Statistical Analysis Plan

Clinical Investigation of the Safety and Effectiveness of the Next-Generation TECNIS® Symfony® Intraocular Lens Model ZHR00

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STATISTICAL ANALYSIS PLAN

Clinical Investigation of the Safety and Effectiveness of the Next-Generation TECNIS® Symfony® Intraocular Lens Model ZHR00

PROTOCOL NUMBER: SUR-IOL-652-2001

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SAP CHANGE HISTORY

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	N/A	Original	N/A
2.0	2.1	2	Clarify worst-case, best-case and tipping point analysis	To address FDA considerations in letter dated February 28, 2018.
	2.1	2	Add sensitivity analysis to BCDVA endpoint	
	2.1	3	Clarify adverse event data reporting	
	2.1	3	Include all randomized subjects for accountability/enrollment/demographic tables	
	2.3 & 2.5	4	Update reference number	
	6.9	11	Add subgroup analysis, including gender	
	7	11 & 12	Clarify sample size calculation. Add sample size calculation for BCDVA and AE rate comparing to ISO SPE rate	
	8.0	13	Add 2 more references for tipping point analysis	
	Appendix I	14	Include all randomized subjects for accountability/enrollment/demographic tables	
	Appendix I	17	Add sensitivity analysis to BCDVA table	
	Appendix I	21	Add subgroup analysis, including gender	
	Footer	All pages	Change version to 2.0 in footer	

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
2.0	Appendix	17	Add sensitivity analysis to primary DCIVA and secondary (DCNVA and spectacle wear) endpoints tables	Version 1.0 of SAP missed listing the sensitivity analysis for these tables
3.0	1, 2.5, 5.2.2, 6.9, Appendix I	1, 5, 7-8, 11, 17, 20-21	Change secondary effectiveness endpoint from spectacle wear to overall spectacle independence	Update with PRSIQv2 validation work to use composite dichotomous score for overall spectacle independence as secondary effectiveness endpoint
	2.1, Appendix I	1-3, 17	Change analysis population for overall spectacle independence endpoint	Imputation is not recommended in the PRO dossier validation. Update to remove imputation from analysis population.
	2.3, 2.5, 8.0	4, 5, 13	Update reference for the rest of the document	Delete one of the references in section 2.1 due to the removal of MI analysis for overall spectacle independence endpoint. Update the numbering of the references for the rest of the document
	2.5	4-5	Clarify multiplicity adjustment for primary endpoints	Clarify multiplicity adjustment for primary endpoint; only DCIVA endpoint requires hypothesis testing.
	Appendix II	23-24	Add contrast sensitivity conversion formula	Previous version missed contrast sensitivity conversion formula
	Appendix III	25	Add algorithm for constructing overall spectacle independence variable	Update with PRSIQv2 validation work to use composite dichotomous score for overall spectacle independence as secondary effectiveness endpoint
	Footer	All pages	Change version to 3.0 in footer	Reflect correct version number

1 INTRODUCTION

This document summarizes the statistical methods to be implemented during the analysis of data for the TECNIS® 1-Piece aspheric acrylic intraocular lens (IOL), Model ZHR00 (SUR-IOL-652-2001) study. This study will be a 6-month, prospective, multicenter, bilateral, subject/evaluator-masked, randomized clinical trial conducted at up to 10 sites. Subjects will be bilaterally implanted with either the Model ZHR00 IOL or the control Model ZCB00 IOL. Up to 264 subjects will be enrolled to achieve approximately 224 subjects randomized and bilaterally implanted, resulting in approximately 200 evaluable subjects (100 in the study arm and 100 in the control arm) at 6 months.

The key time point for reporting and submitting the PMA supplement will be at 6 months. The primary effectiveness endpoints for this study are mean (LogMAR) monocular distance corrected intermediate visual acuity (DCIVA) under photopic conditions, at a fixed distance (66 cm) and monocular distance-corrected defocus curve at 6-months postoperative.

The secondary effectiveness endpoints are mean (LogMAR) monocular distance corrected near visual acuity (DCNVA) at 40 cm, and overall spectacle independence at 6-months postoperative.

The safety endpoints are monocular best corrected distance visual acuity (BCDVA) non-inferior to control, the rates of adverse events compared to ISO 11979-7[1] SPE (safety and performance endpoints) including SSI due to optical issues causing visual symptoms, contrast sensitivity and visual symptoms via PRO questionnaire evaluated at 6 months.

Other key endpoints include binocular defocus curve testing, other visual acuity, refractive data, medical findings, lens findings, ocular/visual symptoms (non-directed), fundus visualization, subject satisfaction and other questionnaire responses.

2 ANALYSIS POPULATIONS

2.1 ANALYSIS POPULATIONS/HANDLING OF MISSING DATA

The primary analysis population for the primary DCIVA and secondary DCNVA endpoints will be a modified Intent-to-Treat (mITT) analysis for all first-eyes randomized and implanted with either a test or control study IOL. Sensitivity analyses using all randomized subjects will be performed as described below. Since the PRO dossier does not recommend imputation and the validation work for the PRO dossier was based on complete data set (i.e., with non-missing value) for each composite dichotomous score, overall spectacle independence endpoint will follow the guideline of PRO dossier and only use non-missing values for analysis. Therefore, the primary analysis

population for overall spectacle independence will be the safety population (SP) with subjects who are bilaterally implanted with the same study lens in both eyes. For all subjects with missing data for the spectacle independence endpoint at the 6-month visit, information (e.g., percentage missing, reason for missing data, etc.) will be provided. There are no inferential statistics for the defocus curve primary endpoint; therefore, safety population (SP) will be the primary analysis population for this endpoint. The mITT population will be used for the statistical success criterion of the primary DCIVA endpoint and secondary effectiveness endpoint DCNVA where SP will be used for the clinical success criterion of those endpoints since there is no inferential statistics comparison for the clinical success criterion. The primary analysis population for all safety endpoints will be the safety population. The key timeframe for the study endpoint will be at 6-months postoperative visit unless states otherwise.

