Statistical Analysis Plan

CLINICAL INVESTIGATION OF THE TECNIS® NEXT-GENERATION INTRAOCULAR LENSES

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STATISTICAL ANALYSIS PLAN

CLINICAL INVESTIGATION OF THE TECNIS® NEXT-GENERATION INTRAOCULAR LENSES

PROTOCOL NUMBER: EDOF-121-NGPC

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STATISTICAL ANALYSIS PLAN CHANGE HISTORY

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	N/A	Original	N/A

1 INTRODUCTION

This document summarizes the statistical methods to be implemented during the analysis of data for the TECNIS® Next-Generation IOLs, Models ZHR00 and ZQR00, clinical study (Protocol EROV-121-NGPC). This study will be a prospective, multicenter, randomized, bilateral, subject/evaluator-masked clinical trial conducted at up to 14 sites. The two test lenses, TECNIS Model ZHR00 and Model ZQR00 IOLs, will be compared to the control lens, TECNIS Symfony® Extended Range of Vision IOL, Model ZHR00, separately and independently. Subjects are to be implanted with the same IOL in both eyes, the ZHR00 IOL, the ZQR00 IOL or the Symfony control IOL. Up to 260 subjects will be enrolled to achieve approximately 220 randomized and bilaterally-implanted subjects, resulting in approximately 195 evaluable subjects (65 in each IOL group) at 1 and 6 months.

The primary effectiveness endpoints for this study are mean (LogMAR) monocular, photopic, distance corrected near visual acuity (DCNVA) at 40 cm. The primary safety endpoints are adverse event rates versus ISO 11979-7:2006/ Amd.1:2012(E) Safety and Performance Endpoint (SPE) rates.

Other effectiveness endpoints include mean monocular diopters of defocus, monocular and binocular uncorrected distance, best corrected distance, uncorrected intermediate, distance corrected intermediate and uncorrected near visual acuities, tolerance to cylinder, monocular 10% low-contrast distance corrected and best corrected intermediate acuity and questionnaire responses.

Additional safety endpoints include the proportion of first implanted eyes achieving 20/40 or better monocular photopic best corrected distance visual acuity vs. the ISO SPE rate, optical/visual symptoms, medical/lens findings, binocular best corrected distance contrast sensitivity and visual symptoms via PRO instrument.

The key study timeframe for effectiveness endpoints will be 1 month and for safety endpoints the key study timeframe is 6 months.

2 ANALYSIS POPULATIONS

2.1 ANALYSIS POPULATIONS

The analysis population will be the safety population, which includes all eyes implanted with either a test or control IOL(s) and with data available at the time of analysis (i.e., no data imputation). For bilateral testing and subject-based questionnaire, only subjects binocularly implanted with the same test lens or the same control lens will be included. If an eye or a subject are discontinued during the study, any available data prior to the study exit will be presented.

The primary analysis will be based on first-eye or binocular outcomes (as appropriate per effectiveness endpoints), unless stated otherwise. However, select data such as medical/lens complications and adverse events will also be reported separately for second eyes. Binocular data will be reported for those who are implanted with the same IOL (test or control) in both eyes.

The two test lens, TECNIS Model ZHR00 and Model ZQR00 IOLs, will be compared to the TECNIS Symfony control IOL separately and independently. All endpoint comparison analysis to the control lens will present in two separate tables as follows:

- ZHR00 vs. control
- ZQR00 vs. control

2.2 VISIT WINDOWS

Subject visits are Preoperative for both eyes; Operative, 1 day and 1 week for each eye; and 1 month 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.

Unless otherwise indicated, alpha will be set to 0.05.

For visual acuity data, letter scores will be converted to LogMAR prior to analysis. 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[1]. Formulas used for refractive data are also included in Appendix II.

2.4 RANDOMIZATION

Subjects are to be implanted with the same IOL in both eyes, the ZHR00 IOL, the ZQR00 IOL or the Symfony control IOL, according to a randomization schedule. AMO will use a centralized electronic randomization system (Merge eClinical OS).

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 actual lens received; however, the number of these events will be reported.

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 (e.g., discontinued, missed visit, etc.) 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 OPERATIVE PARAMETERS

Operative parameters related to surgical complications or procedures for first and second eyes will be reported for each IOL model. The frequency and proportion of eyes with selected responses will be tabulated. 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 these operative parameters.

