

**Short Title:**

**Statistical Analysis Plan**

**ILH297-C001 /**

**NCT03280108**

**Full Title:**

**Statistical Analysis Plan**

**ILH297-C001**

**Protocol Title:** Clinical Investigation of AcrySof® PanOptix™ IOL Model TFNT00

**Project Number:** A10875

**Protocol TDOC Number:** TDOC-0053702

**Author:**

[REDACTED]

[REDACTED]

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

**Job Notes:**

This is the second revision (Version 3.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 4.0 of the study protocol. At the time of revision, 250 subjects enrolled in this study.

[REDACTED]

## **Executive Summary:**

### Key Objectives:

The objective of this study is to compare the visual outcomes of the AcrySof PanOptix IOL Model TFNT00 to that of the AcrySof Monofocal IOL Model SN60AT.

The primary effectiveness objectives are to demonstrate comparable distance vision (4 m), as well as superior near vision (40 cm), of the AcrySof PanOptix IOL Model TFNT00 compared to the AcrySof Monofocal IOL Model SN60AT. Secondary effectiveness objectives are to demonstrate superiority of the AcrySof PanOptix IOL Model TFNT00 compared to the AcrySof Monofocal IOL Model SN60AT, in intermediate vision (66 cm) and in the overall need to wear eyeglasses to see.

The primary safety objectives are to estimate the cumulative rate of secondary surgical interventions related to the optical properties of the IOL and to evaluate the mean contrast sensitivity with and without glare for mesopic and photopic conditions. The secondary safety objective is to estimate the rates of severe and most bothersome visual disturbances as reported by the subject using a questionnaire. The third safety objective is to estimate rates of cumulative and persistent Adverse Events in first eyes in comparison to IS EN ISO 11979-7:2014 Safety and Performance Endpoint Rates.









### Decision Criteria for Study Success:

Primary effectiveness will be considered supported if AcrySof PanOptix IOL Model TFNT00 demonstrates non-inferior distance vision and superior near vision when compared to the AcrySof Monofocal IOL Model SN60AT.

The non-inferiority hypothesis will be considered supported if the upper 95% confidence limit on the difference between the two groups is less than the non-inferiority margin of 0.10 logMAR.

The superiority hypothesis will be considered supported if the upper 97.5% confidence limit on the difference between the two groups is less than 0.0 logMAR.

### Table of Contents

Statistical Analysis Plan ILH297-C001 .....	1
Table of Contents .....	3
List of Tables.....	5
1 Study Objectives and Design.....	6
1.1 Study Objectives.....	6
1.2 Study Description .....	7
1.3 Randomization.....	7
1.4 Masking .....	8
1.5 Interim Analysis.....	8
2 Analysis Sets.....	8
2.1 Effectiveness Analysis Sets .....	8
2.2 Safety Analysis Set .....	9
2.3 Pharmacokinetic Analysis Set .....	9
3 Subject Characteristics and Study Conduct Summaries.....	9
4 Effectiveness Analysis Strategy.....	9
4.1 Effectiveness Endpoints .....	9
4.2 Effectiveness Hypotheses.....	10
4.2.1 Primary Effectiveness Hypotheses .....	10
4.2.2 Secondary Effectiveness Hypotheses .....	10
 .....	11
4.3 Statistical Methods for Effectiveness Analyses.....	11
4.3.1 Primary Effectiveness Analyses .....	11
4.3.2 Secondary Effectiveness Analyses .....	12
4.3.2.1 Distance Corrected Visual Acuity at Intermediate (66 cm) .....	12
4.3.2.2 IOLSAT Questionnaire .....	13
 .....	13
 .....	13
 .....	14
 .....	14
 .....	14
 .....	14
 .....	14

4.4 Multiplicity Strategy..... 15

4.5 Handling of Missing Data ..... 15

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

4.6.1 Subgroup Descriptive Statistics..... 18

4.6.2 Propensity Score Analysis ..... 18

4.7 Interim Analysis for Efficacy ..... 19

5 Safety Analysis Strategy..... 20

5.1 Safety Endpoints..... 20

5.2 Safety Hypotheses ..... 21

5.3 Statistical Methods for Safety Analyses ..... 21

5.3.1 Secondary Surgical Interventions..... 21

5.3.2 Binocular Distance Contrast Sensitivity..... 22

5.3.3 Visual Disturbances ..... 23

5.3.4 Adverse Events..... 23

5.3.5 Intraocular Pressure ..... 25

5.3.6 Slit Lamp Observations ..... 26

5.3.7 Dilated Fundus Observations ..... 26

5.3.8 Fundus Visualization ..... 26

5.3.9 Device Deficiencies..... 26

5.3.10 IOL Observations..... 26

5.3.11 IOL Position Change ..... 26

5.3.12 Subjective Posterior Capsule Opacification ..... 27

5.3.13 Posterior Capsulotomies..... 27

5.3.14 Surgical Problems..... 27

█ █ 27

5.4 Interim Analysis for Safety..... 27

6 Pharmacokinetic Analysis Strategy ..... 28

7 Sample Size and Power Calculations ..... 28

8 References..... 29

9 Revision History ..... 29

### List of Tables

Table 1-1	Study Design.....	7
Table 5-1	Contrast Sensitivity Values for the CSV-1000E in Log Units.....	22
Table 5-2	Adverse Event Safety and Performance Endpoint Rates.....	24

# 1 Study Objectives and Design

## 1.1 Study Objectives

### *Effectiveness Objectives*

The co-primary effectiveness objectives are to:

- Demonstrate non-inferiority of AcrySof IQ PanOptix IOL Model TFNT00 compared to the concurrent control AcrySof Monofocal IOL Model SN60AT in mean photopic monocular best corrected distance visual acuity (4 m) for the first operative eye at month 6 (Visit 4A).
- Demonstrate superiority of AcrySof IQ PanOptix IOL Model TFNT00 compared to the concurrent control AcrySof Monofocal IOL Model SN60AT in mean photopic monocular distance corrected visual acuity at near (40 cm) for the first operative eye at month 6 (Visit 4A).

