Short Title:

Statistical Analysis Plan ILH297-C003 / NCT03090256

Full Title:

Statistical Analysis Plan ILH297-C003

Protocol Title:	Clinical Investigation of the AcrySof® IQ PanOptix™ IOL Model TFNT00
Project Number:	A01875
Protocol TDOC Number:	TDOC-0052975
Author:	[redacted]
Template Version:	Version 4.0, approved 16MAR2015
Approvals:	See last page for electronic approvals.
Job Notes:	

This is the first revision (Version 2.0) Statistical Analysis Plan for this study. [redacted]

Executive Summary:

Key Objectives:

To describe effectiveness and safety of the AcrySof IQ PanOptix Intraocular Lens (IOL) Model TFNT00 when implanted to replace the natural lens following cataract removal.

Decision Criteria for Study Success:

No formal decision criteria for study success are defined.

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1 Study Objectives and Design

1.1 Study Objectives

The objective of this study is to evaluate safety and effectiveness of AcrySof® IQ PanOptix™ IOL Model TFNT00 when implanted to replace the natural lens following cataract removal.

All analysis in this study will be performed for the descriptive purpose.

1.2 Study Description

This is a prospective, single-treatment, open-label and interventional clinical study. The investigational lens will be placed within the capsular bag after removal of the natural crystalline lens following phacoemulsification. Bilateral implantation of the investigational lens is planned for all subjects. The lens is implanted first to the eye with more advanced cataract. If both eyes have a similar degree of cataract, the surgery first for the right eye will be performed. The time of surgery for the remaining eye (2nd eye) will be within 30days from the first surgery which will be decided by the investigators based on the results of the examination and observation at Visit 1 (1-2 days after 1st eye implantation). Both eyes will be followed throughout the study. The 60 subjects (120 eyes) will be enrolled at 2 sites in Japan. A total of 10 scheduled visits are planned including the Preoperative/Visit 0 and the Operative Visit/Visit 00, Visit 00A. Scheduled postoperative visits must occur at the following intervals: 1-2 days, 7-14 days, 30-60 days and 120-180 days. See Table 1-1 Schedule of Study Visits.

Table 1-1 Schedule of Study Visits

Time from Implantation	Study Visit
Preoperative	Visit 0
Operative (Day 0)	Visit 00 / 00A
1-2 days	Visit 1 / 1A
7-14 days	Visit 2 / 2A
30-60 days	Visit 3 / 3A
120-180 days	Visit 4A

1.3 Randomization

This is a single-treatment study. All subjects will be implanted with AcrySof® IQ PanOptix™ IOL Model TFNT00 in both eyes.

1.4 Masking

This is an open label study.

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-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

AAS and BAS will be used for primary effectiveness analysis. The primary analysis set for primary effectiveness analyses will be the AAS. [redacted]

2.2 Safety Analysis Set

The pre-treatment safety analysis set will include all subjects who consented to participate in the study. The pre-treatment safety analysis set will be the set that will be used to summarize occurrence of adverse experiences prior to exposure to the test article. 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).

The treatment-emergent safety analysis set will be used for all safety variables after contact with the test article.

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 sex, age [<60, 60-69, 70-79, ≥80], systemic complication [None/Yes, details] and past ocular surgery [None/Yes, details]), operation records*, 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, N, 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 N excluded exceeds 10%.

