Post-market Clinical Study of AcrySof IQ PanOptix Intraocular Lens In Chinese Population

STUDY ID
ILH297-C004

STATISTICAL ANALYSIS PLAN

NCT04755231

Statistical Analysis Plan

Post-market Clinical Study of AcrySof® IQ PanOptix® Intraocular Lens in Chinese Population

Protocol number: ILH297-C004

[redacted]

Version No. and Date: Version 1.0, Aug 27, 2021

Signature Page of Statistical Analysis Plan

The Statistical Analysis Plan version 1.0 (date: May 21, 2021) is based on the protocol version 2.0 (date: November 5, 2020).

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Revision History

Version No.	Version Date	Author	Major Changes
1.0	20210521	[redacted]	N/A - Version 1

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1.0 Introduction

The statistical methods and rules described in this Statistical Analysis Plan (SAP) are based on the post-market clinical study protocol of AcrySof IQ PanOptix intraocular lens (model: TFNT00) in Chinese population [redacted]

This document describes the rules and specifications for the reporting and analysis of post-market clinical study protocol of AcrySof IQ PanOptix intraocular lens (model: TFNT00) in Chinese population. This document describes the data to be summarized and analyzed, as well as the specific statistical analysis to be implemented. The shells for the tables and lists to be presented in the Statistical Analysis Report (SAR) and Clinical Study Report (CSR) will be elaborated and explained in a separate document.

The objective of this document is to provide guidance on the statistical analysis of relevant study data. This document will be compiled based on the existing version of the protocol, and subsequent revisions must be agreed by the biostatistician of Kun Tuo Medical Research and Development (Beijing) Co., Ltd. ("Kun Tuo") and Alcon related project personnel. In addition, some basic information of this study (such as study objective, study design) involved in the protocol will be listed in this document for readers' understanding. This document must be finalized and signed before the database is locked. This document will replace the statistical analysis section involved in the protocol. If there is any inconsistency between the document and the protocol, it is required to be listed, described and explained in the document. After the document is finalized, any additional exploratory or other non-conclusive analysis and its explanation are required to be elucidated in the SAR and CSR. At this time, there is no need to change this Statistical Analysis Plan. After the database is locked, any analysis inconsistent with this document is required to be agreed by the biostatistician of Kun Tuo and Alcon related project personnel, and elaborated in the SAR and CSR.

2.0 Objectives of Clinical Trial

The primary objective of this clinical study is to assess the clinical performance of PanOptix Intraocular Lens (model: TFNT00) in Chinese population, especially the observation of visual acuity and visual adverse reactions. The data in this clinical study will be submitted to the National Medical Products Administration for renewal of the registration of PanOptix Intraocular Lens.

3.0 Study Design

3.1 General Description

This clinical study is a prospective, single-arm, multi-center, post-marketing clinical study. The study is designed based on the *Guidelines for Clinical Trials of Intraocular Lenses* (hereinafter referred to as the *Guidelines*), and refers to the content about clinical trials in ISO11979-7.

The product in this clinical study is PanOptix Intraocular Lens (model: TFNT00), which is an ultraviolet and blue light filtering foldable multifocal IOL. It is intended for implantation in the capsular bag in the posterior chamber of the human eye to replace the human eye lens. This position allows the IOL to function as a refractive medium, thereby correcting the aphakic state. The IOL is a biconvex optical surface design, and its front surface includes an aspheric design and a diffractive structure. The diffractive structure divides the incoming light to provide distance, intermediate, and near vision ranges. The IOL provides clinicians with more options by increasing a +2.17 D addition power of intermediate visual acuity and a +3.25 D addition

power of near visual acuity. This product is suitable for adult patients who require primary implantation of an intraocular lens in the capsular bag in the posterior chamber after cataract extraction with distance, intermediate and near visual acuity requirements so as to improve near, intermediate and distance visual acuity and reduce spectacle dependence.

In this clinical study, subjects will receive binocular implantation of PanOptix Intraocular Lens. In terms of effectiveness, the study will mainly assess the visual performance at Month 6 after surgery; in terms of safety, the study will mainly assess the safety performance at Month 6 and Month 12 after surgery. All the effectiveness and safety evaluation indicators will be followed up to Month 12 after surgery, and an interim analysis will be performed on the data when all subjects have completed the 6-month follow-up.

