Statistical Analysis Plan

A PROSPECTIVE STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF WAVEFRONT-GUIDED PRK CORRECTION OF MYOPIC REFRACTIVE ERRORS WITH THE IDESIGN ADVANCED WAVESCAN STUDIOSYSTEM AND THE STAR S4 IR EXCIMER LASER SYSTEM

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STATISTICAL ANALYSIS PLAN

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PROTOCOL NUMBER: STAR-115-MIPS

SPONSOR: Abbott Medical Optics Inc.

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1 INTRODUCTION

This document summarizes the statistical methods to be implemented during the analysis of data for the wavefront-guided PRK correction of myopic refractive errors with the iDesign Advanced WaveScan Studio System and STAR S4 IR Excimer Laser System (STAR-115-MIPS) study. This study will be a 12-month, prospective, multi-center, bilateral, open-label, non-randomized clinical trial. The key time point for reporting and submitting the PMA supplement will be at the time of refractive stability. At least 300 evaluable eyes at the point of refractive stability are intended for analyses. The primary effectiveness endpoints for this study are, monocular distance uncorrected visual acuity (UCVA), manifest refraction spherical equivalent (MRSE) predictability and refractive stability. The primary safety endpoints are the maintenance of best distance corrected visual acuity (BSCVA), rates of induced manifest refractive astigmatism and rates of serious device-related adverse events.

Other endpoints include monocular contrast sensitivity (substudy of 65 eyes), binocular UCVA, manifest cylinder, iDesign aberrometry, keratometry, intraocular pressure, anterior segment evaluation Schirmer I Tear Test (with anesthetic), ocular visual symptoms (non-directed and directed from the PRSVQ), and directed patient reported outcomes PROs: NEI-RQL-42, OSDI, and exploratory satisfaction questionnaires.

Table listings are included in Appendix I.

2 ANALYSIS POPULATIONS

2.1 ANALYSIS POPULATIONS/HANDLING OF MISSING DATA

The safety population will be the primary analysis population for all endpoints and includes all eyes that receive study treatment. However, if there are greater than 5% of eyes with missing study exams at the stability time point, an intent-to-treat (ITT) population will be used as the primary analysis population for the primary effectiveness endpoints. In this case, missing data will be imputed. For continuous variables, the planned method to use is the MCMC full-data imputation as described in Little & Rubin[1]. For data with a binary response and a monotone missing pattern, the planned method is to use the monotone logistic regression multiple imputation method. Data imputation and analysis will be performed using the MI and MIANALYZE procedures[2] in SAS® (Version 9.2).

[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. and SAS/STAT User Guide for the MI Procedure: Imputation Methods. Cary, N.C.

In addition to the above imputation methods, sensitivity analyses using different imputation approaches will also be performed for primary effectiveness endpoints for the ITT population. A worst-case scenario with the worst score assigned to the missing data will be performed. A tipping point analysis will also be performed.

2.2 VISIT SCHEDULE

All eyes will be examined preoperatively and at 1 day, 1 week, 1 month, 3 months, 6 months, 9 months and 12 months. 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 intervals 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 two-sided statistical testing.

For visual acuity data, ETDRS letter scores will be converted to LogMAR values prior to analysis. In addition, if the test distance used is not the standard test distance for the chart, then visual acuity data will be adjusted for the actual test distance used. Appendix II provides formulas for LogMAR conversion and distance adjustment.

For refractive data, all values will be converted to minus cylinder format and sphere will be adjusted for optical infinity. Formulas used for refractive data conversions are included in Appendix III.

2.4 SITE POOLABILITY

Baseline demographic data (age, gender, race and contact lens wear) and baseline iDesign refractions (IDS, IDC and IDSE) will be reported by site. To assess the poolability of the sites based on baseline variables, a one-way ANOVA will be used for continuous variables and the Chi-square test or Fisher's Exact test will be used for categorical variables.

For the key primary effectiveness endpoints, data will also be reported by site. A logistic regression analysis will be used to evaluate the effect of significant demographic and baseline factors on the key primary effectiveness endpoints while controlling for site. An alpha level of 0.15 will be used to assess the site poolability.

3 ACCOUNTABILITY/DEMOGRAPHICS AND PREOPERATIVE REFRACTIONS

3.1 ACCOUNTABILITY

Subject accountability will be summarized as a frequency distribution by scheduled visits. The frequency and proportion of available eyes, including those outside of the interval, and the frequency and proportion of missing eyes (forms not yet received, active, missed visit, lost to follow-up or discontinued) will be reported.

3.2 DEMOGRAPHICS

Subject demographic data will be subject-based. Age will be summarized with descriptive statistics with mean, standard deviation, minimum and maximum. The frequency distributions of sex, race, and contact lens history will also be tabulated. The demographic data will also be reported by site.

3.3 PREOPERATIVE REFRACTIONS

Preoperative refractions including iDesign refractions (IDSE, IDS and IDC) and manifest refractions (MRSE, MRS and MRC) will be reported. Preoperative IDSE and IDS by preoperative IDC will be tabulated by each dioptric bin. The frequency and proportion of eyes in each dioptric bin will be reported.

4 INTRAOPERATIVE PARAMETERS

Intraoperative findings will be reported and include the percentages of eyes with operative complications, the use of iris registration during treatment, and any other reported incidents.