For eyes that do not have data available at the 6-month postoperative visit, other than PRSIQv2, data will be imputed for the mITT analyses. For continuous variables (DCIVA and DCNVA), planned method to use is the MCMC full-data imputation as described in Little & Rubin[2]. Data imputation and analysis will be performed using the MI and MIANALYZE procedures[3] in SAS® (Version 9.4).

In addition to the above imputation methods, sensitivity analyses using different imputation approaches (worst-case scenario, best-case scenario and tipping point) will also be performed for primary DCIVA and secondary DCNVA and for the safety endpoint of mean BCDVA. These analyses will be performed using all randomized subjects with the IOL group based on the randomization. A worst-case scenario will be performed with the worst score (poorest visual acuity value from all first eyes) assigned to missing data for the test IOL and the best score (best visual acuity value from all first eyes) assigned to missing data for the control IOL. A best-case scenario will also be performed, assigning the best value (best visual acuity value from all first eyes) to missing test IOL data and the worst value (poorest visual acuity values from all first eyes) to missing control IOL data. A tipping point analysis will also be performed if more than 10% of mITT population is missing at the 6-month visit. The tipping point analysis for visual acuity endpoints (DCIVA and DCNVA) will be evaluated using shift parameters of 0 to 0.30 LogMAR in 0.05 LogMAR increments with these shift parameter values adjust the imputation values for the test IOL group. This results in evaluating significance using missing test IOL data that is from 0 to 3 lines worse than imputed values[4].

A Per-Protocol (PP) analysis will also be used for primary effectiveness and secondary endpoints. The PP population for monocular data will include eyes with a test or control lens implanted, evaluated within the proper study interval and without clinically-relevant protocol deviations (deviations that could potentially impact the primary or secondary endpoints) as determined prior to database lock. The PP population for binocular data

will include subjects that do not have any of the deviations stated above in either eye. PP tables will include available data at the time of analysis.

The safety population will consist of all eyes and subjects implanted with either a test or control IOL(s) and with data available at the time of analysis (i.e., no data imputation). Reporting of cumulative complications and cumulative adverse event (occurring at any time postoperative either at standard visits or interim visits) will include data from all study eyes implanted. Thus, all adverse events at any postoperative visit (including standard or interim visit) will be reported unless it is results at a given visit (i.e., 6 months). For all safety endpoints, only the safety population will be used. For BCDVA, a best-case population will also be used, consisting of eyes in the safety population without any clinically-relevant preoperative ocular pathologies or macular degeneration detected at any time.

For the primary DCIVA, and secondary DCNVA, the mITT, PP and safety populations will be used for data reporting. For the defocus curve primary endpoint and overall spectacle independence secondary endpoint, only safety and PP populations will be used for data reporting. For safety endpoints and other endpoints, only the safety population will be used. The primary analysis will be based on first-eye data, unless stated otherwise. However, select data such as some visual acuity variables will also be reported separately for second eyes as supportive data only. Binocular data will be reported for those who are implanted with the same (test or control) IOL in both eyes. For demographics/enrollment/accountability data will also be reported for all randomized subjects whether an IOL was implanted or not with group assignment based on the randomization. Appendix I lists the analysis tables including the endpoints and the populations used to report the results.

2.2 VISIT WINDOWS

Subject visits will occur at Preoperative for both eyes, Operative, 1 day, 1 week and 1 month for each eye, and 6 months for both eyes together. The exact number of days for each interval is described in the protocol. The number of eyes with missing visits or data outside of the visit interval will be reported.

2.3 DATA CONVENTIONS

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

For continuous variables, statistical tests assuming normality will generally be used. However the data will be reviewed to evaluate whether the normality assumption is appropriate. If it is found not to be appropriate, either an appropriate transformation of the data (i.e., logarithmic) may be used or the corresponding non-parametric tests may

be used. Deviations from the proposed statistical guidelines will be substantiated by sound statistical rationale. For categorical data, Fisher's exact test will be used for comparison between IOL groups. Comparisons for ordinal data will be done using the Wilcoxon rank-sum test.

Unless otherwise indicated, alpha will be set to 0.05 for two-sided statistical testing with alpha set to 0.025 for one-sided testing. See Section 2.5 Multiplicity Adjustment below for the primary and secondary endpoints related to product claims.

For visual acuity data, letter scores will be converted to LogMAR prior to analysis[5]. Formulas used for visual acuity analysis are included in Appendix II. For refractive data, all values will be converted to plus cylinder with sphere adjusted for infinity[6]. Formulas used for refractive data are also included in Appendix II.

2.4 RANDOMIZATION

A randomization list will be created by a JJSV biostatistician for each investigational site and the randomization code will be uploaded into the electronic data capture system (EDC). Subjects will be randomized to the investigational Model ZHR00 IOL or the Model ZCB00 control IOL. Unmasked study personnel at the site will be trained to the randomization process through the EDC system and will randomize subjects after the subject has signed the informed consent form, has met all eligibility criteria and the investigator has documented which eye will be the first implanted.

If a surgeon implants the wrong study lens, i.e., other than the one on the randomization schedule, the subject's study data will be analyzed according to the randomization schedule in the mITT population and will be analyzed according to the lens received in the safety population. The subject will be excluded from the Per-Protocol population analysis. If a surgeon implants a non-study IOL (e.g., due to capsule rupture prior to IOL implantation) or if the surgery is canceled in the few days between randomization and surgery (e.g., due to death, illness), the subject will not be part of the mITT, safety or Per-Protocol populations but will be placed in the intended IOL group (IOL group based on randomization schedule) and included in the worst case/best case sensitivity analyses.

