Short Title:

Statistical Analysis Plan
ILQ732-I001 /
NCT02842151

Full Title:

Statistical Analysis Plan
ILQ732-I001

Protocol Title:	Optimizing the Assessment of Refractive Outcomes after Cataract Surgery and Implantation of a Monofocal IOL
Project Number:	A01983
Protocol TDOC Number:	TDOC- 0050597
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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 1.0 of the study protocol.

Executive Summary:

Key Objectives:

To demonstrate equivalency, at each of the 3 clinical sites, between IOL SRK/T A-constant (Retzlaff et al., 1990) estimated based on postoperative manifest spherical equivalent refraction at 3 months and IOL A-constant estimated based on postoperative spherical equivalent from autorefraction using *Topcon® KR-1W* at 3 months.

Decision Criteria for Study Success:

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

A two-sided 90% confidence interval will be constructed for the mean of the paired difference between the two estimated SRK/T A-constants separately for each site. If all the two-sided 90% confidence intervals fall within (-0.15, 0.15), then equivalence will be concluded.

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1 Study Objectives and Design

1.1 Study Objectives

The primary objective of this study is to demonstrate equivalency at each of the 3 clinical sites, between IOL SRK/T A-constant estimated based on postoperative manifest spherical equivalent refraction at 3 months and IOL SRK/T A-constant estimated based on postoperative spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months. The primary endpoints to be used for the primary analysis are:

- IOL SRK/T A-constant estimated based on the preoperative biometry, IOL power and postoperative manifest spherical equivalent refraction at 3 months and
- IOL SRK/T A-constant estimated based on the preoperative biometry, IOL power and postoperative spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months.

1.2 Study Description

This is a prospective, non-randomized, observer-masked *(examiner performing manifest refraction is masked to the refractive target and refractive error from the surgical planning and the operative visit),* interventional clinical study. The Investigator will determine the study eye to be included in this study. Only the study eye will be followed throughout the study. At a minimum 165 subjects will be enrolled at up to 3 sites in the United States and Ireland.

Subjects require cataract surgery with implantation of a monofocal IOL Model SN60WF in the capsular bag in one or both eyes to qualify for enrollment into this study. One eye will be enrolled per subject.

A total of 4 scheduled visits are planned including the Screening/Visit 0 and the Operative Visit/Visit 00. Scheduled postoperative visits must occur at the following intervals:
20-40 days and 80-100 days. See Table 1-1 Schedule of Study Visits.

Table 1-1 Schedule of Study Visits

Time from Implantation	Study Visit
Screening / Preoperative (Day -28 to Day 0)	Visit 0
Operative (Day 0)	Visit 00
20-40 days	Visit 1
80-100 days	Visit 2

1.3 Randomization

This is a non-randomized study. All subjects will be implanted with Model SN60WF IOL in the selected study eye.

1.4 Masking

The examiner performing the manifest refraction will be masked to the refractive target and refractive error from the surgical planning and the operative visit, respectively. There is no other masking.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

2.1 Efficacy Analysis Sets

All Implanted Analysis Set (AAS):

All subjects with successful IOL implantation in the study eye will be included in the AAS. The primary analysis set for the primary and exploratory analyses will be the AAS.

Best Case Analysis Set (BAS):

BAS will include the subjects in AAS who had:

- at least 1 postoperative visit,
- no macular degeneration at any time; and
- no major protocol violation

The BAS is a supportive analysis set for the primary and exploratory analyses.

2.2 Safety Analysis Set

All subjects with attempted IOL implantation (successful or aborted after contact with the eye) in the study eye will be considered evaluable and included in the safety analysis set. The safety analysis set will be used for the safety analyses. Additionally, any AE experienced by a subject during the screening period will be presented separately in a listing.

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, and ethnicity, 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.

Subject characteristics and study conduct summaries will be presented for the AAS (Overall and by site) and safety set (overall only). Subject characteristics and study conduct summaries for the BAS (overall and by site) will be presented if the total number of subjects excluded exceeds 10%.

4 Effectiveness Analysis Strategy

4.1 Efficacy Endpoints

The primary [redacted] endpoints are:

- IOL SRK/T A-constant estimated based on the preoperative biometry, IOL power and postoperative manifest spherical equivalent refraction at 3 months and
- IOL SRK/T A-constant estimated based on the preoperative biometry, IOL power and postoperative spherical equivalent from autorefraction using *Topcon KR-1W* at 3 months.

[redacted]

4.2 Efficacy Hypotheses

4.2.1 Primary Effectiveness Hypothesis

The null and alternative hypotheses for the primary analysis are:

$$H_0: \mu_{diff} \leq -0.15 \text{ or } \mu_{diff} \geq 0.15$$

$$H_A: -0.15 < \mu_{diff} < 0.15$$

Where μ_{diff} refers to the mean paired difference between the first two endpoints listed in section 4.1 for each site.