3.2 Sample size

The study plans to recruit (signing of informed consent form) approximately 158 subjects at no more than 8 sites in China in order to include 142 subjects (284 eyes). It is expected that 127 subjects (254 eyes) will complete the study.

According to the CSRs summarized in PanOptix DL Response for China registration, the ocular SAE rate is 1.80%. A sample size of 127 subjects would ensure more than a 90% probability of observing at least one AE for any event that has a true incidence of 1.8% or greater.

Allowing for a 10% screening failure rate, approximately 158 subjects will be enrolled to obtain about 142 subjects who will undergo IOL implantation in both eyes. Assuming a further 10% dropout rate at Month 12 of follow-up, it is expected that 127 subjects (254 eyes) will complete the study.

3.3 Report text

Please refer to Figure 7-1 Study Design Flowchart in the protocol for the trial flowchart.

3.4 Changes from the Protocol

Demographics and baseline characteristics in the protocol will be summarized using FAS and PP. In this analysis plan, only FAS will be used.

4.0 Planned Analysis

This section will record the analysis of all study plans in order. This section will include the interim analysis in the plan and the analysis of the final plan. All analysis of all plans will be implemented by the biostatistician of Kun Tuo after the SAP is authorized, the database is locked and subject eligibility is determined by the Sponsor.

This study will implement the following analyses:

- Interim Analysis
- Final Analysis

4.1 Interim Analysis

This study plans to conduct an interim analysis of all data 6 months after all subjects have their second eye implanted.

4.2 Final Analysis

The final analysis of this project will be performed 12 months after all subjects are implanted with the second eye. Unless stated otherwise, all final planned analyses specified in this SAP will be implemented by the biostatistician of Kun Tuo.

5.0 Analysis Sets

5.1 Safety Set (SS)

The safety analysis set includes all subjects who have tried the implantation of the investigational intraocular lens (IOL) (successfully implanted or aborted after IOL contact with the eye).

5.2 Full Analysis Set (FAS)

The full analysis set (FAS) includes all subjects who have had the investigational IOL successfully implanted in at least one eye and have undergone at least one postoperative effectiveness assessment (BCDVA, UCDVA).

5.3 Per Protocol Set (PP)

The per protocol analysis set (PP) is a subset of FAS and excludes all data/subjects that have met any of the critical deviation or evaluability criteria identified in the DEP.

6.0 General Considerations

6.1 Reference Start Date and Number of Study Days

The number of study days will be calculated from the reference start date and be used to indicate the number of start/end days of the assessment and event.

The reference start date is defined as the date of the first treatment of the investigational device (that is, the day of surgery is Day 0), and will appear in the list of all assessment/event dates.

- If the event date is not earlier than the reference date:

  Number of study days = (event date – reference date) + 1

- If the event date is earlier than the reference date:

  Number of study days = (event date-reference date)

If the event date is incomplete or missing, the date in the list will remain incomplete or missing, and the number of study days and any corresponding duration will be presented based on the filling method specified in Annex II (Specifications for Incomplete Dates).

6.2 Baseline

The baseline is defined as the last non-missing measurement (including unscheduled measurements) taken before the reference start date. Adverse events and device deficiency on the reference start date will be considered post-baseline.

6.3 Data on Repeated Tests, Unscheduled Visits and Early Withdrawal

The summary by visit generally only presents the data recorded by the routine visit. Unscheduled measurements are not included in the summary by visit. For repeated tests (with the same visit number), the latest available measurement for that visit will be used for the summary by visit. Data on early withdrawal is not included in the summary by visit. The list will include data on scheduled, unscheduled visits and early withdrawal.

6.4 Appointment of visit windows

According to protocol version 2.0, the following table describes the visit window for this study.