The secondary effectiveness objectives are to:

- First secondary: Demonstrate superiority of AcrySof IQ PanOptix IOL Model TFNT00 compared to the concurrent control AcrySof Monofocal IOL Model SN60AT in mean photopic monocular distance corrected visual acuity at intermediate (66 cm) for the first operative eye at month 6 (Visit 4A).
- Second secondary: Demonstrate superiority of AcrySof IQ PanOptix IOL Model TFNT00 compared to the concurrent control AcrySof Monofocal IOL Model SN60AT 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?) at month 6 (Visit 4A).

### *Safety Objectives*

The co-primary safety objectives are to:

- Estimate the cumulative rate of secondary surgical interventions (SSIs) related to the optical properties of the IOL for first operative eye up to month 6 (Visit 4A).
- Evaluate the mean binocular contrast sensitivity with and without glare for photopic and mesopic conditions at month 6 (Visit 4A).

The secondary safety objective is to:

- Estimate rates of severe and most bothersome (separately) visual disturbances as reported by the subjects using a questionnaire (QUVID) at month 6 (Visit 4A).

The third safety objective is to:

- Evaluate rates of cumulative and persistent Adverse Events in first eyes at 6 months (Visit 4A) in comparison to IS EN ISO 11979-7:2014 Safety and Performance Endpoint grid rates.

## 1.2 Study Description

This study is a prospective, multi-center, non-randomized, vision assessor-masked, parallel group confirmatory trial. It compares an investigational trifocal IOL and a commercially available monofocal IOL. Approximately 125 subjects will be implanted bilaterally with the investigational lens and approximately 125 subjects will be implanted bilaterally with the control lens. Potential subjects will be screened for enrollment into the trial. Those qualifying will attend a total of 10 visits (7 visits occur postoperatively) over a 7 month period.

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

The schedule of visits is presented in Section 6 of the protocol.

**Table 1-1 Study Design**

Time From Implantation	1st Eye	2nd Eye
-30 to 0 days pre-operatively	Visit 0 (monocular [1st and 2nd eye] and binocular)	
Operative (IOL implantation)	Visit 00	Visit 00A*
1 - 2 days post-operatively	Visit 1 (monocular)	Visit 1A (monocular)
7 - 14 days post-operatively	Visit 2 (monocular)	Visit 2A (monocular)
30 - 60 days post-operatively	Visit 3 (monocular)	Visit 3A (monocular)
120 - 180 days post-operatively (after 2nd eye implantation)	Visit 4A** (monocular [1st and 2nd eye] and binocular)	

\*NOTE: IOL implantation in the second eye is intended to occur between 7 and 30 days after IOL implantation in the first eye.

## 1.3 Randomization

Not applicable. This is a non-randomized study.

## 1.4 Masking

Site personnel performing [REDACTED] all visual acuity assessments [REDACTED] [REDACTED] and all contrast sensitivity assessments will be masked with regard to treatment assignment until after the final database lock (Visit 4A). The surgeons and subjects will not be masked in this study.

## 1.5 Interim Analysis

No interim analyses are planned for this study.

## 2 Analysis Sets

All monocular measures from eyes implanted with a non-study lens and binocular measures assessed in subjects with at least one non-study IOL implant will be excluded from all analysis sets. Treatment assignments for final analysis will be based on the lens implanted.

Although all sites are expected to contribute both test and control subjects, due to the non-randomized nature of the study it is possible that a site may enroll all subjects in one group. Such sites, and possibly additional sites with low enrollment, will be combined into one pseudo site to ensure that at least two subjects are in each IOL group to avoid estimation issues with the use of mixed effects models. Sites will not be combined for all other descriptive effectiveness and safety summaries

### 2.1 Effectiveness Analysis Sets

The All-Implanted Analysis Set (AAS) includes all eyes with successful IOL implantation with at least one post-operative visit and will be the primary analysis set for all effectiveness analyses except [REDACTED] [REDACTED] [REDACTED]

The Best-Case Analysis Set (BAS) will be the primary analysis set for [REDACTED] and contrast sensitivity, and includes all eyes successfully implanted that had:

- at least 1 post-operative visit;
- no preoperative ocular pathology;
- no macular degeneration detected at any time; and
- no major protocol deviations.



## 2.2 Safety Analysis Set

The Safety Analysis Set (SAS) will include all eyes with attempted IOL implantation (successful or aborted after contact with the eye). The SAS will be the primary set for all safety analyses except contrast sensitivity.

## 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 an accountability table (similar to Table A.1 in IS EN ISO 11979-7:2014), demographics (including age, gender, race, ethnicity) and baseline characteristics (including axial length, anterior chamber depth, lens thickness) tables, summary of screen failures by reason, and listing of subjects excluded from 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/eyes, minimum, and maximum for continuous data. Tables will be presented by IOL group and overall.

Subject characteristics and study conduct summaries will be presented for the all-implanted analysis set, the best-case analysis set and the safety analysis set.

## 4 Effectiveness Analysis Strategy

### 4.1 Effectiveness Endpoints

Primary and secondary endpoints are listed below. All endpoints are based on assessments at Visit 4A and all visual acuity endpoints are assessed in photopic conditions.