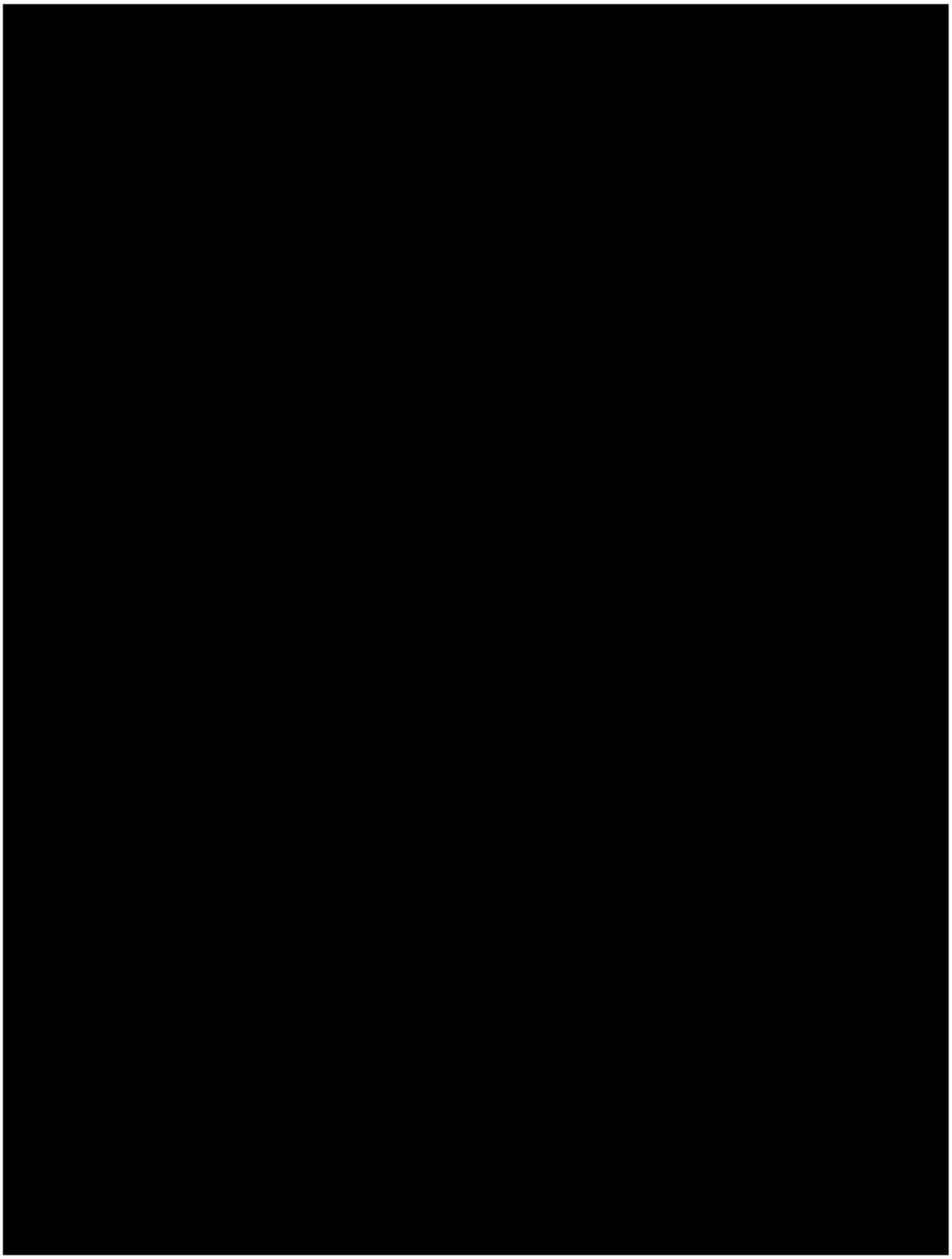
* : Operative Eye, Problems During Surgery, Other Procedures at Surgery, Insertion Instrument, Incision Site, Final Incision Size, anterior capsulotomy size, and Lens Information.

4 Effectiveness Analysis Strategy

4.1 Effectiveness Endpoints

Primary effectiveness variables are as follows.

- Monocular photopic best corrected distance visual acuity (5 m)
- Monocular photopic distance corrected intermediate visual acuity (60 cm)
- Monocular photopic distance corrected near visual acuity (40 cm)



[redacted]

4.2 Efficacy Hypotheses

No formal hypothesis testing is planned.

4.3 Statistical Methods for Efficacy Analyses

Distance visual acuity (5 m), intermediate visual acuity (60 cm) and intermediate visual acuity (80 cm) will be categorized as follows.

