Statistical Analysis Plan

POST–APPROVAL STUDY OF THE TECNIS® TORIC IOL EXTENDED CYLINDER RANGE (ECR), MODELS ZCT450, ZCT525 AND ZCT600

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STATISTICAL ANALYSIS PLAN

Protocol

TIOL-204-EPAS

POST-APPROVAL STUDY OF THE TECNIS® TORIC IOL, MODELS ZCT450, ZCT525, AND ZCT600

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 ZCT450, ZCT525 and ZCT600. The purpose of this study is to evaluate the rate of severe visual distortion with these lenses in clinical practice. This study will be a prospective, multicenter, bilateral, open-label clinical investigation. Subjects are to be bilaterally implanted with at least one eye having a ZCT450, ZCT525 or ZCT600 IOL and the fellow eye having a high cylinder toric IOL (models ZCT300 to ZCT600).

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 the overall circumstance and the with and without correction circumstances.

Other endpoints include: refraction results, uncorrected and corrected distance visual acuity, medical/lens findings and adverse events.

2. Analysis Populations and Data Conventions

2.1 Analysis Population

The primary analysis population will be all bilaterally implanted subjects having available data at the six month visit. In addition, data for severe visual distortions (based on the 5 defined items) will also be reported for all subjects including bilateral subjects and those with only one eye implanted and the fellow eye having phakic status, a cataract, or another IOL. If a subject does not have overall severe visual distortion data available at the six month visit (or had a repositioning procedure or IOL removal performed) then data for the endpoint will be carried forward from the most recent postoperative visit (for general missing data) or the postoperative visit prior to the IOL repositioning or removal. If a subject had an IOL repositioning/removal procedure and did not have visual distortion data available prior to the procedure, then the subject will be considered to have had severe visual distortions for the primary endpoint. For overall 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 questionnaire data at any time point. Imputation for those with no questionnaire data will be performed using multiple imputation techniques as described in Little and Rubin[1] and implemented using the MI and MIANALYZE procedures[2] in SAS® (Version 9.2 or later

version if available). Additional sensitivity analyses will be performed including worst-case analysis where all missing visual distortion data (using the 5 defined items) will be treated as having a severe visual distortion and best-case analysis where missing data is treated as having no severe visual distortion. If more than 10 percent of visual distortion data (using the 5 defined items) are missing then a tipping point analysis will also be evaluated.

Data will typically be reported for all bilateral subjects, however, for some analyses, such as the overall visual distortion endpoint, data will also be reported by IOL group. Subjects who have a lower cylinder IOL in one eye (e.g. ZCT300) and a higher cylinder IOL in the fellow eye (e.g. ZCT450) will be placed in the higher cylinder group for analysis when reporting data by subject.

When reporting data by eye (refraction, monocular visual acuity, complications), the primary eye will be the eye with the higher cylinder IOL (or the first eye if the same IOL is implanted in both eyes). The data will be reported separately for the fellow eye.

Refraction, visual acuity and medical and lens findings for primary and fellow eyes will be reported separately for those eyes with a ZCT450 to ZCT600 IOL and those with a ZCT300-ZCT400 IOL. Adverse events will be reported for all primary and fellow eyes in the study and will indicate the IOL implanted.

2.2 Data Conventions

Descriptive statistics will typically include sample size (N), mean, standard deviation (SD), minimum (Min), 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 primary and fellow eyes.

3.2 Accountability

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

3.3 Demographics/Preoperative/Operative Parameters

Subject demographic data including age, sex, race, ethnicity and eye color will be presented. 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, mean 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 primary and fellow eyes.

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 95% confidence interval at the 6 month visit Thus, the statistical focus is to estimate the rate of severe visual distortions.

4.2 Other Visual Distortion Endpoints Related to Severe Visual Distortions

In addition to the above analysis related to the primary endpoint, other analyses will also be performed for severe visual distortion rates (based on the 5 defined items) in the overall circumstance and will include the frequency and proportion with severe visual distortions. Severe visual distortion data for the overall circumstance will be reported by the IOL group for bilateral subjects. The severe visual distortion rate will also be reported for all subjects enrolled in the study including bilateral subjects and those implanted in one eye (with a cataract, phakic condition or having another IOL (i.e. not a ZCT300-ZCT600 IOL) in the fellow eye). A trend analysis will be performed by plotting the severe visual distortion rate by increasing toric IOL cylinder power. To examine within subject changes for visual distortions (based on the 5 defined items in the overall circumstance) for subjects with data at both the 1 month and 6 month visits, the frequency and proportion will be reported for the following categories: those with severe distortions at both visits, those with severe distortions only at 1 month, those with severe distortions only at 6 months and those with no severe distortions at 1 month or 6 months. In addition, for subjects with severe visual distortions (based on the 5 defined items) at any time point, data will be provided indicating when the severe visual distortions were reported and the status at 6 months. Results for severe visual distortions will also be reported by investigational site. Any unusual patterns due to site will be noted (i.e. all severe visual distortions at 1 or 2 sites) and further analyses performed to address any site issues. Details on age, sex, race and cylinder will be reported for subjects experiencing severe visual distortions.

