Short Title:

Statistical Analysis Plan
ILX140-C001

Full Title:

Statistical Analysis Plan
ILX140-C001 / NCT04542525

Protocol Title: Clinical Investigation of AcrySof IQ PanOptix Toric Intraocular Lens Model TFNT20

[redacted]

Protocol TDOC Number: TDOC-0057192

Author: [redacted]

[redacted]

[redacted]

Executive Summary:

Key Objectives:

The objective of this study is to evaluate effectiveness and safety of the TFNT20 when implanted to replace the natural lens following cataract removal.

Decision Criteria for Study Success:

Primary effectiveness variable is percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60). The superiority of TFNT20 to non-Toric group (T0) regarding refractive cylinder is to be demonstrated when there is a statistically significant difference between the outcome in this study and the historical threshold of 29.2%.

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1 Study Objectives and Design

1.1 Study Objectives

The purpose of this study is to evaluate effectiveness and safety of the TFNT20 when implanted to replace the natural lens following cataract removal. [redacted] this is intended to confirm the safety of the test product and examine its effectiveness as a Toric lens by examining the subject's astigmatism power.

1.2 Study Description

This study is a prospective, single-center and non-comparative study. The study will include subjects must be ≥ 20 years of age with cataract who would be eligible to receive a TFNT20 lens in at least one eye based on a new Alcon Toric calculator that incorporates ocular trends in Toric IOL planning. Subject with no ocular pathology that could confound study outcome, must require clear cornea cataract extraction, and must desire an IOL that provides the potential for near, intermediate and distance vision and corrects astigmatism. Potential subjects will be screened for enrollment into this clinical trial. Those qualifying will attend a total 5 visits. If the investigational products will be implanted to both eye, the maximum number of visits is total 9 visits. Primary endpoint data will be collected at the final visit, Visit3/3A (30-60 days post implantation). No interim analysis is planned.

1.3 Randomization

This is a single-treatment study. All subjects will be implanted with AcrySof IQ PanOptix Toric Intraocular Lens Model TFNT20 unilaterally or bilaterally.

1.4 Masking

This is an open-label study. Treatment assignment may be known to the investigators, subjects or Alcon personnel involved with the planning and execution of the study.

1.5 Interim Analysis

No interim analysis is planned.

2 Analysis Sets

2.1 Efficacy Analysis Sets

All-Implanted Analysis Set (AAS)

All-Implanted Analysis Set (AAS) will include all eyes with successful test article implantation.

Best-Case Analysis Set (BAS)

Best-Case Analysis Set (BAS) will include all eyes with successful test article implantation that had

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

2.2 Safety Analysis Set

The treatment-emergent safety analysis set will include all eyes with attempted implantation with the test article (successful or aborted after contact with the eye).

3 Subject Characteristics and Study Conduct Summaries

For all analysis datasets (Safety Analysis Set, AAS and BAS), demographics (sex, age [<60, 60-69, 70-79, ≥80 years], systemic complication [None/Yes, details] and past ocular surgery [None/Yes, details]) will be summarized with the number and percent of subjects in each category for the variable. Age will also be summarized with descriptive statistics (mean, standard deviation, number of subjects or eyes, median, min and max).

4 Efficacy Analysis Strategy

4.1 Efficacy Endpoints

The followings are efficacy endpoints for this study. Absolute value will be used for evaluating primary endpoint and secondary endpoints.

Primary Endpoint

- Percentage of eyes with ≤ 0.25 D absolute refractive cylinder at Visit 3/3A (Day 30-60)

Secondary Endpoints

- Percentage of eyes with ≤ 0.5 D absolute refractive cylinder at Visit 3/3A (Day 30-60)
- Average absolute manifest refractive cylinder at Visit 3/3A (Day 30-60)

[redacted]

4.2 Efficacy Hypotheses

The primary analysis will be performed using an exact test of binomial proportion (one-sided alpha = 2.5%). The null (H_0) and alternative (H_1) hypotheses are;

H_0: $\pi(T2) = 29.2\%$

H_1: $\pi(T2) > 29.2\%$

, where $\pi(T2)$ is the population proportion of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60) for TFNT20 (T2 hereafter) group. The 29.2% is the percentage of non-Toric (T0, hereafter) group estimated from historically combined studies [redacted] that would have qualified for T2 according to the new Alcon Toric calculator.

For secondary effectiveness analyses [redacted], no confirmatory statistical hypothesis testing will be conducted.

4.3 Statistical Methods for Efficacy Analyses

All eligible eyes will be used for the analysis. For unilaterally implanted subjects, only the eligible eye, for bilaterally implanted subjects, both eyes will be used for the analysis. The superiority of T2 to T0 regarding refractive cylinder is to be demonstrated when there is a statistically significant difference between the outcome in this study and the historical threshold of 29.2%. [redacted]

[redacted]

Secondary effectiveness variables [redacted] will be summarized descriptively. For continuous variables, descriptive statistics (mean, standard deviation, N, median, min and max) will be provided for actual value and change from baseline at each visit. For categorical variables, N and percent will be provided for each category at each visit. Any additional p-values from t-statistics or chi-square type statistics will be provided accordingly only for descriptive purpose. Also, a patient data listings will be provided for all effectiveness analysis data with all eyes at all visits.

Table 4-1 summarizes the key efficacy analyses.