#### *Primary Effectiveness*

- Mean monocular best corrected distance visual acuity (4 m) (first operative eye)
- Mean monocular distance corrected visual acuity at near (40 cm) (first operative eye)

#### *Secondary Effectiveness*

- Mean monocular distance corrected visual acuity at intermediate (66 cm) (first operative eye)
- Proportion of subjects who respond “Never” to Q1 of the IOLSAT questionnaire.

## 4.2 Effectiveness Hypotheses

### 4.2.1 Primary Effectiveness Hypotheses

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

$$H_0: \mu_{TFNT00\_VA} - \mu_{SN60AT\_VA} \geq \Delta$$

$$H_A: \mu_{TFNT00\_VA} - \mu_{SN60AT\_VA} < \Delta$$

Where,  $\Delta$  refers to the non-inferiority margin, set at 0.10 logMAR, and  $\mu_{TFNT00\_VA}$  and  $\mu_{SN60AT\_VA}$  refer to the population mean monocular best corrected distance visual acuity (4 m) for the test and control lenses, respectively, in the first operative eye at month 6.

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

$$H_0: \mu_{TFNT00\_VA} \geq \mu_{SN60AT\_VA}$$

$$H_A: \mu_{TFNT00\_VA} < \mu_{SN60AT\_VA}$$

Where,  $\mu_{TFNT00\_VA}$  and  $\mu_{SN60AT\_VA}$  refer to the population mean monocular distance corrected visual acuity at near (40 cm) for the test and control lenses, respectively, in the first operative eye at month 6.

### 4.2.2 Secondary Effectiveness Hypotheses

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

$$H_0: \mu_{TFNT00\_VA} \geq \mu_{SN60AT\_VA}$$

$$H_A: \mu_{TFNT00\_VA} < \mu_{SN60AT\_VA}$$

Where,  $\mu_{TFNT00\_VA}$  and  $\mu_{SN60AT\_VA}$  refer to the population mean monocular distance corrected visual acuity at intermediate (66 cm) for the test and control lenses, respectively, in the first operative eye at month 6.

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

$$H_0: \pi_{TFNT00\_IOLSAT} \leq \pi_{SN60AT\_IOLSAT}$$

$$H_A: \pi_{TFNT00\_IOLSAT} > \pi_{SN60AT\_IOLSAT}$$

Where,  $\pi_{TFNT00\_IOLSAT}$  and  $\pi_{SN60AT\_IOLSAT}$ , refer to the population proportion of subjects who respond “Never” to Question 1 of the IOLSAT questionnaire at 6 months for the test and control lenses, respectively.

### 4.3 Statistical Methods for Effectiveness Analyses

A total of four hypothesis tests will be conducted to address the co-primary and secondary objectives of the study. To account for multiplicity, the hypotheses will be tested in sequence, two co-primaries, followed by the first secondary hypothesis, followed by the second secondary hypothesis. The primary effectiveness objective is considered met only if both co-primary hypotheses are met. The type I error for the non-inferiority test is 5% (1-sided) and for the superiority test is 2.5% (1-sided). Each of the secondary hypotheses will be tested at 2.5% (1-sided).

Analysis of the co-primary and first secondary endpoints will begin with a model selection step in an effort to select the most parsimonious model. Two mixed effects models, the first with a fixed effect for treatment and random effect for site, and the second with a fixed effect for treatment and random effects for site and treatment by site interaction, will be fit to the first co-primary endpoint (best corrected distance visual acuity). The two models will be compared using Bayesian information criterion (BIC) and the model with lower BIC will be employed for analysis of all three aforementioned endpoints<sup>[1, 2]</sup>.

#### 4.3.1 Primary Effectiveness Analyses

Least Squares Means (LSMEANS) from the mixed effects model chosen during the model selection step will be employed to estimate the difference in means (AcrySof IQ PanOptix IOL Model TFNT00 minus AcrySof Monofocal IOL Model SN60AT) and the associated 90% (two-sided) confidence interval for the non-inferiority test and 95% (two-sided) confidence interval for the superiority test.

The non-inferiority hypothesis (first co-primary) will be deemed supported if the upper 95% confidence limit is less than the non-inferiority margin of 0.10 logMAR.

The superiority hypothesis (second co-primary) will be deemed supported if the upper 97.5% confidence limit is less than 0.0 logMAR.

SAS pseudo code for the above models is provided below.

```
proc mixed data=visual_acuity;
  where OPERATIVE_EYE = 'First' AND VISIT='VISIT4A';
  class LENS_MODEL SITE;
  model VA = LENS_MODEL /DDFM = satterth;
  random SITE SITE*LENS_MODEL; *[OR] random SITE;
  lsmeans LENS_MODEL / pdiff cl;
  estimate 'Trt_Eff' LENS_MODEL 1 -1;
run;
```