To evaluate if IOL axis misalignment changes are associated with severe visual distortions, descriptive statistics for IOL axis misalignment will be reported for 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 for bilateral subjects for the overall circumstance and for the with and without correction circumstances.

4.4 Other Endpoints:

The mean percent reduction in cylinder will be reported for primary and fellow eyes at six months and will also be reported by IOL model. The percent reduction in cylinder is calculated for each eye using the following formula:.

100*((Postop Ref. Cyl. - Preop K. Cyl.)/(Target Ref. Cyl. - Preop K. Cyl.))

Key: Ref. Cyl.=absolute refractive cylinder; K. Cyl.=keratometric cylinder;

Refractive data will be referred to the corneal plane prior to determining percent reduction in cylinder.

To evaluate refractive predictability and refractive cylinder compared to intended, the mean absolute refractive cylinder, absolute refractive cylinder adjusted for the intended cylinder (i.e. target cylinder), spherical equivalent, and spherical equivalent adjusted for the intended spherical equivalent will be reported for primary and fellow eyes. The frequency and proportion of primary and fellow eyes within 0.5D and within 1.0D of intended values will be determined for refractive cylinder and spherical equivalent.

The frequency and proportion of primary and fellow eyes at each acuity line will be reported for monocular uncorrected and best corrected distance visual acuity at six months. Similar statistics will be reported for binocular visual acuity.

The frequency and proportion of medical and lens findings will also be reported for primary and fellow eyes. The frequency and proportion of adverse events at any time postoperative will also be reported for primary and fellow eyes for all subjects.

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 or for subjects who were reported with severe visual distortions at the 6-month visit.

7. Sample Size Calculations

With 80 subjects and a severe visual distortion rate of 0.025, this study has 86% probability of achieving a half-width of 0.05 for a 95% confidence interval for the rate of severe visual distortions.

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

	Primary Eyes	Fellow Eyes	All Subjects	Bilateral Subjects	Comments
ENROLLMENT/PREOP/OP					
Accountability/Enrollment					
No. of implants by IOL model by investigational site	**x**	**x**	**x**		
Accountability			**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**		
Operative Data					
Surgical complications: No. and percent with each response	**x**	**x**			
Surgical other procedures (No. and percent with each response)	**x**	**x**			
POSTOPERATIVE DATA Time frame for reporting: 6 Months					
Prescription offered at one month			**x**		
Primary Endpoint					
Primary endpoint – Overall severe visual distortions) No.,percent and 95% CI for those with and without severe visual distortions at 6 Months				**x**	
Other Visual Distortion Analyses and Endpoints					
Overall severe visual distortions **(** No, percent, for those with and without severe visual distortions			**x**	**x**	Also by IOL group for bilateral subjects
Overall severe visual distortions by site (No. and percent)				**x**	
Individual visual distortions-overall and with and without correction No, percent with each response for each item				**x**	
Listing of subjects with severe visual distortions including IOL group, age, race, gender, cylinder, SEQ, BCDVA, UCDVA.			**x**		
Plot of severe visual distortion rate by increasing IOL cylinder				**x**	
Axis Misalignment Analysis and Severe Visual Distortion					
Difference between IOL axis marker location and steep K meridian (N, mean, SD, median, min., max) for those with and without severe visual distortions	**x**	**x**			

	Primary Eyes	Fellow Eyes	All Subjects	Bilateral Subjects	Comments
Refraction Analyses					
Mean refractive data (Mean, S.D., median, min., max.): Percent reduction in cylinder Preop keratometric cylinder Postop refractive cylinder Difference btw. ref. cyl. and intended cyl. Spherical equivalent (SEQ) Difference btw. SEQ and intended SEQ	x	x			For ZCT450-ZCT600 pooled and by IOL model For ZCT300-ZCT400 pooled
Eyes within 0.5D and 1.0D of intended value (No., percent): Postop refractive cylinder Postop spherical equivalent	x	x			For ZCT450-ZCT600 pooled and by IOL model For ZCT300-ZCT400 pooled
Visual Acuity Analyses					
Monocular visual acuity by acuity line level (No., percent): Postop uncorrected distance visual acuity Postop corrected distance visual acuity	x	x			For ZCT450-ZCT600 pooled and by IOL model For ZCT300-ZCT400 pooled
Binocular visual acuity by acuity line level (No., percent) Postop uncorrected distance visual acuity Postop corrected distance visual acuity				x	
Medical and Lens Findings					
No. and percent with findings at 6 months	x	x			For ZCT450-ZCT600 pooled For ZCT300-ZCT400 pooled
Adverse Events					
No. and percent with adverse events at any time postoperative	x	x		x	For ZCT450-ZCT600 pooled and by IOL model For ZCT300-ZCT400 pooled

Key: Primary eyes=eye with the highest ZCT IOL (or first eye if the same IOL in both eyes), SEQ=spherical equivalent, IOL group=subject assignment based on the highest ZCT IOL implanted in either eye, x indicates tables will be provided, SD=standard deviation, Min=minimum, Max=maximum, CI=Confidence interval, BCDVA=best corrected distance visual acuity, UCDVA=uncorrected distance visual acuity