5 POSTOPERATIVE ANALYSES – PRIMARY EFFECTIVENESS ENDPOINTS

5.1 MODEL ZHR00: MONOCULAR DISTANCE CORRECTED NEAR VISUAL ACUITY (DCNVA) AT 40 CM

The primary effectiveness endpoint for the Model ZHR00 IOL is mean (LogMAR), first-eye, monocular, photopic, distance corrected near visual acuity (40 cm) at 1 month postoperative. The mean, SD, median, minimum, maximum and 95% C.I. will be reported by IOL group. 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 monocular DCNVA for the Model ZHR00 eyes is worse than or equal to that for control eyes. The alternate hypothesis is that the mean monocular DCNVA for Model 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 DCNVA for Model ZHR00 lens
μ_c = mean LogMAR DCNVA for control lens
Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean LogMAR DCNVA score for the Model ZHR00 investigational lens compared to the control lens ($p \leq 0.025$).

5.2 MODEL ZQR00: MONOCULAR DISTANCE CORRECTED NEAR VISUAL ACUITY (DCNVA) AT 40 CM

The primary effectiveness endpoint for the Model ZQR00 IOL is mean (LogMAR), first-eye, monocular, photopic, distance corrected near visual acuity (40 cm) at 1 month postoperative. The mean, SD, median, minimum, maximum and 95% C.I. will be reported by IOL group. 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 monocular DCNVA for the Model ZQR00 eyes is worse than or equal to that for control eyes. The alternate hypothesis is that the mean monocular DCNVA for Model ZQR00 eyes is better than that for control eyes.

H_o: $\mu_c - \mu_t \leq 0$ (ZQR00 is worse than (higher LogMAR) or equal to control)
H_1: $\mu_c - \mu_t > 0$ (ZQR00 is better (lower LogMAR) than control)
where
μ_t = mean LogMAR DCNVA for Model ZQR00 lens
μ_c = mean LogMAR DCNVA for control lens
Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean LogMAR DCNVA score for the Model ZQR00 investigational lens compared to the control lens ($p \leq 0.025$).

6 POSTOPERATIVE ANALYSES - PRIMARY SAFETY ENDPOINTS

6.1 MODEL ZHR00: RATES OF ADVERSE EVENTS VS. ISO SPE RATES

The primary Model ZHR00 safety endpoint for this study is the rate of adverse events vs. ISO[2] SPE rates at 6 months. The frequency and proportion of first eyes, second eyes, and all subjects 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 Model ZHR00 lens 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 AE rate for Model ZHR00 investigational lens eyes is lower than or equal to the ISO SPE values, and the alternative hypothesis is that the AE rate for study eyes is higher than the ISO SPE values.

H_o: $p_t \leq p_i$
H_1: $p_t > p_i$

where
p_t = proportion of Model ZHR00 investigational lens eyes with the AE
p_i = proportion of eyes reported in ISO SPE rates with the AE

Reject the null hypothesis if one-sided p-value < 0.05.

6.2 MODEL ZQR00: RATES OF ADVERSE EVENTS VS. ISO SPE RATES

The primary Model ZQR00 safety endpoint for this study is the rate of adverse events vs. ISO SPE rates at 6 months. The frequency and proportion of first eyes, second eyes, and all subjects 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 Model ZQR00 lens 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 AE rate for Model ZQR00 investigational lens eyes is lower than or equal to the ISO SPE values, and the alternative hypothesis is that the AE rate for study eyes is higher than the ISO SPE values.

H_o: $p_t \leq p_i$
H_1: $p_t > p_i$

where
p_t = proportion of Model ZQR00 investigational lens eyes with the AE
p_i = proportion of eyes reported in ISO SPE rates with the AE

Reject the null hypothesis if one-sided p-value < 0.05.

7 POSTOPERATIVE ANALYSIS: OTHER ENDPOINTS

7.1 OTHER NEAR VISUAL ACUITY ENDPOINTS

Other near endpoints include binocular, photopic UCNVA and DCNVA, and monocular, photopic UCNVA. Statistics similar to DCNVA described above will be used for other near endpoints. In addition, the frequency and proportion achieving each line will be reported over time by IOL group.

