Statistical Analysis Plan

POST-APPROVAL STUDY OF THE TECNIS® TORIC IOL,

MODELS ZCT300 AND ZCT400

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STATISTICAL ANALYSIS PLAN

Protocol

TIOL-202-TPAS

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1. Introduction

This document summarizes the statistical methods to be implemented during the analysis of data for the post-approval study of the TECNIS® Toric IOL models ZCT300 and ZCT400. The purpose of this study is to evaluate the rates of severe visual distortions for the TECNIS Toric IOLs with >2.0 D of cylinder correction at the corneal plane in a larger population in clinical practice compared to a control (model ZCB00). This study will be a prospective, multicenter, bilateral, open-label, parallel group clinical investigation. Subjects are to be bilaterally implanted with the toric ZCT (models ZCT300 and ZCT400) or the control ZCB00 IOL.

The key timeframe for analysis will be the six month visit. The primary endpoint for this study is the rate of severe visual distortions defined as the proportion of subjects who report a severe visual distortion under overall circumstances at 6 months for any of the following 5 visual distortion items of interest:

- lines that slant, tilt, split or separate
- flat surfaces appearing curved
- objects appearing further away or closer than they actually are
- objects appearing to have a different size or shape
- physical discomfort related to vision

For the primary endpoint, severe visual distortions will be assessed using the overall circumstance reply at the 6 month visit. For the primary endpoint, the frequency and proportion of subjects reporting one or more of these items as severe will be used to determine the rate of severe visual distortions.

Results from individual visual distortion items on the PRVDQ questionnaire will also be reported for overall and with and without correction..

Other endpoints include: rates of IOL repositioning procedures (secondary surgical intervention) due to IOL misalignment and rates of other adverse events.

2. Analysis Populations and Data Conventions

2.1 Analysis Population

For questionnaire data, the primary analysis population will be all subjects implanted binocularly with a toric ZCT or control ZCB00 IOL and having available data at the six month visit or at a prior postoperative visit with questionnaire data carried forward. In addition, data for severe visual distortions (based on the 5 defined items) will also be reported for all bilateral subjects and those with only one eye implanted and the fellow eye having phakic status, a cataract, or another IOL. For questionnaire data, subjects with missing data for symptoms of visual distortion at the six month visit will have the last reported value carried forward if the subject had an earlier visit unless the subject had an IOL repositioning procedure or IOL removal in which case the last reported postoperative visual distortion data available prior to the repositioning/removal procedure will be used.

For severe visual distortions (based on the 5 defined items) an additional analysis population will be evaluated that includes all subjects with last observation carried forward for missing data as described above as well as use of data imputation for

subjects with no available data at any time point. Imputation for those with no data will be performed using MCMC multiple imputation techniques as described in Little & Rubin[1] and implemented using the MI and MIANALYZE procedures[2] in SAS® (Version 9.4). The degree of missingness for severe visual distortions based on the 5 defined items will be reported. Sensitivity analyses will be performed for severe visual distortions based on the 5 defined items for the final data analysis to evaluate missing at random assumptions.

Data will be primarily reported for both toric IOL models pooled and for all controls, however, for severe visual distortions (based on the 5-items), analyses will also include reporting the data separately for bilateral subjects in the lower-cylinder group (those implanted with the ZCT300) and the higher-cylinder group (those implanted with the ZCT400). Control subjects will be included in the lower- or higher-cylinder groups based on the toric lens they would have received if they had chosen to get a ZCT IOL. Subjects who have a lower-cylinder IOL in one eye (e.g. ZCT300) and a higher-cylinder IOL in the fellow eye (e.g. ZCT400) will be placed in the higher-cylinder group for analysis.

Adverse events will be reported for all study eyes and reported by IOL model for first and second eyes.

2.2 Data Conventions

Statistics will typically include sample size (N), mean, standard deviation (SD), minimum (Min), and maximum (Max) as appropriate for continuous variables. For categorical data, the frequency and proportion will be computed.

2.3 Randomization

Subjects will not be randomized in this study.

3. Accountability/Demographics

3.1 Enrollment

The number of enrolled subjects will be tabulated by site and by IOL model implanted for first and second eyes. Results will also be reported by low and high cylinder IOL subgroups.