- < 0.5
- 0.5 - < 0.7
- 0.7 - < 1.0
- 1.0 ≤

Near visual acuity (40 cm) will be categorized as follows.

- < 0.4
- 0.4 ≤

The N and percent of each category will be provided by visit. For these decimal visual acuity, descriptive statistics (geometric mean, dispersion factor (DF), N, median, min and max) will be provided by visit. Descriptive statistics (arithmetic mean, standard deviation, N, median, min and max) will also be provided for logMAR visual acuity by visit.

In order to compute the mean of decimal visual acuity correctly, the geometric mean must be used. The formulas for transforming from decimal acuity to logMAR score and back are as follows.

$$\textbf{LogMAR} = -\textbf{Log}_{10}\ \textbf{(Decimal Acuity)}$$

$$\textbf{Decimal Acuity} = \textbf{antiLog}\ (-\textbf{LogMAR}) = 10^{-\textbf{LogMAR}}$$

The mean of decimal acuity is defined as

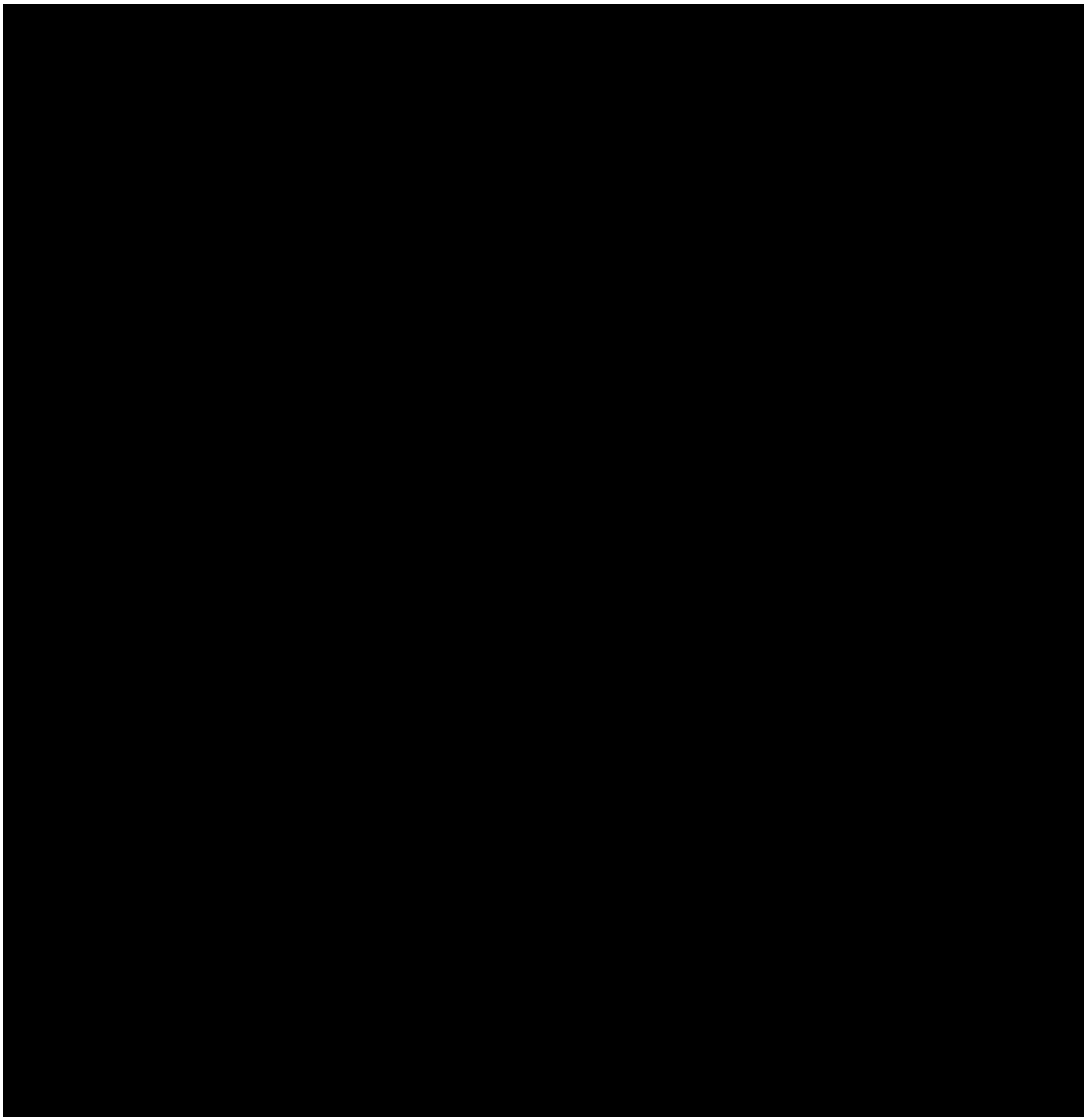
$$\textbf{Mean of Decimal Acuity} = 10^{\textbf{mean of (-Log MAR)}} = 10^{\textbf{mean of Log}_{10}\ \textbf{(Decimal Acuity)}}$$