7.2 INTERMEDIATE AND DISTANCE VISUAL ACUITY ENDPOINTS

For BCDVA, the frequency and proportion achieving each line will be reported over time by IOL group. The proportion of investigational lens eyes achieving 20/40 or better at 6 months will be compared to the ISO SPE rate for posterior chamber IOLs (all first eyes) using a one-sided, exact test based on binomial distribution. The null hypothesis (based on the ISO guidance document) is that the proportion of investigational lens 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 investigational lens eyes achieving 20/40 or better BCDVA is less than the ISO SPE values.

In addition, the mean LogMAR BCDVA will be compared between lens groups for first eyes using a non-inferiority method. The null hypothesis is that the mean difference (control minus investigational lens) between the control and investigational IOLs is ≤-0.1 LogMAR (1 line) with the alternative hypothesis that the mean difference is >-0.1 LogMAR. A 90% confidence interval (CI) of a two-sample, two-sided, t-test will be used for evaluation.

Other distance endpoints, monocular and binocular UCDVA, and binocular BCDVA will be analyzed using the non-inferiority method described above. The frequency and proportion achieving each line will also be reported over time by IOL group.

Intermediate endpoints include binocular and monocular photopic UCIVA and DCIVA, and monocular DCIVA and BCIVA under a low contrast acuity (10%) condition, and will be analyzed using the non-inferiority method similar to BCDVA described above. The frequency and proportion achieving each line will also be reported over time by IOL group.

7.3 DEFOCUS

Best-corrected distance defocus testing will be performed at the 1- and 6-month visits (monocular at 1-month visit and binocular at 6-month visit). The mean visual acuity at each diopter will be plotted. The defocus curve will be presented for monocular and binocular by IOL model. The diopters of defocus where the mean visual acuity of 20/32

or better is achieved will be derived by visual inspection of the defocus curve. In addition, defocus curves will also be stratified by pupil size (≤ 2.5 mm, > 2.5 mm to < 4.0 mm and ≥ 4.0 mm) for each IOL model. For binocular defocus curve, the average of the two pupil sizes will be used for stratification.

Binocular manifest cylinder defocus curve will be performed at the 1-month visits. The mean visual acuity at each diopter will be plotted. The defocus curve will be presented by IOL model.

7.4 CONTRAST SENSITIVITY

Contrast sensitivity testing will be performed at the 1- and 6-month visits (monocular at 1-month visit and binocular at 6-month visit). Contrast sensitivity score will be converted to log unit prior to analysis (see conversion formula in Appendix II). The average of the two contrast sensitivity log score will be used for the analysis. Analyses including mean, standard deviation, median, minimum, maximum and 90% confidence intervals will be presented by IOL group.

In addition, contrast sensitivity will also be stratified by pupil size (photopic condition using photopic pupil size ≤ 2.5 mm, > 2.5 mm to < 4.0 mm and ≥ 4.0 mm; mesopic condition using mesopic pupil size ≤ 4.0 mm, > 4.0 mm to < 5.0 mm and ≥ 5.0 mm) for each IOL model. For binocular testing, the average of the two pupil sizes will be used for stratification.

7.5 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.

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

7.6 MEDICAL AND 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 6.1 and 6.2 Rates of Adverse Events, medical complication rates listed in ISO-11979 will be compared to the ISO SPE rates for test lens first eyes at 6 months using a one-sided, exact test based on the binomial distribution. The null hypothesis is that the study rate for test lens eyes is lower than or equal to the ISO rate and the alternative hypothesis is that the rate for test lens eyes is greater than the ISO rate. For adverse events and other medical and lens findings, data will be reported for first eyes and second eyes will be reported as supportive data.

7.7 NON-DIRECTED OPTICAL/VISUAL SYMPTOMS

The frequency and percentage of non-directed optical/visual symptoms will be reported over time by IOL groups for both eyes.

7.8 SUBJECT QUESTIONNAIRES FOR VISUAL SYMPTOMS, SPECTACLE INDEPENDENCE AND SATISFCATION

The questionnaire data will be reported for subjects who have received the same test lenses or same control lenses in both eyes. Subject questionnaire for visual symptoms, spectacle independence, satisfaction and other questionnaire responses will be tabulated with the frequency and proportion for each response by IOL group. Comparison between IOL groups for categorical data will be performed using Fisher's exact test with the null hypothesis that there is no difference between responses and the alternative hypothesis that there is a difference between responses. Comparisons for ordinal data will be done using the Wilcoxon rank-sum test with the null hypothesis that there is no difference in scores between IOL groups with the alternative hypothesis that there is a difference in scores between IOL groups. Two-sided testing and alpha of 0.05 will be used to evaluate questionnaire data.