3.2 Accountability

The frequency and proportion of subjects with six month data will be provided for toric and control subjects. For those subjects that did not have data available at the six month visit the reasons for the missing visit will be summarized for toric and control subjects.

3.3 Demographics/Preoperative/Operative Parameters

Subject demographic data including age, sex, race, ethnicity and eye color will be presented for toric and control subjects. Age will be classified by less than 60, 60 to 69, 70 to 79, and equal to or older than 80 years old. In addition, age will be summarized with descriptive statistics. The frequency distributions of sex, race, ethnicity and iris color will also be tabulated.

The frequency and proportion of operative complications and additional operative procedures will be reported for first and second eyes for toric and control subjects.

4. Postoperative Analyses – Key Endpoints

4.1 Visual Distortions – Primary Endpoint

The primary endpoint is the rate of severe visual distortions defined as the proportion of subjects who report a severe visual distortion under overall circumstances at 6 months for any of the 5 defined visual distortion items listed in section 1.0. The frequency and proportion of bilateral subjects with severe visual distortions will be reported along with the two-sided 90% confidence interval at the 6 month visit

A non-inferiority test will be performed to compare the proportion of subjects with severe visual distortions between pooled toric lens models and all control subjects using a non-inferiority margin of 0.10. The null and alternative hypotheses are:

H_0: Toric IOL subjects will have a severe visual distortion rate greater than or equal to 10% of that for ZCB00 subjects.

$pToric - pZCB00 \geq 0.10$ (p=proportion with severe visual distortions)

H_1: Toric IOL subjects will not have a severe visual distortion rate greater than or equal to 10% of that for ZCB00 subjects

$pToric - pZCB00 < 0.10$ (p=proportion with severe visual distortions)

The results will be evaluated by examining the upper limit of the two-sided 90% confidence interval of the difference between the two IOL groups (toric minus control) to see if it is greater than or equal to 0.10.

4.2 Other Visual Distortion Endpoints Related to Severe Visual Distortions

In addition to the above information related to the primary endpoint analysis, other analyses will also be performed for severe visual distortion rates (based on the 5 defined items) and will include the frequency and proportion with severe visual distortions. Severe visual distortion data for the overall circumstance will be reported for the low (ZCT300) and high cylinder (ZCT400) subgroups for bilateral subjects to evaluate if there is a trend of increasing severity for the higher cylinder IOL group. The severe visual distortion rate will also be reported by IOL group for all subjects (bilateral plus those implanted in one eye (with a cataract, phakic or having another IOL in the fellow eye). In addition, an analysis including all subjects using imputed data for subjects with no questionnaire data available at any visit will also be reported.

Additional analyses including covariates will also be performed for bilateral subjects. A logistic regression model with overall severe visual distortion rates as the dependent variable and IOL group, age, gender, race, cylinder power (low- vs high-cylinder subgroups) and the interaction of age with IOL group and gender with IOL group as independent variables will be performed to further evaluate the influence of these variables on severe visual distortions. If covariates are shown to be important then additional analyses will be provided for those covariates. Results for severe visual

distortions will also be reported by study site for each IOL group. Although there are a large number of sites, any unusual patterns will be noted (i.e. all severe visual distortions at 1 or 2 sites) and further analyses performed to address any site issues.

To evaluate if IOL axis misalignment changes are associated with severe visual distortions, descriptive statistics for IOL axis misalignment will be reported for Toric subjects with and without severe visual distortions. In this study, axis misalignment is defined as the difference between the Toric IOL axis marker location from the slit lamp evaluation and the steep meridian from the postoperative keratometry measurement. This measurement is intended to evaluate toric IOL misalignment as a possible reason for severe visual distortions experienced by a subject at a specific postoperative timepoint. This axis misalignment measurement is not a measure of toric IOL rotational stability, but a measure of toric IOL alignment relative to post-surgical keratometry steep meridian [as it is known that cataract surgery can induce changes in the cornea].

4.3 Other Visual Distortion Endpoints:

The frequency and proportion with each response will also be reported for individual visual distortion items on the questionnaire and will be reported by IOL group for bilateral subjects for overall and with and without correction.