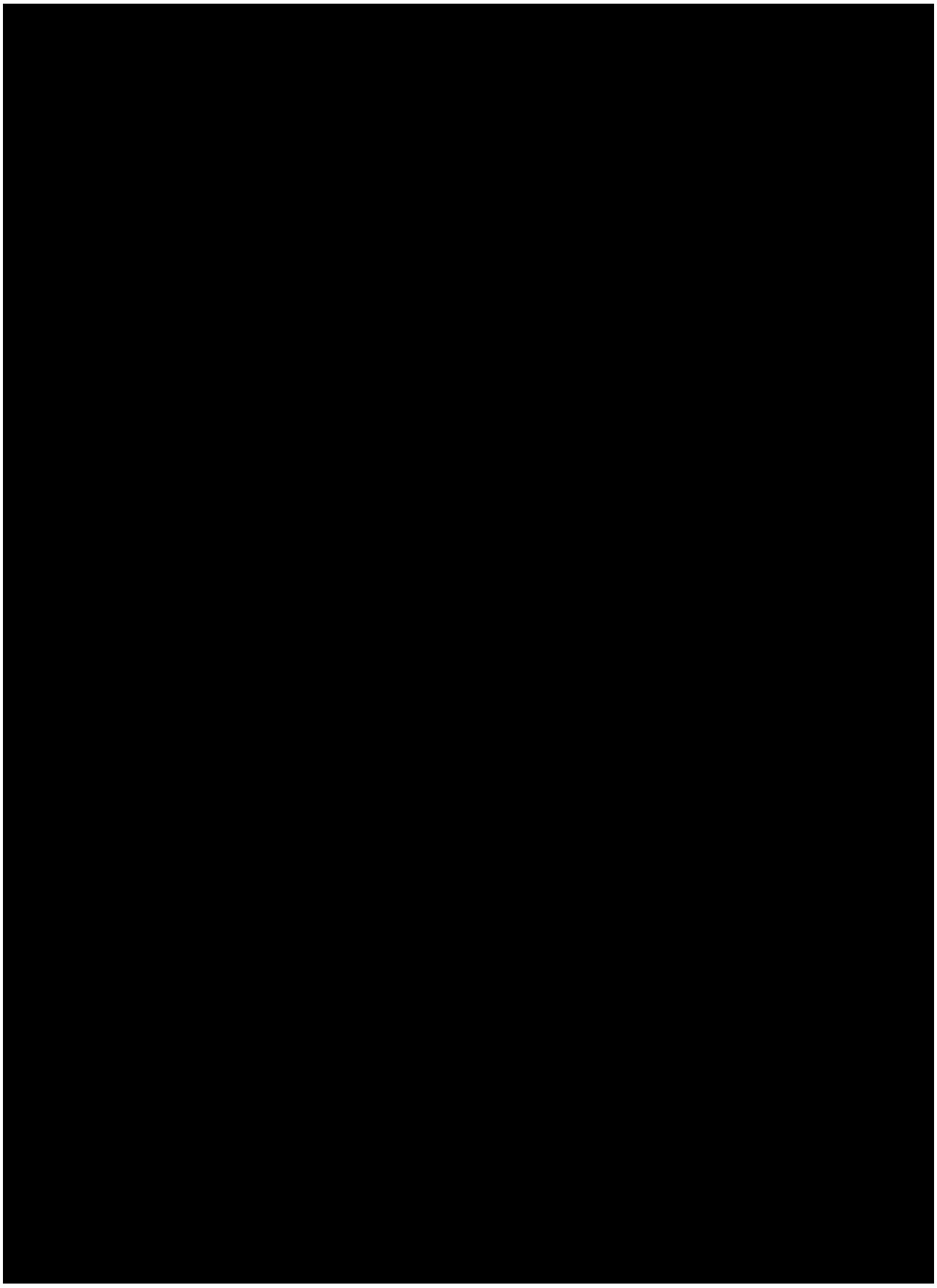
For geometric means, dispersion factors (DF) corresponds to standard deviations and defined as:

$$+DF = 10^{(\text{mean of } \text{Log}_{10} \text{ (Decimal Acuity)} + \text{Log (SD)})} - 10^{\text{mean of } \text{Log}_{10} \text{ (Decimal Acuity)}}$$

$$-DF = 10^{(\text{mean of } \text{Log}_{10} \text{ (Decimal Acuity)})} - 10^{(\text{mean of } \text{Log}_{10} \text{ (Decimal Acuity)} - \text{Log (SD)})}$$

where, Log (SD) is a standard deviation of Log_{10} (Decimal Acuity).





[redacted]

[redacted]

4.4 Multiplicity Strategy

No hypothesis tests are planned.

4.5 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses for number and percentage of categorized primary endpoints as below will be conducted to assess the consistency of treatment effect across various subgroups.

Monocular photopic best corrected distance visual acuity (5 m) and Monocular photopic distance corrected intermediate visual acuity (60 cm)

- < 0.5
- 0.5 - < 0.7
- 0.7 - < 1.0
- 1.0 ≤

Monocular photopic distance corrected near visual acuity (40 cm)

- < 0.4
- 0.4 ≤

The consistency of the treatment effect of the primary endpoints will be assessed descriptively using summary statistics by category of the following subgroup factors:

- Age category (<60, 60-69, 70-79, ≥80 years)
- Sex (Female, Male)
- Investigator

Also, 5m, 60cm and 40cm visual acuity from primary [redacted] effectiveness variables will be analyzed in the same manner by subgroup of photopic pupil size at Visit 4A (≤2.5mm, >2.5 -<4mm, ≥ 4mm), retrospectively.

4.6 Interim Analysis for Efficacy

No interim analysis is planned for this study.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Secondary Surgical Interventions Related to the Optical Properties of the IOL

- Adverse Events (Including Secondary Surgical Interventions Not-Related to the Optical Properties of the IOL)
- Device Deficiencies
- Fundus Visualization
- Intraocular Pressure
- Slit Lamp Examination
- Dilated Fundus Examination
- IOL Observations
- Subjective Posterior Capsule Opacification
- Posterior Capsulotomy
- Lens Decentration and Tilt
- [redacted]
- Laser Flare Meter
- Subjective Symptoms
- Problems during Surgery

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 Secondary Surgical Interventions Related to the Optical Properties of the IOL

Secondary surgical intervention (SSI) will be recorded when secondary surgical intervention was performed. Number and percentage of eyes will be summarized for secondary surgical intervention related to the optical properties of the IOL at any post-operative visit where the

data are collected, separately for first implanted eye and second implanted eye. If secondary surgical intervention is performed, a subject listing that contains subject identification (investigator number, subject number) and visit will be provided, separately for first implanted eye and second implanted eye.

5.3.2 Adverse Events (Including Secondary Surgical Interventions Not-Related to the Optical Properties of the IOL)

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. All information obtained on AEs will be displayed by subject.