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;
  where VISIT='VISIT4A';
  class LENS_MODEL SITE OPERATIVE_EYE;
  model VA = LENS_MODEL /DDFM = satterth;
  random SITE SITE*LENS_MODEL; *[OR] random SITE;
  repeated OPERATIVE_EYE / subject=USUBJID(SITE) TYPE=CS;
  lsmeans LENS_MODEL / pdiff cl;
  estimate 'Trt_Eff' LENS_MODEL 1 -1;
run;
```

## 4.3.2 Secondary Effectiveness Analyses

### 4.3.2.1 Distance Corrected Visual Acuity at Intermediate (66 cm)

Least Squares Means (LSMEANS) from the mixed effects model chosen during the model selection step will be employed to estimate the difference in means (AcrySof IQ PanOptix IOL Model TFNT00 minus AcrySof Monofocal IOL Model SN60AT) and the associated 95% (two-sided) confidence interval.

The first secondary superiority hypothesis will be deemed supported if the upper 97.5% confidence limit is less than 0.0 logMAR.

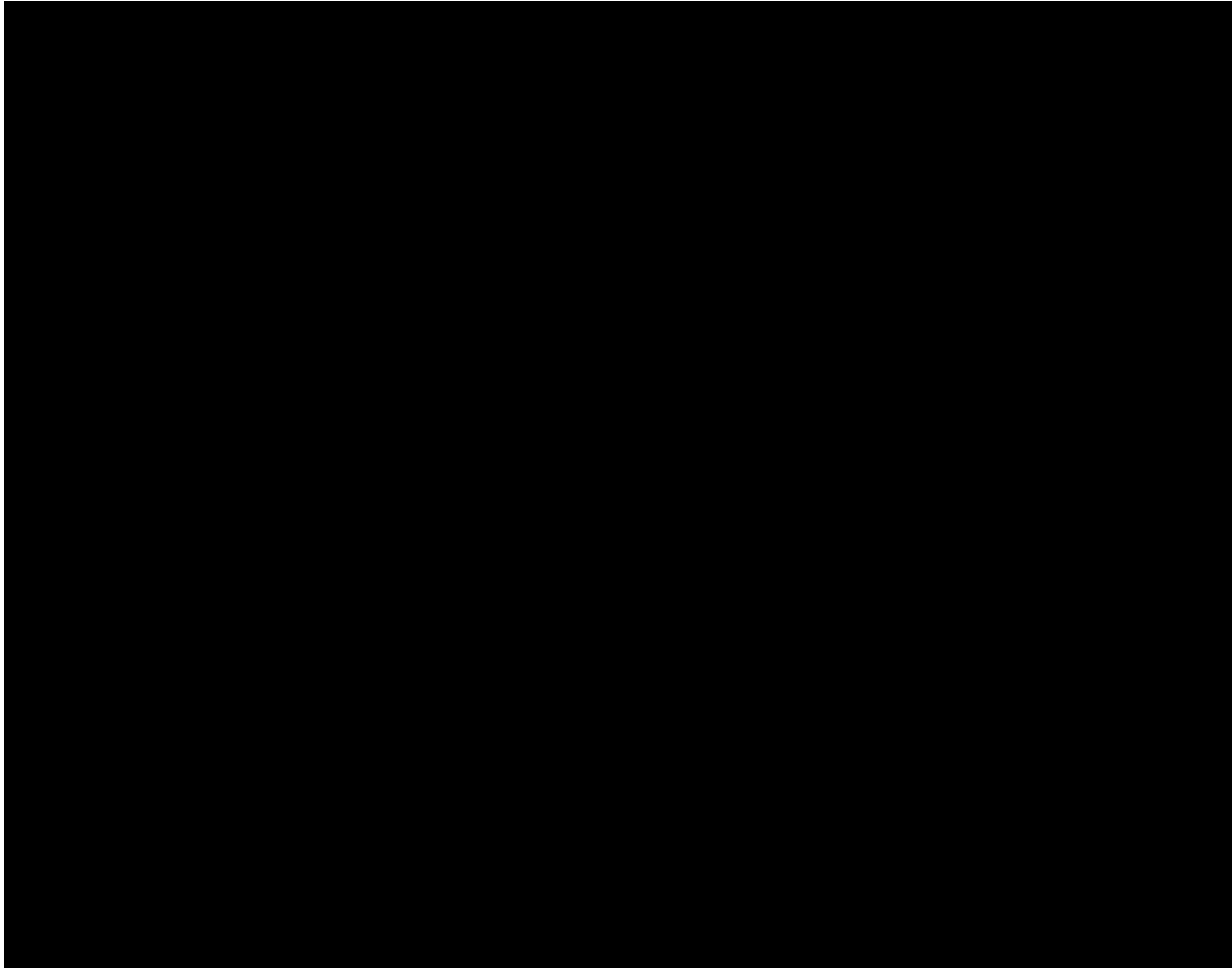
The SAS pseudo code is identical to the primary analysis.

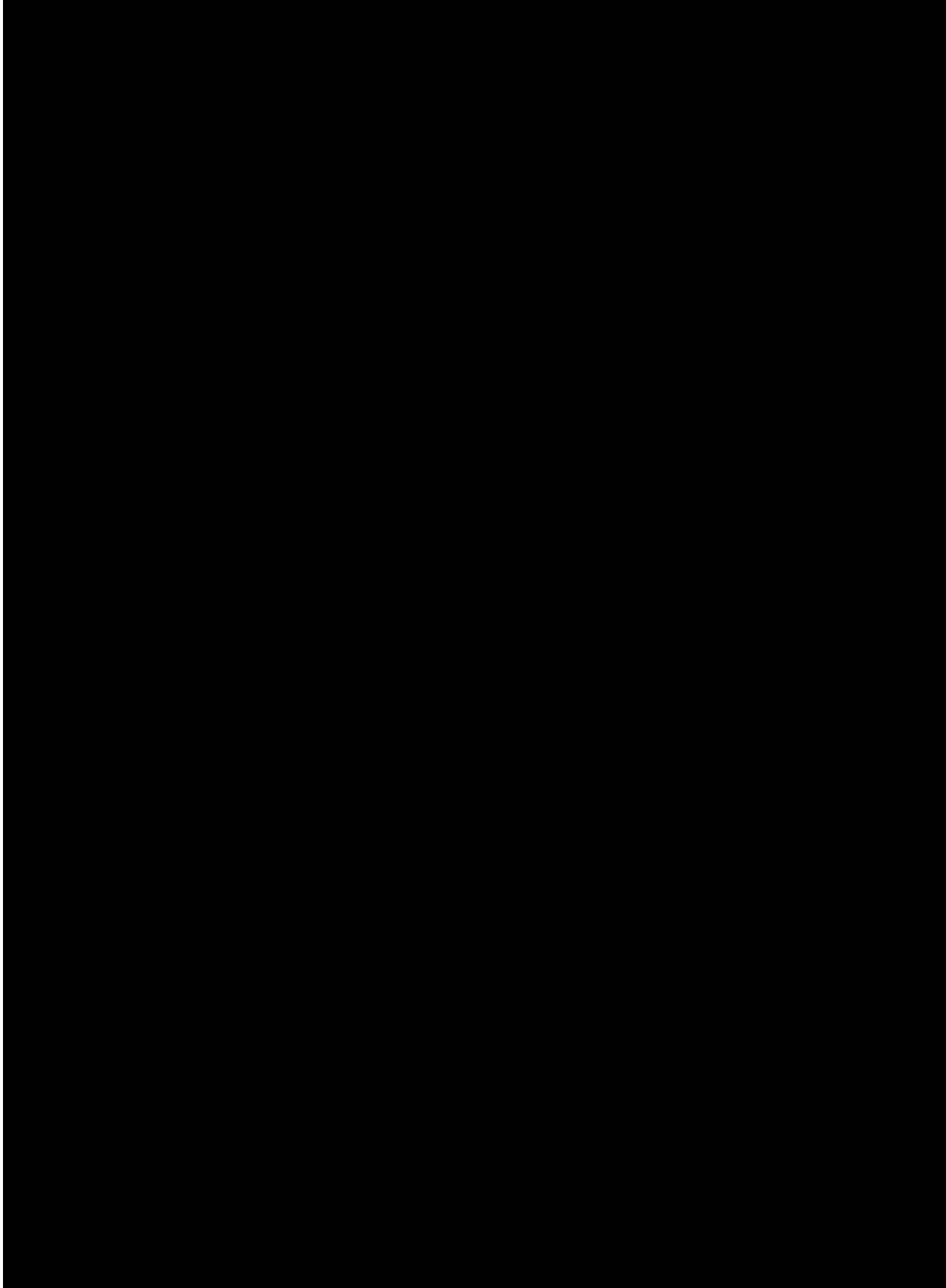
### 4.3.2.2 IOLSAT Questionnaire

The second secondary endpoint will be analyzed by estimating the Mantel-Haenszel common difference in proportions (AcrySof IQ PanOptix IOL Model TFNT00 minus AcrySof Monofocal IOL Model SN60AT) along with the corresponding 95% (two-sided) confidence interval with site as a stratification variable. The superiority hypothesis will be deemed supported if the lower limit of the confidence interval exceeds zero.

SAS pseudo code for the above model is provided below.

