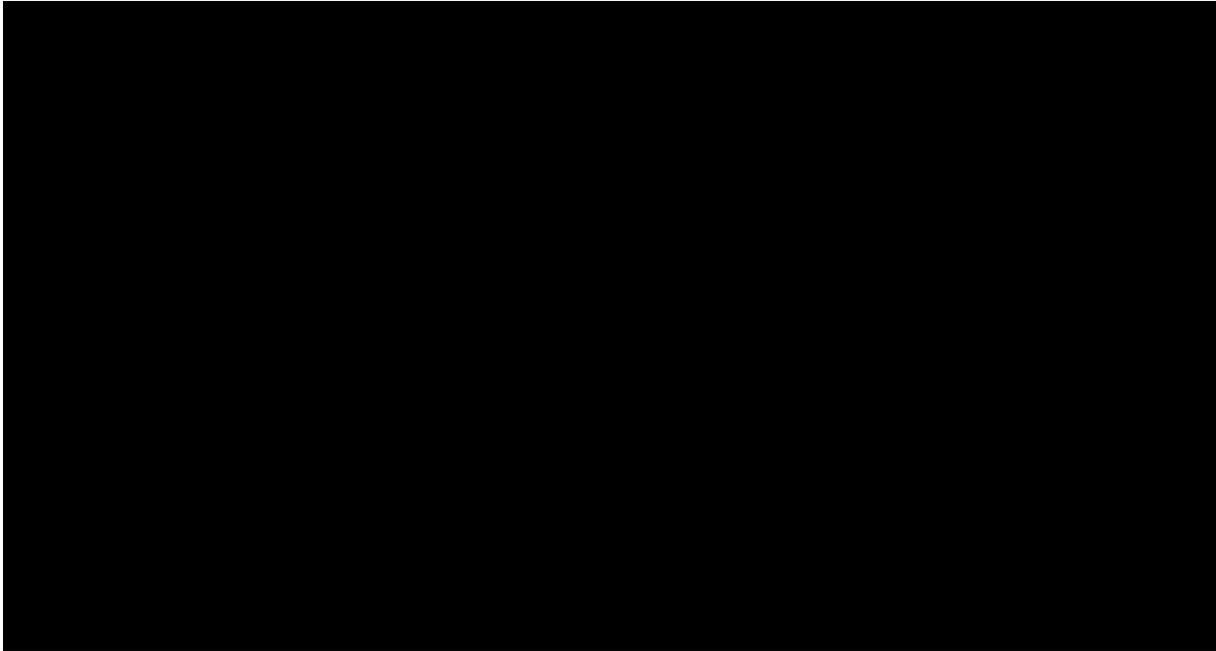
To examine inter-site variation in outcome, forest plots of near, intermediate and distance visual acuity will be produced by plotting the difference in means and associated standard error for each site. Forest plots of near, intermediate and distance visual acuity for the difference in means and two-sided 90% CIs will also be produced.

#### **4.3.2.2 Defocus Curve**

Descriptive statistics (mean, median, standard deviation, number of subjects, minimum, maximum, and two-sided 90% confidence intervals) will be provided for the logMAR VA measured on the ETDRS chart at each defocus value (+0.0 D to -5.0 D in 0.5 D increments) for all subjects. The mean logMAR VA measured on the ETDRS chart at each defocus value will be displayed graphically for all subjects. Mean logMAR visual acuity will be plotted versus defocus value, including two-sided 90% confidence intervals, 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.

#### **4.3.2.3 Contrast Sensitivity**

The following table shows the Contrast Sensitivity logarithmic values to be used in the analysis:



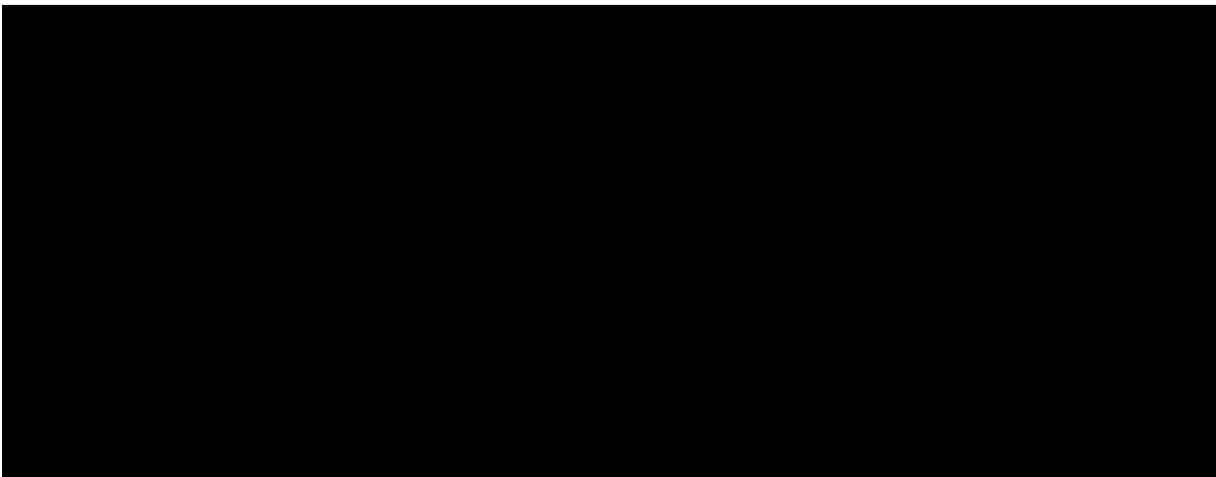
Descriptive statistics (mean, median, standard deviation, number of subjects, minimum, maximum, and 90% confidence intervals) will be provided for binocular distance contrast sensitivity (photopic and mesopic with and without glare).

#### 4.3.2.4 Subject Satisfaction

The subject satisfaction question at Visit 4A is:



Descriptive statistics (numbers and percentages) of subjects reporting each answer will be presented by treatment group.



**Table .4-2 Summary of Analysis Strategy for All Effectiveness Endpoints**

Endpoint	Main vs. Sensitivity Approach <sup>a</sup>	Statistical Method	Analysis Set	Missing Data Approach
<b>Primary</b>				
Mean binocular UCIVA for non-inferiority	M	Repeated measures ANOVA <sup>b</sup>	AAS	Observed data only
Mean binocular UCIVA for non-inferiority	S	Repeated measures ANOVA <sup>b</sup>	BAS	Observed data only
<b>Secondary</b>				
Mean binocular UCIVA for superiority	M	Repeated measures ANOVA <sup>b</sup>	AAS	Observed data only
Mean binocular UCIVA for superiority	S	Repeated measures ANOVA <sup>b</sup>	BAS	Observed data only
Mean binocular UCDVA for non-inferiority	M	Repeated measures ANOVA <sup>b</sup>	AAS	Observed data only
Mean binocular UCDVA for non-inferiority	S	Repeated measures ANOVA <sup>b</sup>	BAS	Observed data only
Mean binocular UCNVA for non-inferiority	M	Repeated measures ANOVA <sup>b</sup>	AAS	Observed data only
Mean binocular UCNVA for non-inferiority	S	Repeated measures ANOVA <sup>b</sup>	BAS	Observed data only
Mean binocular UCNVA for superiority	M	Repeated measures ANOVA <sup>b</sup>	AAS	Observed data only
Mean binocular UCNVA for superiority	S	Repeated measures ANOVA <sup>b</sup>	BAS	Observed data only
Mean binocular UCDVA for superiority	M	Repeated measures ANOVA <sup>b</sup>	AAS	Observed data only
Mean binocular UCDVA for superiority	S	Repeated measures ANOVA <sup>b</sup>	BAS	Observed data only
Forest plots of UCNVA, UCIVA & UCDVA	M	Plot of difference in means with SE and 90% 2-sided CIs	AAS	Observed data only
Forest plots of UCNVA, UCIVA & UCDVA	S	Plot of difference in means with 90% 2-sided CIs	BAS	Observed data only
Mean photopic binocular defocus curve	M	Defocus curves with 90% 2-sided CIs	BAS	Observed data only
Mean photopic binocular defocus curve	S	Defocus curves with 90% 2-sided CIs	AAS	Observed data only
Mean photopic without glare binocular distance contrast sensitivity	M	Continuous descriptive statistics of scores	BAS	Observed data only
Mean photopic with glare binocular distance	M	Continuous descriptive statistics	BAS	Observed data only