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

Also, patient listings will be provided for adverse experiences occurred from informed consent to exposure to the test article with pre-treatment safety analysis set.

5.3.3 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.

5.3.4 Fundus Visualization

Fundus visibility will be assessed by mydriatic slit lamp examination. Fundus visibility will be judged as no (no difficulty) or yes (difficulty). The results of fundus visibility will be summarized in each category using the number and percentage of eyes by first and second implanted eye at each scheduled visit where the data are collected. Eyes with difficulty in fundus visualization will be summarized and sorted by first or second eye, by subject identification (investigator number, subject number) and by visit. Eyes with missing follow-up values of fundus visualization will be summarized and sorted by first or second eye, by subject identification (investigator number, subject number) and by visit. The listing will include the following variables: investigator, subject, age, sex, visit, eye and no difficulty/difficulty at the visit.

5.3.5 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole 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. Eyes with missing follow-up values of intraocular pressure will be summarized and sorted by first or second eye, by subject identification (investigator number, subject number) and by 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, visit, eye, baseline value, value at the visit and a change from baseline value.

5.3.6 Slit Lamp Examination

For each slit-lamp parameter, number and percentage of each category will be provided by visit. Also, number and percentages of eyes that experience abnormality at any post-operative visit will be presented. Eyes with missing follow-up values of slit-lamp examination will be summarized and sorted by first or second eye, by subject identification (investigator number, subject number) and by visit. 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, visit, eye and normal/abnormal findings at the visit.

5.3.7 Dilated Fundus Examination

For each dilated fundus parameter, number and percentage of each category will be provided by visit. Also, number and percentages of eyes that experience abnormality at any post-operative visit will be presented. Eyes with missing follow-up values of dilated fundus examination will be summarized and sorted by first or second eye, by subject identification (investigator number, subject number) and by visit. 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, visit, eye and normal/abnormal findings at the visit.

5.3.8 IOL Observations

IOL observations will be summarized using descriptive statistics, including frequency (N) and percent of eyes at any post-operative visit. The listing will include the following variables: investigator, subject, age, sex, visit, eye, IOL observation including specifying text of other IOL observation at the visit and evaluation of clinical significance.

5.3.9 Subjective Posterior Capsule Opacification

The number and percentage of eyes within each category of subjective posterior capsule opacification will be tabulated by visit.

5.3.10 Posterior Capsulotomy

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

5.3.11 Lens Decentration and Tilt

Tables which include the number and percent in each IOL position measurement category (Tilted > 10 degrees and Decentered > 0.5 mm) will be presented at any post-operative visit. For eyes with IOL tilting or decentering, a table listing the subject, investigator, visit and amount of decentering or tilting will be presented.

[redacted]

5.3.13 Laser Flare Meter

Flare value will be measured by laser flare meter. Descriptive statistics will be provided for flare value including mean, standard deviation, N, median, minimum and maximum at scheduled visit where the data are collected, separately for first implanted eye and second implanted eye. The listing will include the following variables: investigator, subject, age, sex, visit, eye and value at the visit.

[redacted]

[redacted]

5.3.15 Problems during Surgery

Surgical problems will be summarized using descriptive statistics, including number and percent of eyes, separately for first implanted eye and second implanted eye. A listing of eyes with surgical problems will be presented by subject identification (investigator number, subject number), surgical problem(s), separately for first implanted eye and second implanted eye.

5.4 Interim Analysis for Safety

No interim analysis is planned for this study.

6 Pharmacokinetic Analysis Strategy

Not Applicable.