Table .4–1 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint	Main [redacted] Approach[a]	Statistical Method	Analysis Set	Missing Data Approach
Primary				
Percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A	M	Exact test of binomial proportion	AAS	Observed data only
[redacted]				
Secondary				
Percentage of eyes with ≤ 0.5 D refractive cylinder at Visit 3/3A	M	Descriptive statistics	AAS	Observed data only
[redacted]				
Average manifest refractive cylinder at Visit 3/3A	M	Descriptive statistics	AAS	Observed data only
[redacted]				

4.4 Multiplicity Strategy

Multiplicity is not an issue since there is only a single primary endpoint. The hypothesis testing is not planned for the secondary endpoints [redacted].

[redacted]

4.6 Interim Analysis for Efficacy

No interim analysis is planned.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events including secondary surgical intervention (SSI)
- Device deficiencies
- Posterior capsular opacification
- Posterior capsulotomy
- IOL position change (tilt and decentration)
- Intraocular pressure
- Surgical problems
- Slit Lamp Examination
- Dilated Fundus Examination
- IOL Observations

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 including secondary surgical intervention (SSI)

The number and percentage of eyes with ocular adverse events (including secondary surgical interventions not-related to the optical properties of the IOL) will be presented. Also, the number and percentage of subjects with non-ocular adverse events will be presented. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term.

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 data Listings
    - Non-Serious Ocular
    - Non-Serious Non-Ocular
    - Serious Ocular
    - Serious Non-Ocular

Also, a patient listing will be provided for adverse experiences occurred from informed consent to exposure to the test article.

5.3.2 Device Deficiencies

A frequency table showing counts for each Device Deficiency category will be presented. In addition, a listing all device deficiencies, as recorded on the Device Deficiency Form will be provided.

5.3.3 Posterior Capsular Opacification

The number and percentage of eyes within each category of subjective posterior capsule opacification will be tabulated by visit. A listing of all posterior capsular opacification data will be provided with the following variables: subject, visit, eye and posterior capsular opacification including none.

5.3.4 Posterior Capsulotomy

The number and percentage of eyes with posterior capsulotomy will be tabulated. A listing of all posterior capsulotomy data will be provided with the following variables: subject, visit, eye, posterior capsulotomy was performed/not performed, date of the procedure and size.

5.3.5 IOL Position Change (tilt and decentration)

Descriptive statistics (numbers and percentages) on eyes in IOL position category (Tilted, Decentered) will be presented. In addition, a listing of subjects with IOL position change including no change will be provided. The listing will include the following variables: subject, visit, eye and no change/amount of tilting or decentration.

5.3.6 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg. Descriptive summaries (mean, standard deviation, N, median, 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: subject, age, sex, visit, eye, baseline value, value at the visit and a change from baseline value. Also a listing including all intraocular pressure data will be provided.

5.3.7 Surgical Problems

Descriptive statistics (numbers and percentages) on eyes with surgical problems will be presented. A listing of all eyes will be presented by subject, eye, with/without surgical problem and description of surgical problem.

5.3.8 Slit Lamp Examination

For each slit-lamp parameter, number and percentage of each category will be provided by visit. A listing will be provided for all slit-lamp data at all visits with the following variables: subject, visit, eye and normal/abnormal findings at the visit.

5.3.9 Dilated Fundus Examination

For each dilated fundus parameter, number and percentage of each category will be provided by visit. A listing will be provided for all fundus parameter at all visits. The listing will include the following variables: subject, visit, eye and normal/abnormal findings at the visit.

5.3.10 IOL Observations

IOL observations will be summarized using descriptive statistics, including frequency (N) and percent of eyes at any post-operative visit. A listing will be provided for all IOL observation data at all visits with the following variables: subject, visit, eye, IOL observation including specifying text of other IOL observation at the visit and evaluation of clinical significance.

5.4 Interim Analysis for Safety

No interim analysis is planned.

6 Pharmacokinetic Analysis Strategy

Not Applicable.

7 Analysis Strategy for Other Endpoints

Not Applicable.

8 Sample Size and Power Calculations

To enroll more than or equal to 30 eligible T2 eyes used for analysis, at least 30 subjects will be evaluated by a new Alcon Toric calculator and unilaterally or bilaterally implanted with the AcrySof IQ PanOptix IOL (TFNT20).

Using a new Alcon calculator, percentage of eyes with ≤ 0.25 D refractive cylinder at Visit 3/3A (Day 30-60) in T2 group was estimated as 60.9% based on a previous [redacted] (T2) study conducted in US. Using the same calculator, the percentage in T0 group was recalculated as 29.2% from the combined result of studies (non-Toric T0 lenses) conducted in Japan [redacted] Statistical test will be conducted to compare percentage of T2 with a constant of 29.2% as percentage of T0. With 30 eyes from 30 subjects in T2 group, assuming the percentage of T2 is equal to 60.9% [redacted] the statistical power to demonstrate superiority of T2 to T0 is 91.6% with one-sided alpha of 2.5%, using an exact test of binomial proportion.

9 References

No references.

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 2.0 of the study protocol.

[redacted]

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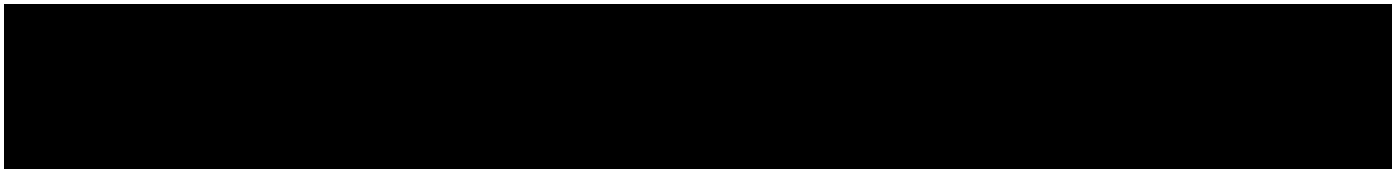

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