2.5 MULTIPLICITY ADJUSTMENT

No multiplicity adjustment is planned for the primary effectiveness endpoints of DCIVA and defocus since only the DCIVA endpoint requires hypothesis testing. One-sided testing with alpha level of 0.025 is planned for this endpoint. No multiplicity adjustment is planned for the safety endpoints.

Due to multiple secondary endpoints, a closed-form hierarchical approach[7,8,9, 10] will be used to evaluate statistical significance. Secondary endpoints will be tested in the following order:

1. Monocular distance corrected near visual acuity at 40cm
2. Overall spectacle independence

Since one-sided testing will be performed, an alpha level of 0.025 will be used. The hierarchical approach for p-value adjustment is based on a statistically significant p-value for each test. Therefore, if other clinical criteria associated with the endpoint are not met but statistical significance is achieved, testing will proceed hierarchically to the following endpoint.

2.6 SITE DIFFERENCES

For the primary and secondary effectiveness endpoints, data will be reported by site. A mixed effects analysis will be used for primary DCIVA and both secondary effectiveness endpoints. The mixed model will be used with IOL group as a fixed effect and site and site by group interaction as random effects. If the interaction term is significant at the 0.15 level than further examination of effects of site or further data stratification by site will be evaluated. Since there is no inferential statistics for the defocus curve primary effectiveness endpoint, only graphs (defocus curve by site) will be presented for the site analysis. Baseline demographic data will also be reported by site.

3 ACCOUNTABILITY/DEMOGRAPHICS

3.1 ACCOUNTABILITY

The number of enrolled subjects will be tabulated by site for first and second eyes. Subject accountability will be summarized as a frequency distribution by scheduled visits. A frequency table by IOL will be generated, showing the number of available eyes (those in interval and outside of the interval) and the number of missing and active subjects.

3.2 DEMOGRAPHICS

Subject demographic data including age, sex, race, and eye color will be presented by IOL group. Age will be determined at the time of the preoperative visit and will be categorized 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, and iris color will also be tabulated.

Comparisons between IOL groups will be performed using Fisher's exact test for demographic categorical data. The null hypothesis is that there is no difference in the proportion with specific responses between IOL groups, whereas the alternative hypothesis is that there is a difference in at least one proportion between IOL groups.

For comparisons between IOL groups for mean age, the two-sample t-test will be used. The null hypothesis is that there is no difference in mean values between IOL groups, whereas the alternative hypothesis is that there is a difference in mean values between IOL groups. Two-sided testing with an alpha level of 0.05 will be used for all demographic variables.

4 PREOPERATIVE/OPERATIVE PARAMETERS

Preoperative and operative parameters for first and second eyes will be reported for each IOL model. The frequency and proportion of eyes with selected responses will be tabulated for categorical data with descriptive statistics used for continuous data. Statistical comparisons between IOL groups will be performed as described above for demographic data. Two-sided testing with an alpha level of 0.05 will be used for all preoperative and operative parameters.

5 POSTOPERATIVE ANALYSES – PRIMARY AND SECONDARY EFFECTIVENESS ENDPOINTS

5.1 PRIMARY EFFECTIVENESS ENDPOINTS

5.1.1 MONOCULAR DISTANCE CORRECTED INTERMEDIATE VISUAL ACUITY (DCIVA)

The first primary effectiveness endpoint is mean (logMAR) first-eye, monocular, distance corrected intermediate visual acuity (66 cm) at 6 months postoperative. Results will be reported by lens group for first eyes using one-sided, two-sample t-tests with alpha level of 0.025. Note that a lower LogMAR value is a better acuity and a higher LogMAR value is a poorer acuity. The null hypothesis is that the mean LogMAR value for ZHR00 eyes is worse than or equal to that for control eyes. The alternative hypothesis is that the mean for ZHR00 eyes is better than that for control eyes.

H_o: $\mu_c - \mu_t \leq 0$ (ZHR00 is worse than (higher logMAR) or equal to control)
H_1: $\mu_c - \mu_t > 0$ (ZHR00 is better (lower logMAR) than control)
where
μ_t =mean LogMAR DCIVA for ZHR00
μ_c= mean LogMAR DCIVA for ZCB00
Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean LogMAR DCIVA score for ZHR00 compared to ZCB00 ($p \leq 0.025$). In addition, clinical significance will be determined by:

- The median DCIVA of the ZHR00 first eyes is at least 0.2 LogMAR.

5.1.2 MONOCULAR, DISTANCE CORRECTED DEFOCUS CURVE

The second primary effectiveness endpoint is monocular mean diopters of defocus where visual acuity is LogMAR 0.2 or better at 6 months postoperative. The diopter of defocus where the mean visual acuity of LogMAR 0.2 or better is achieved will be derived by visual inspection of the defocus curve. The defocus endpoint will only be determined from zero to the negative diopters of defocus; however, the mean LogMAR acuity at each diopter of defocus will be plotted for the defocus range actually tested (+2.0 diopters to -4.0 diopters).

The success criterion is that the Model ZHR00 eyes will demonstrate at least 0.5D greater monocular, photopic, distance-corrected depth of focus compared to the control IOL at 0.2 LogMAR visual acuity threshold, based on visual inspection of the defocus curves.

5.2 SECONDARY EFFECTIVENESS ENDPOINTS

5.2.1 MONOCULAR DISTANCE CORRECTED NEAR VISUAL ACUITY (DCNVA)

The first secondary endpoint is mean (LogMAR) first-eye, monocular, distance corrected near visual acuity under photopic conditions at 40 cm at 6 months postoperative. Results will be compared between lens groups for first eyes using one-sided, two-sample t-tests with alpha level of 0.025. The null hypothesis is that the mean LogMAR value for ZHR00 eyes is worse than or equal to that for control eyes. The alternative hypothesis is that the mean for ZHR00 eyes is better than that for control eyes.