7 Analysis Strategy for Other Endpoints

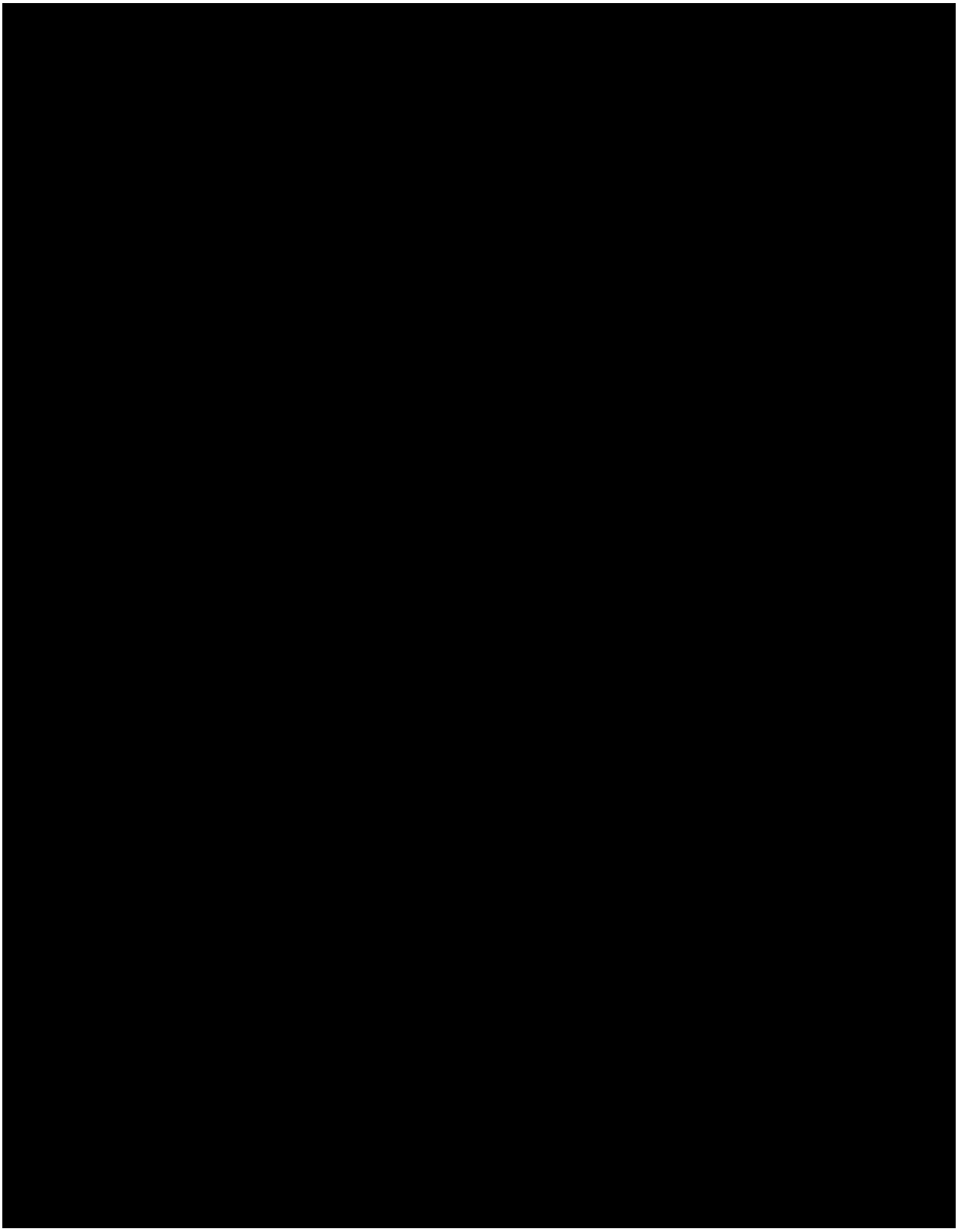
Not Applicable

8 Sample Size and Power Calculations

The 60 eligible subjects will be bilaterally implanted with the AcrySof IQ PanOptix IOL (TFNT00). The purpose of this study is to describe safety and effectiveness of the investigational lens. The sample size is not determined on the basis of a statistical power calculation. With a sample size of 60, a two-sided 95% CI for the mean based on the t-statistic will extend 0.26*SD units from the observed mean. Also, a 95% confidence interval of 50% (30/60) is (36.8%, 63.2%) based on the exact method.

9 References

No references.



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