Visit	EYE	Day
Visit 0 Pre-Op	Both eyes	Day -28-0
Visit 00 OP[1]	1st Eye	Surgery
Visit 1	1st Eye	Day 1-2
Visit 2	1st Eye	Day 7-14
Visit 00A OP[2]	2nd Eye	Surgery
Visit 1A	2nd Eye	Day 1-2
Visit 2A	2nd Eye	Day 7-14
Visit 3A	Both eyes	Day 30-60(Post second eye implant)
Visit 4 A	Both eyes	Day 90-120(Post second eye implant)
Visit 5A	Both eyes	Day 180-210(Post second eye implant)
Visit 6A	Both eyes	Day 360-390(Post second eye implant)
Early Withdrawal	N/A	N/A

1. Visit 00 (1st eye surgery) must occur within 28 calendar days from Pre-operative Visit (Visit 0).
2. Visit 00A (2nd eye surgery) must be performed within 7 to 28 calendar days after Visit 00 (1st eye surgery).

6.5 Statistical test

No inference is made about the primary endpoints. Therefore, no hypothesis tests are formulated.

6.6 General Calculation

Continuous variables will be summarized using number of observations, mean, standard deviation (SD), median, minimum and maximum, as well as confidence interval (CIs) or confidence limit, as applicable.

Frequency and percentage are used for descriptive statistics of the categorical variables.

For quantitative measurements, the calculation of the baseline change is as follows:

- Tested value of visit X – baseline value

6.6.1 Rules for Calculating Precision (Number of Decimal Places)

- The mean, median, and CI precision are the precision of the original data +1. E.g., the original data is x.x, and the mean is x.xx.
- The precision of SD and SE is the precision of the original data +2.
- The min/max precision is the same as the original data.

[redacted]

7.0 Statistical Consideration

7.1 Covariate Adjustment and Factors Included in the Analysis

Not Applicable.

7.2 Multicenter Study

This study will be implemented by multiple investigators in multiple sites. Central factors are not considered in the analysis.

Site combination is not performed for the analyses in this study.

7.3 Missing Data

Missing values will not be processed in this study.

7.4 Examination of Sub-groups

No subgroup analysis will be performed in this study.

8.0 Output Presentation

Appendix 1 describes the specifications for presenting output data.

The template provided with this SAP describes the output presentation of this study, and the format and content of summary tables, figures and lists are provided by the biostatistician of Kun Tuo.

9.0 Distribution and Withdrawal

All subjects enrolled in this study who provided informed consent are included in the calculation.

Discontinuation of the trial and the reason for discontinuation before implantation of the lens, attempt to implant the lens, successful implantation of the lens, completion of the trial, discontinuation of the trial and the reason for discontinuation after implantation of the lens, the number and/or percentage of the enrolled subjects will be described.

In addition, based on the full analysis set, the number and percentage of subjects, the number and percentage of subjects with missing causes, and the number and percentage of subjects with non-missing data will be described in accordance with the first eye, second eye, and visit.

The number and percentage of subjects in each analysis set are summarized according to the first eye, second eye, all eyes, and all subjects.

The number and percentage of subjects undergoing IOLs implantation, the number and percentage of subjects with screening failure, the number and percentage of subjects with trial termination before lens implantation after passing screening, and the number and percentage of all subjects are summarized by the investigator.

10.0 Demographic and Other Baseline Characteristics

Demographic data and other baseline characteristics will be presented to FAS.

This study will report the following demographic and other baseline characteristics in terms of sample size, mean, median, standard deviation, maximum and minimum:

- Age (years)
- Anterior Chamber Depth (mm)
- Axial Length (mm)
- Corneal curvature (D) (corneal astigmatism (D)= $abs(K_1 - K_2)$)
- Monocular BCDVA (logMAR)
- Binocular BCDVA (logMAR)

The number and percentage of subjects will be described for:

- Age group (< 65 years old; ⩾ 65 years old)
- Gender

11.0 Effectiveness Results

11.1 Effectiveness Analysis

This study defines 4 primary effectiveness endpoints [redacted] The primary effectiveness endpoints will be statistically analyzed in the FAS and PP analysis sets. [redacted]

11.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoints of this study include the following, with the Month 6 results as the most critical endpoints:

- Percentage of eyes with BCDVA equal to or better than 0.3 logMAR
- Mean monocular and binocular BCDVA
- Mean monocular and binocular DCIVA(60cm)
- Mean monocular and binocular DCNVA(40 cm)

11.1.2 Analysis Method of Primary Effectiveness

All primary effectiveness endpoints will be descriptively statistically summarized.