contrast sensitivity		of scores		
Mean mesopic without glare binocular distance contrast sensitivity	M	Continuous descriptive statistics of scores	BAS	Observed data only
Mean mesopic with glare binocular distance contrast sensitivity	M	Continuous descriptive statistics of scores	BAS	Observed data only
Mean photopic without glare binocular distance contrast sensitivity	S	Continuous descriptive statistics of scores	AAS	Observed data only
Mean photopic with glare binocular distance contrast sensitivity	S	Continuous descriptive statistics of scores	AAS	Observed data only
Mean mesopic without glare binocular distance contrast sensitivity	S	Continuous descriptive statistics of scores	AAS	Observed data only
Mean mesopic with glare binocular distance contrast sensitivity	S	Continuous descriptive statistics of scores	AAS	Observed data only
Subject satisfaction	M	Categorical descriptive statistics	AAS	Observed data only
Subject satisfaction	S	Categorical descriptive statistics	BAS	Observed data only

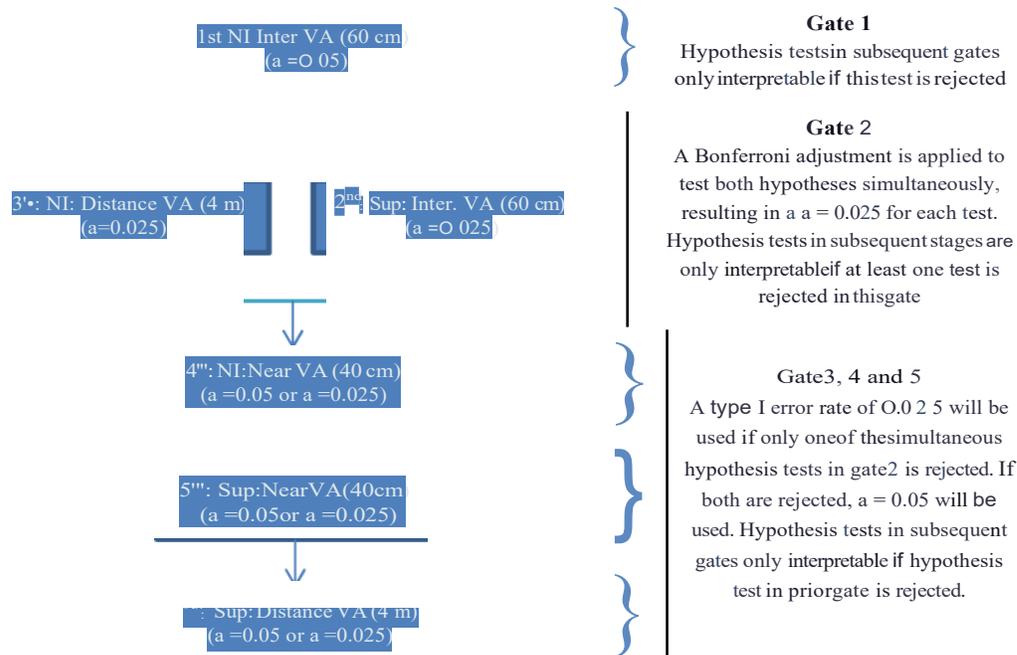


M=Main analysis approach; S=Sensitivity analysis approach  
<sup>b</sup>Repeated measures analysis of variance with terms for treatment and visit

#### 4.4 Multiplicity Strategy

A total of six hypothesis tests will be conducted to address the primary and secondary objectives of the study. All type-I error rates in the following figure are I-sided.

Figure .4-1 Multiple Testing Strategy



#### 4.5 Handling of Missing Data

All data obtained in evaluable subjects will be used in the analysis. No imputation for missing data is planned in the analyses.

#### 4.6 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of the primary endpoint will be conducted to assess the consistency of treatment effect across various subgroups.

The consistency of the treatment effect for binocular UCIVA, binocular UCDVA and binocular UCNVA will be assessed descriptively using summary statistics by category of the following subgroup factors:

- Age category (<65 vs. 65 years)
- Sex (Female, Male)

## **4.7 Interim Analysis for Effectiveness**

An interim analysis will be performed when all subjects complete Visit 3A (20-40 days post 2nd eye implantation) in order to support the study publication plan of the test articles for near, intermediate and distance visual acuity, contrast sensitivity, defocus curves and adverse events.