H_o: $\mu_c - \mu_t \leq 0$ (ZHR00 is worse than (higher LogMAR) or equal to control)
H_1: $\mu_c - \mu_t > 0$ (ZHR00 is better (lower LogMAR) than control)
where
μ_t =mean DCNVA LogMAR for ZHR00
μ_c= mean DCNVA LogMAR for ZCB00
Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean LogMAR value for ZHR00 compared to ZCB00 ($p \leq 0.025$). In addition, clinical significance will be determined by:

- The median DCNVA of ZHR00 first eyes is at least 0.3 LogMAR

5.2.2 OVERALL SPECTACLE INDEPENDENCE

The second secondary effectiveness endpoint is overall spectacle independence via binocular PRO questionnaire responses and is defined as the subject reporting “No” need for correction for all 3 conditions (distance, intermediate and near), “None of the time” for correction wear for all 4 conditions (distance, intermediate, near and overall) and “None of the time” for strain to see for all 4 conditions (distance, intermediate, near

and overall). Please see Appendix III for further detail. Spectacle independence results will be reported by lens group and analyzed by Fisher's exact test with a one-sided alpha of 0.025. The null hypothesis is that the proportion of ZHR00 subjects who are spectacle independent is less than or equal to the proportion of control subjects. The alternative hypothesis is that the proportion of ZHR00 subjects who are spectacle independent is greater than that for control subjects.

H_o: $p_t - p_c \leq 0$
H_1: $p_t - p_c > 0$
where
p_t =Proportion of ZHR00 subjects who are spectacle independent
p_c= Proportion of ZCB00 subjects who are spectacle independent
Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly greater proportion of ZHR00 subjects who are spectacle independent compared to ZCB00 subjects (p≤ 0.025). In addition, clinical significance will be determined as follows:

- The proportion of Model ZHR00 subjects who are spectacle independent will be at least 25 percentage points higher than that for the control group

5.3 SAFETY ENDPOINT

5.3.1 MONOCULAR BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)

The first safety endpoint is mean (LogMAR) first-eye, monocular, best corrected distance visual acuity (BCDVA) at 6 months postoperative. Results will be compared between lens groups for first eyes using a non-inferiority approach. The null hypothesis is that the mean difference (control minus test) between the control and test IOLs is ≤-0.1 LogMAR (1 line) with the alternative hypothesis that the mean difference is >-0.1 LogMAR. A two-sided, 90% confidence interval (CI) will be used for evaluation.

H_o: $\mu_c - \mu_t \leq -0.1$ (ZHR00 is worse than (higher LogMAR) or equal to control by 0.1 LogMAR)
H_1: $\mu_c - \mu_t > -0.1$ (ZHR00 is better (lower logMAR) than control by 0.1 LogMAR)
where
μ_t = mean BCDVA LogMAR for ZHR00
μ_c= mean BCDVA LogMAR for ZCB00
Reject the null hypothesis if lower 2-sided 90% CI is >-0.1.

The success criterion is if the lower 2-sided 90% confidence interval for the difference between the IOLs is greater than -0.1.

5.3.2 RATE OF ADVERSE EVENT VS. ISO SPE RATE

Rates of adverse events as determined by ISO 11979-7 will be reported through 6 months. The frequency and proportion of first eyes and second eyes with these events will be reported over time by IOL group. Statistical comparisons to ISO SPE rates will be based on first eye data; adverse event rates for ZHR00 first eyes will be compared to the ISO SPE rates using a one-sided, exact test based on the binomial distribution. The null hypothesis is that the study rate for ZHR00 eyes is lower than or equal to the ISO rate and the alternative hypothesis is that the rate for ZHR00 eyes is greater than the ISO rate. This criterion will be used for all ISO SPE rates. For secondary surgical intervention (SSI), rates for ZHR00 eyes with any SSI will be compared to ISO rates. In addition, rates for lens-related SSI due to optical issues causing visual symptoms will be presented with descriptive statistics.

H_o: $p_t \leq p_i$
H_1: $p_t > p_i$
where
p_t = proportion of ZHR00 eyes with the AE
p_i = ISO SPE rate with the AE
Reject the null hypothesis if one-sided p-value < 0.025.

5.3.3 CONTRAST SENSITIVITY

For the safety endpoint of monocular contrast sensitivity at 6 months postoperative, descriptive statistics including mean, standard deviation, median, minimum, maximum and two-sided 90% confidence intervals will be presented by IOL group for all levels of contrast and lighting conditions.

5.3.4 VISUAL SYMPTOMS VIA PRO INSTRUMENT

For the safety endpoint of visual symptoms via the Patient Reported Vision Symptoms Questionnaire (PRVSQ) at 6 months postoperative, the frequency and proportion of each response will be tabulated by IOL group.

6 POSTOPERATIVE ANALYSIS: OTHER ENDPOINTS

6.1 OTHER INTERMEDIATE AND NEAR VISUAL ACUITY ENDPOINTS

Other intermediate and near endpoints include binocular UCIVA, UCNVA; monocular UCIVA, UCNVA; and monocular low-contrast (10%) DCIVA and BCIVA. These endpoints will be evaluated at 6 months using the safety population. Mean LogMAR values will be reported by IOL group with one-sided two-sample t-tests used for evaluation with alpha set at 0.025. The null hypothesis is that mean LogMAR scores for ZHR00 eyes are worse than or equal to those for ZCB00 eyes. The alternative hypothesis is that mean LogMAR scores for ZHR00 eyes are better than those for ZCB00 eyes.

In addition, the frequency and proportion of first eyes and binocular subjects achieving each line of visual acuity will be reported at 6 months.