[redacted]

[redacted]

4.3 Statistical Methods for Efficacy Analyses

The primary hypothesis will be tested by generating a 2-sided 90% confidence interval for the paired difference at each site. Equivalence will be declared if the bounds of the 90% CI are contained within the equivalence range (-0.15, 0.15). SAS PROC TTEST will be used to generate the confidence interval based on the pseudo code below:

```
proc ttest data=Aconst alpha=0.1;
      paired AconstMR*AconstAR;
run;
```

Additionally, as a sensitivity analysis, a mixed effects model will be fit to estimate overall effect of refraction method as well as by site. The pseudo code is provided below:

```
proc mixed data=Aconst;
      class subj RefMethod Site;
      model SBP=RefMethod|site;
      repeated RefMethod / subject=subj type=un;
      lsmeans RefMethod*site/diffs cl ;
run;
```

Descriptive statistics (mean, median, standard deviation, number of eyes, minimum, maximum, and two-sided 90% confidence interval) will be provided for each site for the A-constants calculated using manifest refraction and autorefraction and also for the difference.

[redacted]

[redacted]

4.4 Multiplicity Strategy

No multiplicity adjustments are planned for primary or exploratory analyses. The primary hypothesis tests must be rejected at every site for the study to be considered a success.

4.5 Interim Analysis for Efficacy

No interim analysis is planned.

5 Safety Analysis Strategy

5.1 Safety Endpoints

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
- 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 subject.
The number and percentage of all ocular adverse events, including secondary surgical interventions (SSIs), will be tabulated by preferred term. 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.

Adverse events will be summarized in the following tables:

- All Adverse Events (Serious and Non-Serious Combined)
  - Ocular
  - Non-Ocular
- All Adverse Device Effects
  - Ocular
  - Non-Ocular
- All Serious Adverse Events (including Serious Adverse Device Effects)
  - Ocular
  - Non-Ocular
- Subject Listings
  - Non-Serious Ocular
  - Non-Serious Non-Ocular
  - Serious Ocular
  - Serious Non-Ocular

5.3.2 Device Deficiencies

The number and percentage of all device deficiencies will be tabulated. A listing of all device deficiencies, as recorded on the Device Deficiency Form, will also be provided.

5.3.3 Surgical Problems

The number and percentage of eyes with surgical problems will be presented. In addition, a listing of subjects with surgical problems will be provided. The listing will include the following variables: investigator, subject, age, sex, race, ethnicity, 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. 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. 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, 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. 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: 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 using descriptive statistics, including frequency (N) and percent of eyes, at each scheduled and unscheduled visit where the data were collected. A listing of "Other" IOL observations will be provided with the following variables: investigator, subject, age, sex, race, ethnicity, visit, eye, and description.

5.3.7 IOL Position Change

Descriptive statistics (numbers and percentages) on eyes with a change from baseline in IOL position category (Tilted, Decentered) will be presented by visit. In addition, a listing of subjects 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 by visit.

5.3.9 Posterior Capsulotomy

The number and percentage of eyes with posterior capsulotomy will be tabulated.

5.3.10 Dilated Fundus Examination

For each dilated fundus parameter, number and percentages of eyes that experience abnormality at any post-operative visit will be presented. 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, visit, eye, baseline value and value at the visit.

5.4 Interim Analysis for Safety

No interim analysis is planned.

6 Analysis Strategy for Other Endpoints

Not Applicable.

7 Sample Size and Power Calculations

A minimum of 165 subjects will be enrolled to ensure at least 144 evaluable subjects (48 evaluable subjects per site) complete the study.

With 48 evaluable subjects per site, study has 90% chance to show that the mean difference in IOL A-constants calculated with postoperative manifest spherical equivalent refraction at 3 months and postoperative spherical equivalent from autorefraction at 3 months is within the equivalence margin of ±0.15 for each site assuming that the mean and the standard deviation (SD) of a paired difference are 0 and 0.35 respectively.

The SD of 0.35 is based on the SD of the difference in the estimated A-constant between the first and the second eyes in subjects implanted with ACRYSOF IQ Monofocal IOL [redacted] (ACRYSOF IQ ReSTOR Multifocal +2.5 D).

8 References

Retzlaff, J et al.: Development of the SRK/T intraocular lens implant power calculation formula. J Cataract Refract Surg, 16, 1990: 333-340

Retzlaff, J et al.: Development of the SRK/T intraocular lens implant power calculation formula - Erratum. J Cataract Refract Surg, 16, 1990: 528

Wilcox, R: Comparing the variances of two dependent variables. J. Stat. Distr. Appl. 2, 7 (2015).

9 Deviations from Protocol

- The individual C-value computation was added to the second exploratory analysis.
- The analysis associated with third exploratory hypothesis test was amended to ensure that with-in subject correlation between measures is appropriately accounted for.

10 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 1.0 of the study protocol.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
09/01/2016 16:06:43	[redacted]	[redacted]
09/01/2016 16:14:18	[redacted]	[redacted]
09/01/2016 17:54:40	[redacted]	[redacted]
09/01/2016 21:48:40	[redacted]	[redacted]