8 SAMPLE SIZE CALCULATIONS

For the primary endpoint of distance corrected near visual acuity, there is 90% power to detect a 1-line or greater difference in mean visual acuity between the investigational lens groups and the control group (assume one-sided testing with an alpha of 0.025 and standard deviation of 1.6 lines) with 65 subjects in each lens group.

For contrast sensitivity there is 80% power to detect a non-inferiority margin of 0.15 log units between the investigational lens groups and the control group (assume one-sided alpha=0.05 and standard deviation of 0.34) with 65 subjects in each lens group.

If the dropout rate is assumed at 10%, approximately 73 subjects will be implanted in each lens group to achieve the minimum of 65 subjects in each lens group at 1 and 6 months.

8.0 REFERENCES

1. Holladay, J.T., Dudeja, D.R., Koch, D.D. Evaluating and Reporting Astigmatism for Individual and Aggregate Data, J. Cataract Refract. Surg. Vol. 24, Jan, 1998
2. ISO 11979-7:2006I. International Standard for Ophthalmic Implants – Intraocular Lenses – Part 7: Clinical Investigations, (2006). Amendment 1 to Annex B (2012).

APPENDIX I: TABLE LISTING

	First Eyes ZHR00	First Eyes ZQR00	First Eyes Control	Second Eyes ZHR00	Second Eyes ZQR00	Second Eyes Control	Subjects ZHR00	Subjects ZQR00	Subjects Control	Comments
ENROLLMENT/PREOP/OP										
Accountability/Enrollment										
No. of implants by IOL model by investigational site	X	X	X	X	X	X				
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	X	X				
Out of interval subjects listing – No. of eyes	X	X	X	X	X	X				
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	X	
Operative Data										
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	X	X				
PRIMARY EFFECTIVENESS ENDPOINTS										
Monocular photopic DCNVA at 40cm (LogMAR) (N, Mean, SD, Median, Min., Max, 95% CI.)	X	X	X							
PRIMARY SAFETY ENDPOINTS										
AE rate vs. ISO SPE rate	X	X	X							
OTHER ENDPOINTS										
Visual Acuity – Near										

	First Eyes ZHR00	First Eyes ZQR00	First Eyes Control	Second Eyes ZHR00	Second Eyes ZQR00	Second Eyes Control	Subjects ZHR00	Subjects ZQR00	Subjects Control	Comments
Monocular photopic DCNVA at 40cm by acuity line over time (No. and percent within each category)	X	X	X							
Monocular photopic UCNVA at 40cm (LogMAR) (N, Mean, SD, Median, Min, Max, 95% CI) Monocular photopic UCNVA, DCNVA at 40cm by acuity line over time (No. and percent within each category)	X	X	X							
Binocular photopic UCNVA and DCNVA at 40cm (LogMAR) (N, Mean, SD, Median, Min, Max, 95% CI) Binocular photopic UCNVA, and DCNVA at 40cm by acuity line (No. and percent within each category)							X	X	X	
Visual Acuity – Intermediate										
Monocular photopic UCIVA and DCIVA at 66cm (LogMAR) (N, Mean, SD, Median, Min, Max, 90% CI) Monocular photopic UCIVA and DCIVA at 66cm by acuity line over time (No. and percent within each category)	X	X	X							
Binocular photopic UCIVA and DCIVA at 66cm (LogMAR) (N, Mean, SD, Median, Min, Max, 90% CI) Binocular photopic UCIVA and DCIVA at 66cm by acuity line over time (No. and percent within each category)							X	X	X	
Monocular low contrast acuity (10%) DCIVA and BCIVA at 66cm (LogMAR) at 6M (N, Mean, SD, Median, Min, Max, 90% CI) Monocular low contrast acuity (10%) DCIVA and BCIVA at 66cm by acuity line (No. and percent within each category) Add power for low contrast BCIVA (No. and percent)	X	X	X							
Visual Acuity – Distance										