6.2 OTHER DEFOCUS CURVE ENDPOINTS

In addition to monocular defocus results described above under secondary endpoints, binocular mean diopters of defocus where visual acuity is LogMAR 0.2 or better will also be evaluated at 6 months using the same methods as described for monocular testing. Monocular and binocular results will be also be stratified by pupil size. For monocular data, defocus curves will also be produced by pupil size (under photopic no glare condition): ≤ 2.5 mm, > 2.5 mm to < 4.0 mm and ≥ 4.0 mm, for each IOL model. For binocular data, average of the two pupil sizes (under photopic no glare condition) will be used. Same pupil size category as monocular data will be presented for binocular data.

6.3 DISTANCE VISUAL ACUITY

The proportion of ZHR00 eyes achieving 20/40 or better BCDVA will be compared to the ISO SPE rates for posterior chamber IOLs (all first-eyes and best-case first eyes) using a one-sided, exact test based on the binomial distribution. The null hypothesis (based on the ISO guidance document) is that the proportion of ZHR00 eyes achieving 20/40 or better BCDVA is greater than or equal to the ISO SPE values and the alternative hypothesis is that the proportion of ZHR00 eyes achieving 20/40 or better BCDVA is less than the ISO SPE values.

The proportion of first eyes achieving each acuity line equivalent for BCDVA will also be reported over time. Descriptive statistics for mean LogMAR and acuity by line will also be reported for monocular and binocular UCDVA.

6.4 MEDICAL/LENS FINDINGS

Rates of postoperative medical and lens findings will be tabulated with the frequency and proportion of eyes with these events reported over time by IOL group. As mentioned above in Section 5.3.2 Safety Endpoints: Rates of Adverse Events, medical complication rates listed in ISO-11979 will be compared to the ISO SPE rates for ZHR00 first eyes using a one-sided, exact test based on the binomial distribution. The null hypothesis is that the study rate for ZHR00 eyes is lower than or equal to the ISO rate and the alternative hypothesis is that the rate for ZHR00 eyes is greater than the ISO rate.

6.5 FUNDUS VISUALIZATION

The fundus exam findings (within normal limits vs. abnormal) and ability to adequately visualize the fundus will be reported by IOL groups. The frequency and proportion with each outcome will be tabulated by IOL groups.

6.6 SATISFACTION AND OTHER QUESTIONNAIRE DATA

Satisfaction and other results from the 1-month and 6-month questionnaire data will be reported for subjects who have received the same test lenses or same control lenses in both eyes. The frequency and proportion with each response will be tabulated by IOL groups.

6.7 MANIFEST REFRACTION

Descriptive analysis of refractive sphere, cylinder and spherical equivalent (MRSE) will be reported by IOL groups for both eyes. Since refraction was performed at 4M, 0.25D will be subtracted from the sphere value. Refractive data will then be converted to plus cylinder notation (see Appendix II).

MRSE is then calculated by the following formula: MRSE = sphere + ½ cylinder.

6.8 IOL POWER CONSTANT ANALYSIS

Descriptive statistics will be provided for IOL power constant analyses with refractive data at 6 months used for the evaluation.

6.9 SUBGROUP ANALYSIS (INCLUDING GENDER)

For the primary and secondary effectiveness endpoints, data will be reported by demographic variables including gender, race and age group (≤59, 60-69, 70-79, >80). Descriptive statistics will be presented by subgroup for DCIVA and DCNVA endpoints. Number and percentage will be reported by subgroup for overall spectacle independence endpoint. Defocus curve will be plotted by subgroup for defocus curve endpoint.

7 SAMPLE SIZE CALCULATIONS

Study sample sizes are based on revision 07 of the draft ANSI Z80.35 standard for extended depth of focus (EDF) lenses, for a modification of a parent lens. Based on this standard, the minimum sample size requirement to assess the safety and performance of an EDOF IOL with an identified parent is 100 bilaterally implanted evaluable subjects per lens group.

7.1 MONOCULAR, DISTANCE CORRECTED INTERMEDIATE VISUAL ACUITY (DCIVA)

For monocular DCIVA, there is over 90% power to detect a 1-line or greater difference in mean visual acuity between the test and control IOL groups (assumes 1-sided testing

with an alpha of 0.025 and standard deviation of 1.6 lines) with 100 subjects in each group.

7.2 MONOCULAR, DISTANCE CORRECTED NEAR VISUAL ACUITY (DCNVA)

For monocular DCNVA, there is over 90% power to detect a 1-line or greater difference in mean visual acuity between the test and control IOL groups (assumes 1-sided testing with an alpha of 0.025 and standard deviation of 1.6 lines) with 100 subjects in each group.

7.3 MONOCULAR, BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)

For monocular BCDVA, there is over 90% power to detect a non-inferiority margin of 1 line between the test and control IOL groups (assumes one-sided alpha=0.05, no difference in mean BCDVA between IOL groups and a standard deviation of 1.2) with 100 subjects in each group.

7.4 SAFETY ENDPOINTS COMPARED TO ISO SPE RATES

For the percent of first eyes achieving 20/40 or better BCDVA compared to ISO SPE rates and for adverse event rates compared to ISO SPE rates, the sample size of 100 test subjects was chosen based on revision 07 of the draft ANSI Z80.35 standard that specifies a minimum of 100 test subjects when the investigational lens is a modification of an approved monofocal parent. This document also specifies that there should be 100 subjects in the control arm. To achieve 100 evaluable subjects in each IOL group and allowing for screen failures and drop outs, it was determined that 264 subjects needed to be enrolled. The following calculations were performed to determine the overall number of subjects in the study. The number of randomized subjects needed (assuming a 10% drop-out): 200/0.9=222.2. This was rounded to 224 so there would be an even number for the two IOL groups. The number of enrolled subjects needed (assuming a 15% screen failure rate): 224/0.85=263.5. This was rounded to 264.