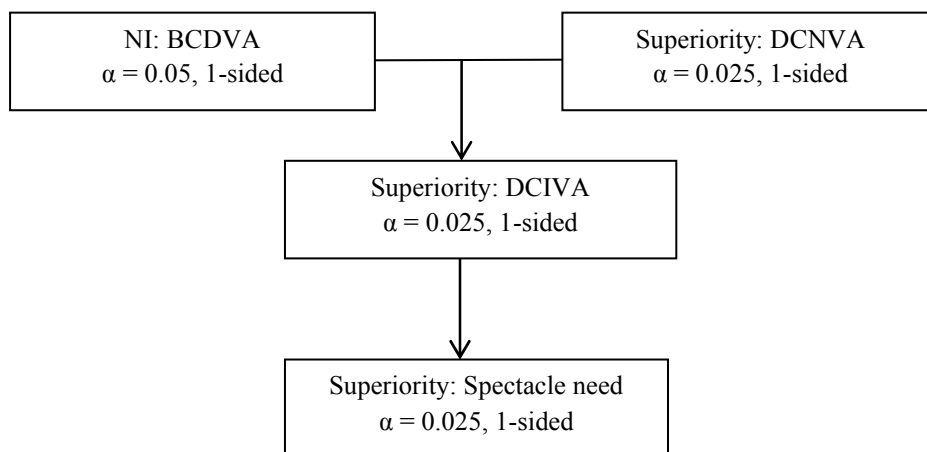
```
proc freq data=IOLSAT;  
  tables SITE*LENS_MODEL*IOLSATQ1 / riskdiff(common) alpha=0.05;  
run;
```





## 4.4 Multiplicity Strategy

To account for multiplicity, the effectiveness hypotheses will be tested in sequence, two co-primaries, followed by first secondary, followed by second secondary. The primary effectiveness objective is considered met only if both co-primary hypotheses are met. The type I error for the non-inferiority test is 5% (1-sided) and for the superiority test is 2.5% (1-sided). Each of the secondary hypotheses will be tested at 2.5% (1-sided).



## 4.5 Handling of Missing Data

The AAS and BAS do not include any imputed values for the co-primary effectiveness endpoints, best corrected distance visual acuity and distance corrected near visual acuity. 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 co-primary effectiveness analyses.

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 missing-at-random (MAR) assumption will be examined using a pattern-mixture model approach (with a control-based pattern imputation<sup>[3]</sup>).



*Sensitivity Analysis 1:*

A fully conditional specification (FCS) method will be used to impute missing monocular best corrected distance visual acuity at 4 m (first operative eye) values and monocular distance corrected visual acuity at near (first operative eye) at month 1 and month 6 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 BCDVA values (or DCNVA) using FCS method:

```
/* multiple imputation w/ MAR assumption          */
/* BCDVA3-BCDVA4 should be in wide format */
proc mi data=mi_in seed=1561 nimpute=100 mu0=.1 .0 out=mi_out;
  fcs nbiter=100 reg; *reg(/details);
  var BCDVA3 BCDVA4;
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          */
/* BCDVA3-BCDVA4 should be in wide format          */
proc mi data=mi_in seed=1561 nimpute=100 mu0=.1 .0 out=mi_out;
  class LENS_MODEL;
  fcs nbiter=100 reg; *reg(/details);
  mnar model(BCDVA3 BCDVA4 / modelobs=(LENS_MODEL='SN60AT'));
  var BCDVA3 BCDVA4;
run;
```

Datasets obtained using each of the methods specified above will be analyzed using the model chosen for the primary analysis. The treatment effects and estimates of standard error obtained from each iteration within each method will be combined using PROC MIANALYZE and will be used to draw inferences about each sensitivity analysis. The SAS pseudo code to analyze the imputed datasets and combine the estimates is provided below.

```
/* run mixed model on each iteration of mi */
proc mixed data=mi_out;
  by _imputation_;
  class LENS_MODEL SITE;
  model BCDVA4 = LENS_MODEL /DDFM = satterth;
  random SITE SITE*LENS_MODEL; *[OR] random SITE;
  lsmeans LENS_MODEL / pdiff cl;
  estimate 'Trt_Eff' LENS_MODEL 1 -1;
  ods output Estimates = mimxd_out;
run;

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

For the second co-primary safety analysis, a sensitivity analysis imputing some missing data for contrast sensitivity measures is described in the corresponding section (5.3.2).

## 4.6 Subgroup Analyses and Effect of Baseline Factors

### 4.6.1 Subgroup Descriptive Statistics

The consistency of the treatment effect for the co-primary and first secondary endpoints will be assessed descriptively, for both the AAS and BAS, using summary statistics by categories of the following:

- Age category (<65 vs. ≥65 years)
- Site
- Ocular Adverse Events (study eyes with vs. study eyes without)
- Preoperative Ocular Pathology (study eyes with vs. study eyes without)

To examine inter-site variation in outcomes, forest plots of co-primary and first secondary endpoints will be produced by plotting the difference in means and corresponding 95% (two-sided) confidence intervals at each site (and by pseudo-site described in Section 2).

### 4.6.2 Propensity Score Analysis

A propensity score is the conditional probability of being in the treatment group based on individual covariates at baseline. In a non-randomized study, baseline differences in covariates, amongst groups, may lead to a biased estimate of the treatment effect. To account for these differences the following two-step methodology outlined in (D'Agostino, 1998<sup>[4]</sup>) will be employed.

Step 1: Fit a logistic regression model with the following baseline covariates to estimate the probability of being in the treatment group and creating the propensity score weights.

- 1) Age, continuous
- 2) Gender
- 3) Site
- 4) Baseline photopic best-corrected distance visual acuity

The SAS pseudo code for this step is provided below:

```
proc logistic data=Visual_acuity;
  where OPERATIVE_EYE = 'First' AND VISIT='VISIT4A';
  class SEX SITE LENS_MODEL;
  model LENS_MODEL (event='TFNT00') = AGE SEX SITE
        BCDVA_B /link=logit rsquare;
  output out=ps_set pred=ps;
run;

data ps_set;
  set ps_set;
  if TRT='TFNT00' then ps_weight=1/ps;
  else ps_weight=1/(1-ps);
run;
```

Step 2: Fit a propensity score-weighted linear regression model, using the GLM procedure.

```
proc glm data=ps_set;
  where OPERATIVE_EYE = 'First' AND VISIT='VISIT4A';
  class LENS_MODEL;
  model VA = LENS_MODEL /solution;
weight ps_weight;
  lsmeans LENS_MODEL /pdiff cl;
  estimate 'Trt_eff' LENS_MODEL 1 -1;
run;
```

The estimated treatment effect from the above model will be compared to the estimated effect from the primary analysis mixed effects model. Meaningful differences will be investigated with additional exploratory analyses.

## 4.7 Interim Analysis for Efficacy

There are no planned interim analyses of the endpoints. Interim reports pertaining to the progress of this study will be submitted to the US FDA for review annually until study completion.

## 5 Safety Analysis Strategy

### 5.1 Safety Endpoints

The safety endpoints are:

#### *Primary Safety (6 months)*

- Cumulative rate of secondary surgical interventions (SSIs) related to the optical properties of the IOL
- Binocular Distance Contrast Sensitivity
  - Photopic without glare (3, 6, 12, 18 cycles per degree)
  - Photopic with glare (3, 6, 12, 18 cycles per degree)
  - Mesopic without glare (1.5, 3, 6, 12 cycles per degree)
  - Mesopic with glare (1.5, 3, 6, 12 cycles per degree)

#### *Secondary Safety (6 months)*

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

#### *Third Safety (6 months)*

- Cumulative and persistent rates of Adverse Events in first operative eyes

#### *Other Safety*

- Rates of all visual disturbances as reported by the subjects using the QUVID questionnaire at 6 months
- IOP
- Slit lamp observations
- Dilated fundus observations
- Ability to evaluate the fundus at 1 month
- Rates of ocular adverse events, including SSIs related to the optical properties for either eye
- Adverse events
- Device deficiencies
- IOL observations

- IOL position change
- Subjective PCO
- Posterior Capsulotomies
- Surgical Problems

- [REDACTED]

## 5.2 Safety Hypotheses

Rates of cumulative and persistent adverse events listed in IS EN ISO 11979-7:2014 will be compared to historical control Safety and Performance Endpoint (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 Secondary Surgical Interventions

Descriptive summaries (count, rate and 95% (two-sided) exact confidence interval) of secondary surgical interventions will be presented for each IOL group and the difference between the groups, separately for first operative eyes and all eyes in each of the following categories:

- 1) Related to IOL - due to optical properties
- 2) Related to IOL - not due to optical properties
- 3) Unrelated to IOL
- 4) Overall

A listing of all SSIs will also be presented.