## **5 Safety Analysis Strategy**

### **5.1 Safety Assessments**

The safety assessments are:

- Adverse events (AEs) including secondary surgical intervention (SSI)
- Device deficiencies (DD)
- Surgical problems
- Intraocular pressure (IOP)
- Slit lamp examination
- IOL observations
- IOL position change
- Subjective posterior capsule opacification (PCO)
- Posterior capsulotomy
- Fundus visualization
- Dilated fundus examination

### **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 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

### 5.3.2 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.

### 5.3.3 Surgical Problems

Descriptive statistics (number and percentages) on eyes with surgical problems will be presented, separately for first and second implanted eyes. In addition, a listing of subjects with surgical problems will be provided. The listing will include the following variables: investigator, subject, age, sex, race, ethnicity, treatment, eye and description of surgical problem.

### 5.3.4 Intraocular Pressure

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

All analyses will be presented by eye (first eye versus second eye).

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 treatment, separately for first and second implanted eyes. A plot of mean change in IOP by study visit and by treatment with error bars representing +/- 1 standard error will be presented, separately for first and second implanted eye. The x-axis will be study visit and the y-axis will be the change in IOP from baseline.

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. The listing will include the following variables: investigator, subject, age, sex, race, ethnicity, treatment, visit, eye, baseline value, value at the visit and a change from baseline value.

### **5.3.5 Slit Lamp Examination**

For each slit-lamp parameter, number and percentages of eyes that experience abnormality at any post-operative visit will be presented, separately for first and second implanted eyes.

A listing will be provided which presents all eyes with an abnormality in any slit-lamp parameter at any post-operative visit. The listing will include all slit-lamp data from all visits with the following variables: treatment, investigator, subject, age, sex, race, ethnicity, visit, eye, parameter, baseline value, and value at the visit.

### **5.3.6 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 (investigator number, subject number), treatment, and by visit, separately for first and second implanted eyes.

### **5.3.7 IOL Position Change**

Descriptive statistics (number and percentages) on eyes with a change from baseline in IOL position category (Tilted, Decentered) will be presented, separately for first and second implanted eyes. In addition, a listing of eyes with IOL position change will be provided. The listing will include the following variables: investigator, subject, age, sex, race, ethnicity, treatment, visit, eye and amount of tilting or decentration.

### **5.3.8 Subjective Posterior Capsule Opacification**

The number and percentage of eyes within each category of subjective posterior capsule opacification will be tabulated with a breakdown by treatment, separately for first and second implanted eyes.

### **5.3.9 Posterior Capsulotomy**

The number and percentage of eyes with posterior capsulotomy will be tabulated with a breakdown by treatment, separately for first and second implanted eyes.

### **5.3.10 Fundus Visualization**

The fundus visualization will be performed to document whether the lens causes any difficulty in viewing and/or examining the retina or posterior segment, or affects the

surgeon's ability to administer vitreal/retinal treatments, as compared to experience with monofocal IOLs.

Descriptive statistics (number and percentages) on eyes with difficulty in viewing and/or examining the retina or posterior segment will be presented, separately for first and second implanted eyes. In addition, a listing of eyes with fundus visualization difficulty will be provided. The listing will include the following variables: investigator, subject, age, sex, race, ethnicity, treatment, visit, eye and type of difficulty.

### **5.3.11 Dilated Fundus Examination**

For each dilated fundus parameter, number and percentages of eyes that experience abnormality at any post-operative visit will be presented, separately for first and second implanted eyes.

A listing will be provided which presents all eyes with abnormality in any fundus parameter at any post-operative visit. The listing will include the following variables: investigator, subject, age, sex, race, ethnicity, treatment, visit, eye, baseline value and value at the visit.

## **5.4 Interim Analysis for Safety**

An interim analysis will be performed when all subjects complete Visit 3A (20-40 days post 2<sup>nd</sup> eye implantation) in order to support the study publication plan of the test articles for adverse events.

Adverse events analyses as described in Section 5.3.1 will be generated for the interim analysis results.

## **6 Analysis Strategy for Other Endpoints**

Not applicable.