8.0 REFERENCES

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APPENDIX I: TABLE LISTING

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
ENROLLMENT/PREOP/OP							
Accountability/Enrollment							
No. of implants by IOL model by investigational site	X	X	X	X	X	X	mITT/SF/PP and all randomized subjects
Accountability table over time – (No of eyes will be reported for: available for analysis, missing data - discontinued, In interval (no form), missed visit, lost to follow-up, active	X	X	X	X			mITT/SF/PP and all randomized subjects
Out of interval subjects listing – No. of eyes	X	X	X	X			SF
Demographics							
Demographic –Age in years (N, Mean, SD, Min., Max), age in groups (<60,60-69,70-79,>=80), race, sex, iris color					X	X	mITT/SF/PP and all randomized subjects
Age by Site (N, Mean, SD, Min. Max.)					X	X	SF
Other demographic data by site (race, sex)					X	X	SF
Preoperative Characteristics							
Visual Acuity: No. & percent of eyes for each category BCDVA in groups (≤20/30, 20/40, 20/50-20/80, 20/100, >20/100) BCDVA with glare in groups (as above) for those with <20/40 BCDVA Potential Visual Acuity (≤20/30,>20/30)	X	X	X	X			mITT/SF-1st eyes SF-2nd eyes

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
Other Preop Items: No. and percent of eyes for each category Inclusion/exclusion Status (Criteria Met or Criteria Not Met) Medical findings (by finding) Contact lens wear (yes/no) Fundus finding (within normal limits/abnormal) Cataract status (by type) Cataract density (by level) Biometry method (by type) Targeted refraction in diopter groups (<-0.50,-0.50 to -0.26,Plano: 0±0.25,+0.26 to +0.50,>+0.50) Keratometric cylinder in diopter groups (<=1.00, 1.01 to1.50,>1.50)	X	X	X	X			mITT/SF-1st eyes SF-2nd eyes
Other Preoperative Data: (N, Mean, SD ,Median, Min., Max. for each variable) Target spherical equivalent (D) Keratometric cylinder (D)	X	X	X	X			mITT/SF-1st eyes SF-2nd eyes
Preop Optical/Visual Symptoms (No. and percent of eyes with each item) Non-directed optical visual symptoms reported for each symptom indicated)	X	X	X	X			SF
Preop Patient Expectation Questionnaire (No. and percent with each response for each item)					X	X	SF

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
Operative Data							
General Surgical Parameters: No. and Percent with each response Incision type (by type) Incision size in mm (<2.6, 2.6 to 2.7, 2.8 to 3.0, >3.0) Capsulorhexis diameter in mm (≤4.0, 4.1 to 5.0, >5.0) Capsulorhexis centration (centered/eccentric) Capsulotomy method (by type) Lens Removal Method (by method) Viscoelastic agent (by type) Implant instrument (by type) Lens placement (capsular bag, other) Type of closure (sutureless, suture)	X	X	X	X			SF
Surgical Complications: No. and percent with each response Surgical complications (none, all items listed on CRF, other) Other surgical procedures (none, all items listed on CRF, other)	X	X	X	X			SF
Lens Power Implanted (N, Mean, SD , Median, Min., Max. in Diopters (D)	X	X	X	X			SF

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
PRIMARY EFFECTIVENESS ENDPOINTS							
Monocular DCIVA at 66cm (LogMAR) at 6M (N, Mean, SD, Median, Min., Max., 95% CI)	X	X	X	X			mITT/SF/PP/Sensitivity–1st eyes (SF-2nd as supportive data only)
Monocular defocus curve at 6M	X	X					SF/PP
SECONDARY EFFECTIVENESS ENDPOINTS							
Monocular DCNVA at 40cm (LogMAR) at 6M (N, Mean, SD, Median, Min., Max., 95% CI)	X	X	X	X			mITT/SF/PP/Sensitivity–1st eyes (SF-2nd as supportive data only)
Overall Spectacle independence at 6M (No. and percent of the response)					X	X	SF/PP bilateral subjects
SAFETY ENDPOINTS							
Monocular BCDVA (LogMAR) at 6M (N, Mean, SD, Median, Min., Max., 90% CI)	X	X	X	X			SF -1st eyes Sensitivity -1st eyes (SF-2nd as supportive data only)
The number and percent of eyes with adverse events as described in ISO11979-7	X	X	X	X			SF – 1st eyes (SF-2nd as supportive data only)
Monocular contrast sensitivity at 6M (N, Mean, SD, Median, Min., Max., 90% CI)	X	X					SF
Ocular visual symptoms via questionnaire at 6M					X	X	SF
OTHER ENDPOINTS							
Visual Acuity – Intermediate							
Monocular DCIVA at 66cm (LogMAR) at 6M by Site (N, Mean, SD, Median, Min., Max,)	X	X					SF

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
Monocular DCIVA by acuity line over time (No. and percent within each category)	X	X	X	X			SF
Monocular UCIVA by acuity line over time (No. and percent within each category)	X	X	X	X			SF
Monocular UCIVA at 66 cm (LogMAR) at 6M (N, Mean, SD, Median, Min., Max., 95% CI)	X	X	X	X			SF
Binocular UCIVA by acuity line at 6M (No. and percent within each category)					X	X	SF Bilateral subjects
Binocular UCIVA (LogMAR)) at 6M (N, Mean, SD, Min, Max,95% CI)					X	X	SF Bilateral subjects
Monocular low contrast (10%) DCIVA (LogMAR) at 6M (N, Mean, SD, Median, Min., Max., 95% CI)	X	X	X	X			SF
Monocular low contrast (10%) DCIVA by acuity line at 6M	X	X	X	X			SF
Monocular low contrast (10%) BCIVA (LogMAR) at 6M (N, Mean, SD, Median, Min., Max., 95% CI)	X	X	X	X			SF
Monocular low contrast (10%) DCIVA by acuity line at 6M	X	X	X	X			SF
Visual Acuity – Near							
Monocular DCNVA at 40cm by Site (LogMAR) at 6M (N, Mean, SD, Median, Min., Max,)	X	X					SF
Monocular DCNVA by acuity line over time (No. and percent within each category)	X	X	X	X			SF
Monocular UCNVA by acuity line over time (No. and percent within each category)	X	X	X	X			SF
Monocular UCNVA (LogMAR)) at 6M (N, Mean, SD, Median, Min, Max,95% CI)	X	X	X	X			SF
Binocular UCNVA by acuity line at 6M (No. and percent within each category)					X	X	SF Bilateral subjects
Binocular UCNVA (LogMAR)) at 6M (N, Mean, SD, Median, Min, Max,95% CI)					X	X	SF Bilateral subjects
Visual Acuity –Distance							