The following SAS pseudo code will be used.

```
proc freq data=SSI;  
tables LENS_MODEL*SSI / alpha=0.05;  
exact riskdiff;  
run;
```

### 5.3.2 Binocular Distance Contrast Sensitivity

Contrast sensitivity testing is conducted at 3.0, 6.0, 12.0 and 18.0 cycles per degree (CPD) for photopic testing and 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 5-1) followed by 8 gratings of decreasing contrast levels for testing (represented by numbers 1 to 8 in Table 5-1). 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 5-1 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

CPD = cycles per degree



[REDACTED]

[REDACTED]

[REDACTED]

### 5.3.3 Visual Disturbances

The secondary safety endpoint is rates of severe and most bothersome visual disturbances as reported by subjects using the QUID questionnaire at month 6. Descriptive summaries (rates and 95% (two-sided) exact confidence intervals) of severe and most bothersome visual disturbances will be presented for each IOL group and the difference between the IOL groups.

The number and percentages of subjects in each category of responses to each question on the QUID questionnaire will be reported by IOL group at each visit this questionnaire is administered.

### 5.3.4 Adverse Events

The third safety endpoint is adverse events. Incidence rates observed for each IOL group will be compared to the cumulative and persistent adverse event Safety and Performance Endpoint rates in IS EN ISO 11979-7:2014. An eye with multiple ocular adverse events of the same preferred term is only counted once toward the total of this preferred term. The Safety and Performance Endpoint rate is considered not exceeded if the lower exact binomial 95% confidence limit does not exceed the Safety and Performance Endpoint rate.

The following SAS pseudo code will be used to generate the summaries above.

```
proc freq data=AE_SPE;
  by SPE_AE;
  tables LENS_MODEL / binomial (exact) alpha=0.05;
run;
```

The frequencies of adverse events will be presented overall, and by subcategories of age (<65 years vs. ≥65 years) and investigative site, separately for cumulative and persistent adverse events. Additionally, frequencies and 95% (two-sided) exact confidence intervals will be reported for adverse events related to the IOL for each IOL group. Adverse events related to the IOL are referred to as adverse device effects.

Adverse events will be summarized in the following tables, by IOL group:

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

All ocular tables will be presented separately for first operative eyes and all eyes.

In addition, listings of adverse events will be provided. The listings will include the following variables: treatment, site, subject, eye, days from surgery, duration, adverse event description, causality, severity, seriousness, outcome and preferred term.

**Table 5-2 Adverse Event Safety and Performance Endpoint Rates**

Adverse Event	SPE Rate (%)
<b>Cumulative</b>	
Cystoid Macular Oedema	3.0
Hypopyon	0.3



Endophthalmitis <sup>a</sup>	0.1
Lens dislocated from posterior chamber	0.1
Pupillary block	0.1
Retinal detachment	0.3
Secondary surgical intervention <sup>b</sup>	0.8
<b>Persistent</b>	
Corneal stroma oedema	0.3
Cystoid macular oedema	0.5
Iritis	0.3
Raised IOP requiring treatment	0.4

<sup>a</sup> Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.

<sup>b</sup> 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.

### 5.3.5 Intraocular Pressure

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

All analyses will be presented by IOL group, separately for first and second operative eyes.

Descriptive summaries (N, mean, median, standard deviation, minimum, maximum and 95% (two-sided) confidence interval) of observed values and change from baseline values will be presented at each study visit by IOL group, separately for first and second operative eyes.

A summary table with number and percentages of eyes in each category of IOP change from baseline to last on-treatment intraocular pressure assessment and to any visit by operative eye will be presented by IOL group 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 operative 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 intraocular pressure of more than 10 mmHg at any visit compared to the same eye at baseline. The listing will include the following variables: treatment, site, subject, age, sex, visit, days from surgery, eye, baseline value, value at the visit and a change from baseline value.

### **5.3.6 Slit Lamp Observations**

For each slit-lamp parameter, number and percentages of eyes that experience abnormality at any post-operative visit will be presented by IOL group, separately for first and second operative 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, site, subject, age, sex, visit, eye, parameter, baseline value, and value at the visit.

### **5.3.7 Dilated Fundus Observations**

For each dilated fundus parameter, number and percentages of eyes that experience abnormality at any post-operative visit will be presented by IOL group, separately for first and second operative 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: treatment, site, subject, age, sex, visit, days from surgery, eye, baseline value and value at the visit.

### **5.3.8 Fundus Visualization**

The ability to visualize the fundus (yes/no) will be tabulated by IOL group and operative eye.

### **5.3.9 Device Deficiencies**

The number and percentage of all device deficiencies will be tabulated with a breakdown by IOL group and operative eye. A listing of all device deficiencies will also be provided.

### **5.3.10 IOL Observations**

IOL observations will be summarized by lens model using descriptive statistics, including frequency (N) and percent of eyes, by IOL group, separately for first and second operative eyes, at each scheduled and unscheduled visit where the data were collected.

### **5.3.11 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 operative eyes. In addition, a listing of eyes with IOL position change will be

provided. The listing will include the following variables: treatment, site, subject, age, sex, visit, days from surgery, eye and amount of tilting or decentration.

### **5.3.12 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 operative eyes. Subjective posterior capsule opacification will be summarized using descriptive statistics, including number and percent of eyes, at each scheduled and unscheduled visit where the data were collected, by IOL group, separately for first and second operative eyes.