## **7 Sample Size and Power Calculations**

The multiplicity adjustment strategy is outlined in Figure .4-1. Sample size estimations are based on the minimum sample size needed to achieve 90% power for all hypothesis tests. A type I error rate of 2.5%, one-sided, is used for calculations to account for simultaneous testing in Gate 2 (see Figure .4-1).

Assuming a dropout rate of 5%, approximately 160 subjects will be bilaterally implanted in 1:1 allocation ratio (test: control) to achieve at least 152 subjects who complete the study. With 152 subjects (76 per group) there is 98% probability that an upper one-sided 97.5%

confidence limit on the difference (test-control) in visual acuity will be less than 0.1 logMAR, assuming the mean difference of 0.0 logMAR and a common standard deviation of 0.16 logMAR, the maximum observed for binocular uncorrected distance, intermediate and near visual acuity in a previous Alcon study (C-06-40, ReSTOR +3.0 D IOL).

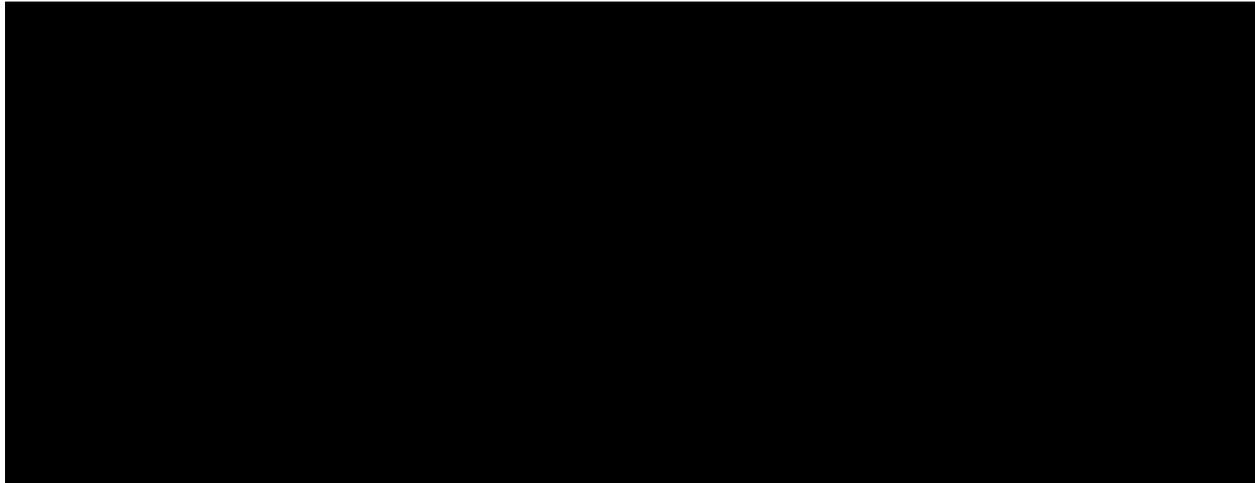
Also, with 76 subjects per group, there is more than 90% power to detect a difference of 0.09 logMAR (4.5 letters) between means in a two sample t-test conducted at a 2.5% chance of a Type I error and assuming a standard deviation of 0.16 logMAR for binocular uncorrected distance, intermediate and near visual acuity.

## **8 References**

Not applicable.

## **9 Revision History**

This is the original (Version 1.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 of the study protocol.



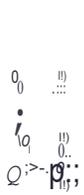
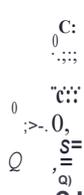
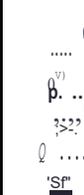
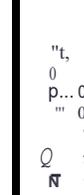
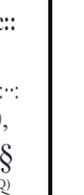
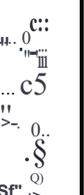
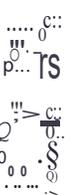
11 Appendix