The percentage of eyes with BCDVA equal to or better than 0.3 logMAR will be used as a categorical variable for summary: 0.0 LogMAR and better, 0.1 LogMAR and better, 0.2 LogMAR and better, and 0.3 LogMAR and better, lower than 0.3 LogMAR, including counts and percentages.

Monocular BCDVA, DCIVA and DCNVA are presented by the first eye, the second eye and all implanted eyes; binocular BCDVA, DCIVA and DCNVA are presented by subject, including sample size, mean,

median, standard deviation, maximum and minimum, and two-sided 95% confidence interval and categorical analysis. If necessary, provide a listing of the test results.

[redacted]

11.2 Safety Analysis

11.2.1 Primary Safety Endpoint

The primary safety endpoints of this study are as follows, mainly assessing the safety performance at 6 and 12 months after surgery:

Incidence of ocular adverse events, incidence of secondary surgery, and incidence of severe and most bothersome visual disturbances as reported by the subjects using a questionnaire (QUVID).

11.2.2 Primary Safety Analysis Method

There is no safety hypotheses planned in this study. The focus of safety analysis is to conduct a comprehensive descriptive assessment of adverse events and other listed parameters in the safety analysis set, and list them if necessary.

All AEs occurring from the time a subject signs informed consent to study exit will be accounted for in the reporting. Subjects who have had AEs after signing the informed consent form and before exposure to IP will be displayed in the form of a list; the AEs after exposure to IP (TEAE, treatment emergent adverse event) will be summarized as follows:

1. All adverse events (combined serious and non-serious) form

    a. Ocular

    b. Non-ocular

[redacted]

The number and percentage of secondary surgical interventions (SSIs) will be presented for first implanted eyes, second implanted eyes and for all eyes combine[redacted]

A listing of SSIs will be presented. The listing will include all SSI data with the following variables: subject, age, sex, surgery eye, eye, days from surgery, relationship, and description.

Descriptive summaries (counts and percentages) for rates of severe and most bothersome (separately) visual disturbances as reported by the subjects using the QUVID questionnaire will be presented per user manual.

[redacted]

[redacted]

The types of device deficiencies will be tabulated and a list will be provided.

[redacted]

Appendix 2. Specifications for Incomplete Dates

The filled date is not displayed in the list.

Algorithm of adverse events during treatment

Start Date	End Date	Action
Found	Found	If the start date is < the date of investigational IOL implantation, it will not be considered as a TEAE If the start date is >= the data of investigational IOL implantation, it will be considered as a TEAE
	Incomplete	If the start date is < the date of investigational IOL implantation, it will not be considered as a TEAE If the start date is >= the data of investigational IOL implantation, it will be considered as a TEAE
	Loss	If the start date is < the date of investigational IOL implantation, it will not be considered as a TEAE If the start date is >= the data of investigational IOL implantation, it will be considered as a TEAE
Incomplete, but the known part shows that it is unlikely to be the same day or later than the start date of the investigational drug	Found	Non-TEAE
	Incomplete	Non-TEAE
	Loss	Non-TEAE
Incomplete, it may be the same day or later than the start date of the investigational drug	Found	If the end date is considered as the date of investigational IOL implantation, it will not be considered as a TEAE If the end date is >= the data of investigational IOL implantation, it will be considered as a TEAE
	Incomplete	First, fill in the latest possible date as the end date (that is, if the day is missing, fill in the last day of the month, if both day and month are missing, fill in December 31 of the current year): If the end date is considered as the date of investigational IOL implantation, it will not be considered as a TEAE If the end date is >= the data of investigational IOL implantation, it will be considered as a TEAE
	Loss	Assumed it as a TEAE
Loss	Found	If the end date is considered as the date of investigational IOL implantation, it will not be considered as a TEAE If the end date is >= the data of investigational IOL implantation, it will be considered as a TEAE
	Incomplete	First, fill in the latest possible date as the end date (that is, if the day is missing, fill in the last day of the month, if both day and month are missing, fill in December 31 of the current year): If the end date is considered as the date of investigational IOL implantation, it will not be considered as a TEAE If the end date is >= the data of investigational IOL implantation, it will be considered as a TEAE
	Loss	Assumed it as a TEAE

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