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
Monocular UCDVA by acuity line over time (No. and percent within each category)	X	X	X	X			SF
Monocular UCDVA (LogMAR)) at 6M (N, Mean, SD, Median, Min, Max,90% CI)	X	X	X	X			SF
Binocular UCDVA by acuity line at 6M (No. and percent within each category)					X	X	Bilateral SF
Binocular UCDVA (LogMAR)) at 6M (N, Mean, SD, Median, Min, Max,90% CI)					X	X	Bilateral SF
Monocular BCDVA by acuity line over time (No. and percent within each category)	X	X	X	X			SF and Best Case – 1st eyes, SF – 2nd eys
Monocular BCDVA by Site at 6M (No and percent 20/40 or better)	X						SF
Listing at 6M for eyes with BCDVA worse than 20/40	X	X	X	X			SF
Other Defocus Curve							
Monocular defocus curve at 6M by site	X	X					SF
Monocular defocus curve at 6M by photopic no glare pupil size (≤2.5 mm, >2.5 to <4 mm and ≥4.0 mm)	X	X					SF
Binocular defocus curve overall at 6M					X	X	SF Bilateral subjects
Binocular defocus curve at 6M by averaged photopic no glare pupil size (≤2.5 mm, >2.5 to <4 mm and ≥4.0 mm)					X	X	SF Bilateral subjects
Pupil Size							
Photopic Pupil Size at 6M (No. and percent ≤2.5 mm, >2.5 to <4.0 mm and ≥4.0 mm).	X	X	X	X			SF
Mesopic Pupil Size at 6M (No. and percent (≤4.0 mm, >4.0 to ≤5.0 mm, and >5.0 mm).	X	X	X	X			SF
Refractive Outcomes							
Refractive Outcomes (N, Mean, SD, Median, Min, Max, 95% CI)	X	X	X	X			SF

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
Spherical Equivalent at 6M Adjusted Spherical Equivalent at 6M (Postop minus target) Absolute Refractive Cylinder at 6M							
Absolute Spherical Equivalent by Diopter Level (<=0.50, 0.51-1.00, 1.01-1.50, 1.51-2.00,>2.00) at 6M (No. and percent within each category)	X	X	X	X			SF
Absolute Refractive Cylinder by Diopter Level (<=0.50, 0.51-1.00, 1.01-1.50, 1.51-2.00,>2.00) at 6M (No. and percent within each category)	X	X	X	X			SF
Questionnaire Data							
No. and percent for all questionnaire responses at 1M and 6M					X	X	SF Bilateral subjects
Overall spectacle independence (second secondary effectiveness endpoint) by site (No and percent of the response) at 6M					X	X	SF Bilateral subjects
Other Contrast Sensitivity							
Monocular contrast sensitivity at 6M by pupil size (N, Mean, SD, Median, Min, Max, 90% C.I.) For mesopic lighting condition, by mesopic pupil category (≤4.0 mm, >4.0 to ≤5.0 mm and >5.0 mm) For photopic condition, by photopic pupil size category ((≤2.5 mm, >2.5 to <4.0 mm and ≥4.0 mm	X	X					SF
Medical/Lens Findings and Other Adverse Event Tables							
Medical and Lens Findings at each visit and Cumulative (No. and percent with each item)	X	X	X	X			SF
Fundus finding at 6M (No. and percent Normal/Not Normal)	X	X	X	X			SF

	First Eyes	First Eyes	Second Eyes	Second Eyes	Subjects	Subjects	Comments (population used for analysis)
	ZHR00	ZCB00	ZHR00	ZCB00	ZHR00	ZCB00	
Fundus visualization at 6M (No. and percent adequate/not adequate)							
Listing of Adverse Events by site	X	X	X	X			SF
Listing of Adverse Events with last reported status including UCDVA, BCDVA, complication)	X	X	X	X			SF
Adverse Event table (No. and percent of adverse event)	X	X	X	X			SF
Non-ocular serious adverse events (No. and percent of non-ocular serious adverse event)	X	X	X	X			SF
Non-adverse event procedures	X	X	X	X			SF
Ocular/Visual Symptoms							
Non-directed optical/visual symptoms at each visit and Cumulative (No. and percent with each item)	X	X	X	X			SF
Ocular visual symptoms via questionnaire at 1M					X	X	SF Bilateral subjects
Subgroup analysis							
DCIVA and DCNVA at 6M by subgroup: gender, race and age group (≤59, 60-69, 70-79, ≥80) (N, Mean, SD, Median, Min, Max.)	X	X					SF
Defocus curve at 6M by subgroup: gender, race and age group (≤59, 60-69, 70-79, ≥80)	X	X					SF
Overall spectacle independence at 6M by subgroup: gender, race and age group (≤59, 60-69, 70-79, ≥80) (No. and percent of the response)					X	X	SF Bilateral Subjects

KEY:VA=Visual acuity, UCIVA=uncorrected intermediate VA at 66cm, DCIVA=distance corrected intermediate VA at 66cm, UCNVA=uncorrected near VA at 40cm, DCNVA=distance corrected near VA at 40cm, , UCDVA=uncorrected distance visual acuity, BCDVA=best-corrected distance visual acuity, BCIVA=best-corrected intermediate visual acuity with add power at 66cm, mITT=modified Intent to Treat, PP=Per Protocol Population, SF=Safety Population, SD=Standard Deviation, D=Diopter, X=tables will be provided – blank indicates table will not be generated, Bilateral subjects=Subjects implanted with the same study IOL in

both eyes, Best Case=Subjects without preoperative clinically relevant medical findings or macular degeneration at any time postop, 6M=6-month postoperative visit, 1M=1-month postoperative visit