Table .11-1 Schedule of Visits

Activity	Bin-ocular	1 <sup>st</sup> Eye			2 <sup>nd</sup> Eye			Binocular		Mon-ocular
	Visit 0	Visit 00	Visit 1	Visit 2	Visit 00A	Visit 1A	Visit 2A	Visit 3A	Visit 4A <sup>1</sup>	UNSV <sup>2</sup>
	Day -60 to 0 Preoperative	Day 0 1 <sup>st</sup> Eye Implantation	1-2 Day Post 1 <sup>st</sup> Eye Implantation	7-14 Days Post 1 <sup>st</sup> Eye Implantation	2-21 Days Post Visit 00 2 <sup>nd</sup> Eye Implantation	1-2 Day Post 2 <sup>nd</sup> Eye Implantation	7-14 Days Post 2 <sup>nd</sup> Eye Implantation	20-40 Days Post 2 <sup>nd</sup> Eye Implantation	120-180 Days Post 2 <sup>nd</sup> Eye Implantation	N/A
Informed Consent	X									
Demographics	X									
Medical History	X									
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test <sup>3,4</sup>	X									
Inclusion/Exclusion	X	X			X					
Randomization <sup>5</sup>		X								
Surgery/Treatment		X			X					
Report Implanted Lens Model		X			X					

Activity	Binocular	1 <sup>st</sup> Eye			2 <sup>nd</sup> Eye			Binocular		UNSV <sup>2</sup>
	Visit 0	Visit 00	Visit 1	Visit 2	Visit 00A	Visit 1A	Visit 2A	Visit 3A	Visit 4A <sup>1</sup>	
Surgical Report (Including: lens power, implant success, target refractive error <sup>6</sup> and success of implantation)		X				X				
Problems During Surgery		X				X				
Other Surgical Procedures		X				X				
Patient Satisfaction									X	
Distance VA (4 m)										
• Monocular Uncorrected										X



	Bin-ocular	1 <sup>st</sup> Eye			2 <sup>nd</sup> Eye			Binocular		Mon-ocular
	Visit 0	Visit 00	Visit 1	Visit 2	Visit 00A	Visit 1A	Visit 2A	Visit 3A	Visit 4A <sup>1</sup>	UNSV <sup>2</sup>
Acuity										
Contrast Sensitivity (Binocular)										
<ul style="list-style-type: none"> <li>Mesopic without Glare</li> </ul>								X	X	
<ul style="list-style-type: none"> <li>Mesopic with Glare</li> </ul>								X	X	
<ul style="list-style-type: none"> <li>Photopic without Glare</li> </ul>								X	X	
<ul style="list-style-type: none"> <li>Photopic with Glare</li> </ul>								X	X	
Slit-Lamp Examination (Including IOL Observations)	X		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 (Repeat if performed)			X	X		X	X	X	X	X
Fundus Visualization								X	X	

Printed By:

Print Date:

Activity	Bin-ocular	1 <sup>st</sup> Eye			2 <sup>nd</sup> Eye			Binocular		Mon-ocular
	Visit 0	Visit 00	Visit 1	Visit 2	Visit 00A	Visit 1A	Visit 2A	Visit 3A	Visit 4A <sup>1</sup>	UNSV <sup>2</sup>
	Day -60 to 0 Preoperative	Day 0 1 <sup>st</sup> Eye Implantation	1-2 Day Post 1 <sup>st</sup> Eye Implantation	7-14 Days Post 1 <sup>st</sup> Eye Implantation	2-21 Days Post Visit 00 2 <sup>nd</sup> Eye Implantation	1-2 Day Post 2 <sup>nd</sup> Eye Implantation	7-14 Days Post 2 <sup>nd</sup> Eye Implantation	20-40 Days Post 2 <sup>nd</sup> Eye Implantation	120-180 Days Post 2 <sup>nd</sup> Eye Implantation	N/A
Dilated Fundus Examination	X							X	X	X
IOP	X		X	X		X	X	X	X	X
Adverse Events (Including SSI)	X	X	X	X	X	X	X	X	X	X
Device Deficiencies		X	X	X	X	X	X	X	X	X

<sup>1</sup> If a subject exits early, the Visit 4A procedures should be performed at the last available visit, if at all possible.

<sup>2</sup> UNSV assessments listed are recommended. Only complete assessments required per the PI medical judgment.

<sup>3</sup> Women of child-bearing potential only

<sup>5</sup> Within 10 business days of treatment (Visit 00).

<sup>6</sup> Data is reported in EDC at the surgical visit, but may be collected at a previous visit.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
07/11/2016 14:38:01	██████████ ██████████	██████████
07/12/2016 13:26:33	██████████ ██████████	██████████
07/12/2016 18:52:23	██████████ ██████████	██████████
07/12/2016 20:51:37	██████████ ██████████	██