4.4 Other Safety Endpoints:

The frequency and proportion of medical and lens findings will also be reported for first and second eyes of toric (ZCT) and control (ZCB00) subjects. The frequency and proportion of adverse events at any time postoperative will also be reported.

For subjects with serious or device related adverse events or reports of severe visual distortions, additional detailed information will be provided as appropriate and may include such items as uncorrected and corrected distance visual acuity, manifest refraction, keratometry, intraocular pressure, slit-lamp and dilated fundus exam findings, ocular medications, questionnaire responses and prognosis and treatment.

5. One Month Prescription Data:

The frequency and proportion of responses to the question related to offering of spectacle or contact prescription will be reported by IOL group at the one month visit.

6. One Year Data:

Visual distortion findings, adverse events and medical/lens findings at one year will be reported for subjects who experienced a repositioning procedure during the study and for subjects who were reported with severe visual distortions at the 6-month visit.

7. Sample Size Calculations

With 200 toric (ZCT) subjects and 150 control (ZCB00) subjects, this study has over 90% power to evaluate the rate of severe visual distortions for toric subjects as being no more than 10 percent higher than control subjects. This assumes use of one side of a two-sided 90% confidence interval and severe visual distortion rates of 0.02 for toric and control subjects.

With approximately 70 subjects in the higher cylinder toric subgroup (those with a ZCT400 IOL in one or both eyes) the precision of the one-sided upper confidence limit for the proportion of those with severe visual distortions is approximately 0.05 to 0.06 assuming a rate for severe visual distortions of 0.02.

REFERENCES

1. Little, R.and Rubin, D. Statistical Analysis with Missing Data, John Wiley & Sons, Inc. New York, Second Edition, (2002)

2. SAS Institute. The MI and MIanalyze Procedures. SAS/STAT 9.2 User Guide. Cary, N.C.

APPENDIX I

TABLE LISTING

	First Eyes Toric ZCT	First Eyes Control ZCB00	Second Eyes Toric ZCT	Second Eyes Control ZCB00	Toric ZCT Subjects	Control ZCB00 Subjects	Comments
ENROLLMENT/PREOP/OP							
Accountability/Enrollment							
No. of implants by IOL model by investigational site	**x**	**x**	**x**	**x**			Overall and by low/high cylinder subgroup
Accountability					**x**	**x**	
Demographics							
Demographic–Age in years (N, Mean, SD, Min., Max), age in groups (<60,60-69,70-79,>=80), race, ethnicity, gender, iris color					**x**	**x**	
Operative Data							
Surgical Complications: No. and percent with each response	**x**	**x**	**x**	**x**			
Surgical Other Procedures (No. and percent with each response)	**x**	**x**	**x**	**x**			
POSTOPERATIVE DATA Time frame for Reporting: 6 Months							
Prescription Offerred at One Month Visit					**x**	**x**	
Overall Severe Visual Distortions No.,percent and 90%CI for those with and without severe visual distortions at 6 Months or if missing 6 month data at an earlier visit					**x**	**x**	Bilateral subjects
Other Severe Visual Distortion Analyses							
Overall Severe Visual Distortions (No, percent)					**x**	**x**	All subjects and by cylinder subgroup
Overall Severe Visual Distortions By Site (No. and percent)					**x**	**x**	Bilateral subjects

	First Eyes Toric ZCT	First Eyes Control ZCB00	Second Eyes Toric ZCT	Second Eyes Control ZCB00	Toric ZCT Subjects	Control ZCB00 Subjects	Comments
Other Visual Distortion Endpoints							
Individual Visual Distortions-Overall and With and Without Correction No, percent with each response for each item					x	x	Bilateral subjects
Axis Misalignment analysis and Severe Visual Distortion Difference between IOL axis marker location and steep K meridian (N, Mean, SD, Min. Max)					x		Bilateral subjects
Medical, Lens Findings							
No. and Percent with findings at 6 months	x	x	x	x			
Adverse Events							
No. and Percent with adverse events at any time postoperative	x	x	x	x	x	x	