	First Eyes ZHR00	First Eyes ZQR00	First Eyes Control	Second Eyes ZHR00	Second Eyes ZQR00	Second Eyes Control	Subjects ZHR00	Subjects ZQR00	Subjects Control	Comments
Monocular photopic UCDVA and BCDVA at 4 m (LogMAR) (N, Mean, SD, Median, Min., Max, 90% CI) Monocular photopic UCDVA and BCDVA at 4 m by acuity line over time (No. and percent within each category)	X	X	X							
Binocular photopic UCDVA and BCDVA at 4 m (LogMAR) (N, Mean, SD, Median, Min., Max, 90% CI) Binocular photopic UCDVA and BCDVA at 4 m by acuity line over time (No. and percent within each category)							X	X	X	
Defocus Testing										
Best-corrected monocular defocus curve overall and by pupil size (≤2.5 mm, >2.5 to <4 mm and ≥4.0 mm) at 1M	X	X	X							
Best-corrected binocular defocus curve overall and by pupil size (≤2.5 mm, >2.5 to <4 mm and ≥4.0 mm) at 6M							X	X	X	
Best-corrected binocular manifest cylinder defocus curve at 1M							X	X	X	
Contrast Sensitivity										
Monocular contrast sensitivity testing overall and by pupil size (photopic: ≤2.5 mm, >2.5 to <4 mm and ≥4.0 mm mesopic: ≤4.0 mm, >4.0 to <=5.0 mm and >5.0 mm) (N, Mean, SD, Median, Min, Max, 90% CI) at 1M	X	X	X							
Binocular contrast sensitivity testing overall and by pupil size (photopic: ≤2.5 mm, >2.5 to <4 mm and ≥4.0 mm mesopic: ≤4.0 mm, >4.0 to <=5.0 mm and >5.0 mm) (N, Mean, SD, Median, Min, Max, 90% CI) at 6M							X	X	X	
Refractive Outcomes										
Sphere, absolute cylinder and spherical equivalent (N, Mean, SD, Median, Min, Max)	X	X	X	X	X	X				
Absolute spherical equivalent by diopter level (<=0.50, 0.51-1.00, 1.01-1.50, 1.51-2.00,>2.00) (No. and percent	X	X	X	X	X	X				

	First Eyes ZHR00	First Eyes ZQR00	First Eyes Control	Second Eyes ZHR00	Second Eyes ZQR00	Second Eyes Control	Subjects ZHR00	Subjects ZQR00	Subjects Control	Comments
within each category)										
Absolute refractive cylinder by diopter level (<=0.50, 0.51-1.00, 1.01-1.50, 1.51-2.00,>2.00) (No. and percent within each category)	X	X	X	X	X	X				
Ocular/Visual Symptoms										
Non-directed optical/visual symptoms at each visit and Cumulative (No. and percent with each item)	X	X	X	X	X	X				
Visual symptoms from questionnaire							X	X	X	
Questionnaire Data										
Subject questionnaire for spectacle independence, satisfaction and other questionnaire (No. and percent within each category)							X	X	X	
Medical/Lens Findings and Other Adverse Event Tables										
Serious and/or device-related Adverse events listing and table	X	X	X	X	X	X				
Medical and Lens Findings at each visit and Cumulative (No. and percent with each item)	X	X	X	X	X	X				
Dilated Fundus (No. and percent Normal/Not Normal)	X	X	X	X	X	X				
Non-adverse events (No. and Percent – all items listed in the database)	X	X	X	X	X	X				

KEY:VA=Visual acuity, UCDVA= uncorrected distance visual acuity at 4m, BCDVA= best-corrected distance visual acuity at 4m, UCIVA=uncorrected intermediate visual acuity at 66cm, DCIVA=distance corrected intermediate visual acuity at 66cm, BCIVA=best-corrected intermediate visual acuity at 66cm, UCNVA=uncorrected near visual acuity at 40cm, DCNVA=distance corrected near visual acuity at 40cm, SD=Standard Deviation, D=Diopter, X=tables will be provided – blank indicates table will not be generated, Bilateral=Subjects implanted with the same study IOL in both eyes

TIME FRAME: Key study timeframe for effectiveness endpoints will be 1 month and 6 months for key safety endpoints.

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 REFRACTIVE DATA AND CONTRAST SENSITIVITY

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

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

Formulas for Converting from LogMAR to Snellen and Decimal Equivalent:

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

Example: A subject has LogMAR score of 0.183
The Snellen denominator is: 20*(10**(0.183) = 20*(1.52) = 30
Decimal VA = 20/30=0.67

Formulas for Refractive Data

Converting to Plus Cylinder Notation:

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