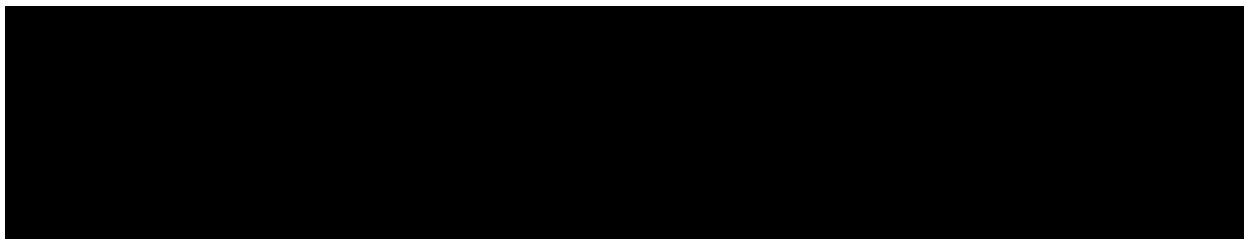
A listing of eyes with clinically significant posterior capsule opacification, clinically significant posterior capsule opacification requiring YAG or posterior capsulotomy will be presented which includes the posterior capsule opacification or capsulotomy values at all visits. The listing will include the following variables: treatment, site, subject, age, sex, visit, days from surgery, eye and posterior capsule opacification or capsulotomy value at the visit.

### **5.3.13 Posterior Capsulotomies**

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

### **5.3.14 Surgical Problems**

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



## **5.4 Interim Analysis for Safety**

There are no planned interim analyses of the endpoints. Interim reports pertaining to the progress of this study will be submitted to the US FDA for review annually until study completion.

## 6 Pharmacokinetic Analysis Strategy

Not Applicable.

## 7 Sample Size and Power Calculations

Approximately 250 subjects will be bilaterally implanted with either the AcrySof IQ PanOptix IOL Model TFNT00 or the AcrySof Monofocal IOL Model SN60AT in a 1:1 ratio in order to ensure that at least 113 eligible subjects complete the study in the test group and the control group. This assumes a drop-out rate of 10%, approximately.

For co-primary and first secondary effectiveness objectives, the proposed sample size will provide  $\geq 98\%$  power for each of the hypotheses, with  $\alpha=0.05$ , 1-sided, for the non-inferiority test, and  $\alpha=0.025$ , 1-sided, for superiority tests. For tests of superiority, assumptions include a difference in means of 0.1 logMAR between the groups for distance corrected visual acuity at intermediate (66 cm) (DCIVA) and distance corrected visual acuity at near (40 cm) (DCNVA) and a common standard deviation of 0.18 logMAR. For test of non-inferiority, assumptions include a difference in means of zero between the groups for best corrected distance visual acuity (4 m) (BCDVA), a non-inferiority margin of 0.1 logMAR and a common standard deviation of 0.18 logMAR. The standard deviation of 0.18 is based on the maximum variability of logMAR observed in study C-06-40 (Clinical Study Report: Clinical Investigation of ACRYSOF ReSTOR Aspheric +3.0 D Add Power IOL).

For the second secondary effectiveness objective, the proposed sample size will provide 83% power, with  $\alpha=0.025$ , 1-sided, to detect a difference in proportion of 20%, assuming a  $\geq 50\%$  rate in the AcrySof IQ PanOptix IOL test group. The estimates of rates of spectacle need for the test and control lenses are inferred from studies ILH297-P002 and C-10-016, respectively, using a binocular [REDACTED] visual acuity threshold of 0.2 logMAR or better at near (40 cm) and distance (4 m) as a proxy measure.

Power calculations for the effectiveness objectives are summarized in the table below:

	Margin	Expected Difference	Std. dev	Type I error (1-sided)	Power
Non- Inferiority					
BCDVA (4 m)	0.1	0.0	0.18	5%	99%
Superiority					
DCNVA (40 cm)		0.1	0.18	2.5%	98%
DCIVA (66 cm)		0.1	0.18	2.5%	98%
Spectacle need		20%		2.5%	83%

All expected differences for tests of superiority favor the test lens. Estimates for VA endpoints reported

in logMAR.

Adverse Events: For any event where a zero incidence is observed in 113 first-operative eyes in the AcrySof IQ PanOptix IOL test group, the upper exact binomial 95% confidence limit is less than 3%. Thus, with 95% confidence, the true adverse event rate is less than 3%.



## 8 References

1. Littell, R. C., Stroup, W. W., Milliken, G. A., Wolfinger, R. D., & Schabenberger, O. (2006). *SAS for mixed models*. SAS institute. (Section A1.6.1)
2. Dmitrienko A., Moleberghs G., Chuang-Stein C., Offen W. (2005). *Analysis of Clinical Trials Using SAS: a Practical Guide*.
3. Ratitch, B. and 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).
4. D’Agostino, R.B. 1998. “Tutorial on Biostatistics: Propensity Score Methods for Bias Reduction in the comparison of a treatment to a non-randomized control group”. *Statistics in Medicine* 17, 2265-2281

## 9 Revision History

Changes in the first revision include clarifying confidence limits for the hypothesis tests and multiplicity strategy to match the protocol, detailing which personnel will be masked, adding a sensitivity analysis for primary effectiveness, revising the categories for visual acuity, adding a propensity score analysis to account for baseline differences in covariates, updating the contrast sensitivity analysis, updating the sample size justification section to reflect modified Type I error rates, and minor corrections throughout for consistency and typographical errors.

Change in the second revision includes adding categorical statistics of subjects who meet visual acuity thresholds at all distances.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
09/14/2018 18:51:00	[REDACTED]	[REDACTED]
09/17/2018 19:51:29	[REDACTED]	[REDACTED]
09/18/2018 16:56:30	[REDACTED]	[REDACTED]
09/26/2018 15:22:27	[REDACTED]	[REDACTED]