TIME FRAME: The 6-month postoperative visit is the key timeframe for reporting.
STATISTICS: See text portion of the statistical analysis plan for information on inferential statistics for comparisons between IOL groups

APPENDIX II: FORMULAS USED FOR VISUAL ACUITY, REFRACTION AND CONTRAST SENSITIVITY DATA

Postoperative distance and intermediate visual acuity testing will be performed using the M&S Technologies CTS-1000 Smart System© computerized vision testing system (M&S system). Postoperative near visual acuity testing will be performed using the Good-Lite self-calibrating, retro-illuminated box with 100% contrast ETDRS near charts at a test distance of 40 cm.

Key : " * " = multiplication, " - " = subtraction, " / " = division, " ** " = exponent,
log10 = log in base 10, CRF = Case Report Form

Formulas for Converting Distance and Intermediate VA to LogMAR Values (M&S System):

LogMAR value = (85-letter score)/50

Example: A subject has distance letter score of 78
Converting to LogMAR: (85-78)/50 = 0.14 LogMAR

If the standard distance is not used for M&S system, no calculation adjustment will be needed since the M&S system already takes that into account.

Formulas for Converting Near VA to LogMAR Values (ETDRS chart):

LogMAR value = (70-letter score)/50

If the standard distance for the chart was not used then the following formulas are used:

For near VA not tested at 40cm:
LogMAR=LogMAR(from formulas above) + (log10(40)-log10(test distance in cm))

Example: A subject has a near letter score of 65 and a test distance of 33 cm.
Converting to LogMAR: (70 - 65)/50 = 0.10 LogMAR
Adjusting for test distance=0.1 + (log10(40)-log10(33))=0.10 + 0.083 = 0.183

Converting from LogMAR to Snellen and Decimal Equivalent:

Snellen denominator=20*(10**(LogMAR value))
Decimal VA= 20/(Snellen Denominator)

Example: A subject has a LogMAR score of 0.20
The Snellen denominator is: 20*(10**(0.20) = 20*(1.585) = 31.7=20/32
Decimal VA = 20/32=0.625

Formulas for Refractive Data

Converting to Plus Cylinder Notation:

If the original cylinder value is positive then the following formulas are used:

1. New sphere value=original sphere value
2. Final cylinder value=absolute value of the original cylinder value
3. Final axis value=original axis value

If the original cylinder value is negative then the following formulas are used:

1. New sphere value=original sphere value + original cylinder value
2. Final cylinder value=absolute value of the original cylinder value
3. Final axis value: if original axis is >0 and ≤90 then final axis=original axis +90; if the original axis >90 and ≤180 then final axis=original axis – 90

Adjusting for Infinity: Final sphere=new sphere (in plus cylinder notation) – 0.25

Spherical Equivalent

1. Spherical equivalent=final sphere + (0.5*final cylinder)
2. Adjusted spherical equivalent=spherical equivalent – target spherical equivalent

Examples:

Refraction: sphere: -0.25 cylinder: -0.50 axis: 80 with target SEQ=-0.13

In plus cylinder notation: sphere=-0.75, cylinder=0.50 axis=170
Adjusting for infinity: sphere=-1.00, cylinder=0.50 axis=170
Spherical equivalent=-1.00 + 0.5*(0.50) = -0.75
Adjusted spherical equivalent= -0.75 – (-0.13) = -0.62

Formulas for Converting Contrast Sensitivity to Log Units (M&S System):

Log units = log10(1/% value from the CRF)
For example: 50% contrast will be log10(1/0.5) = log10(2) = 0.3010

APPENDIX III: ALGORITHM FOR OVERALL SPECTACLE INDEPENDENCE

A composite dichotomous (0 or 1) Overall Spectacle Independence score classifies overall spectacle independence based on all of the Need (Questions 1a-1c), Wear (Questions 2a-d), and Strain (Questions 3a-d) items from PRSIQ. Answering all of Need items (Questions 1a-c) with "No" and all of the Wear (Questions 2a-d) and Strain (Questions 3a-d) items with "None of the time" results in a score of 1. Answering any of the Need items (Questions 1a-c) with "Yes," or any of the Wear (Questions 2a-d) or Strain (Questions 3a-d) items with "All of the time," "Most of the time," "Some of the time," or "A little of the time" results in a score of 0.

Overall Spectacle Independence is scored as follows:

- Overall Spectacle Independence is achieved (score=1)
  - For questions 1a-1c, participants indicate "No" to the Need for correction for distance, intermediate, and near vision; and
  - For question 2a-d, participants indicate "None of the time" to the Wear of correction for distance, intermediate, near vision, and overall vision; and
  - For question 3a-d, participants indicate "None of the time" to Strain to see when not wearing glasses for distance, intermediate, near, and overall vision.
- Overall Spectacle Independence is not achieved (score=0)
  - For questions 1a or 1b or 1c, participants indicate "Yes" to the Need for correction for distance, intermediate, and near vision; or
  - For question 2a or 2b or 2c or 2d, participants indicate "All of the time" or "Most of the time" or "Some of the time" or "A little of the time" to the Wear of correction for distance, intermediate, near vision, and overall vision; or
  - For question 3a or 3b or 3c or 3d, participants indicate "All of the time" or "Most of the time" or "Some of the time" or "A little of the time" to Strain to see when not wearing glasses for distance, intermediate, near, and overall vision.

Complete data is needed for each composite dichotomous score; no imputations for missing values should be used. Any individual missing response on at least one relevant item will be assigned as a missing value for overall spectacle independence variable.