5 POSTOPERATIVE ANALYSES – PRIMARY ENDPOINTS

Primary effectiveness and safety endpoints will be evaluated at the stability time-point.

5.1 PRIMARY EFFECTIVENESS ENDPOINTS

Monocular UCVA

The frequency, proportion and 95% confidence interval of the proportion of eyes with each acuity line of UCVA (20/16 or better, 20/20 or better, 20/25 or better, 20/40 or better, 20/100 or better and worse than 20/100) will be summarized over time.

The success criterion is the proportion of eyes achieving the target of 20/40 or better is at least 85%.

MRSE Predictability (within 0.50 D and 1.00 D of Target)

Summary statistics (mean, standard deviation, median, minimum and maximum) will be reported over time for MRSE.

For this study, the attempted MRSE is emmetropia and therefore is calculated as " – Preop MRSE". The achieved MRSE is defined as "Postop MRSE – Preop MRSE". Eyes that are under-corrected will have a residual MRSE <0.00 D (e.g., myopic eyes that are under-corrected by more than 1.00 D will have a postoperative MRSE < -1.00 D). Eyes that are over-corrected will have a residual MRSE >0.00 D (e.g., myopic eyes that are over-corrected by more than 1.00D will have a postoperative MRSE >1.00 D).

The frequency, proportion and 95% confidence intervals of eyes with achieved MRSE within 0.50 D and 1.00 D of attempted MRSE will be summarized over time. The frequency and proportion of eyes under-corrected MRSE by more than 1.00 D or 2.00 D and eyes over-corrected MRSE by more than 1.00 D or 2.00 D will also be summarized over time.

The success criterion for MRSE predictability within 0.50 D is that the proportion of eyes with MRSE within 0.50 D at the stability time-point is at least 50%. In addition, the success criterion for MRSE predictability within 1.00 D is proportion of eyes with MRSE within 1.00 D at the stability time-point is at least 75%.

Refractive Stability

Refractive stability will be evaluated for two cohorts: a "consecutive cohort" (eyes with data at two consecutive visits) and a "consistent cohort" (eyes with data at all periodic visits through the point of stability and the confirmatory time point). The frequency, proportion and 95% confidence intervals of eyes with MRSE and MRC changes ≤1.00 D, as well as ≤0.50 D, between visits will be reported.

Refractive stability requires at least 95% of the eyes to have a change ≤1.00 D of MRSE and MRC between refractions performed at 1 month and 3 months after surgery or any two refractions performed at least 3 months apart.

Additionally, the mean change (paired differences) in MRSE and MRC between visits will be calculated to evaluate the additional refractive stability criteria. The mean rate of change in MRSE and MRC should be ≤0.50 D per year (≤ 0.04 D/month) to meet the stability requirement. The mean rate of change in MRSE and MRC should decrease monotonically over time. At the point of stability, the 95% confidence intervals of the mean rate of change in MRSE and MRC between visits should include zero. Lastly, stability is to be confirmed at least 3 months after the stability time point by a statistically adequate subgroup using the same refractive stability criteria.

5.2 PRIMARY SAFETY ENDPOINTS

Maintenance of BSCVA

The frequency, proportion and 95% confidence intervals of eyes with each acuity line of BSCVA (i.e. 20/20 or better, 20/25 or better, 20/40 or better, etc.) will be reported over time. The frequency

and proportion of eyes with BSCVA acuity line changes from preoperative (decreases of >2 lines, =2 lines, =1 line, no change, increases of =1 line, =2 lines and > 2 lines) will be summarized over time.

The success criteria for the endpoints regarding maintenance of BSCVA are achieved if the proportion of eyes with a loss of >2 lines of BSCVA from preoperative is <5%, the proportion of eyes with haze beyond 6 months with a loss > 2 lines of BSCVA is <1%, and the proportion of eyes with BSCVA of 20/20 or better preoperatively and BSCVA 20/40 or worse postoperatively is <1%.

Induced Manifest Refractive Astigmatism

Induced manifest refractive astigmatism is defined as the absolute change in manifest refractive cylinder (MRC) from preoperative. The following formula will be used to determine absolute change in MRC (rounded to the nearest 0.25 increment):

Absolute Change in Cylinder = |Preop MRC| - |Postop MRC|

The frequency, proportion and 95% confidence intervals of eyes with absolute changes in manifest cylinder from preoperative visit will be summarized in categories (increases of >2.00 D, 2.00 D, 1.75 D, 1.50 D, 1.25 D, 1.00 D, 0.75 D, 0.50 D, 0.25 D, no change, decreases of 0.25 D, 0.50 D, 0.75 D, 1.00 D, 1.25 D, 1.50 D, 1.75 D, 2.00 D, > 2.00 D) at each periodic study visit.

The success criterion is achieved if the proportion of eyes with induced manifest refractive astigmatism of >2.00 D is <5%.

Serious, Device-Related Adverse Events

The frequency and proportion of eyes with serious, device-related adverse events throughout the study will be summarized. The success criterion is achieved if the proportion of eyes with serious, device-related adverse events is <1% cumulatively.

6 POSTOPERATIVE ANALYSIS: OTHER ENDPOINTS

6.1 MONOCULAR CONTRAST SENSITIVITY: MESOPIC WITH AND WITHOUT GLARE AT 1.5, 3, 6 AND 12 CPD AND PHOTOPIC WITHOUT GLARE AT SPATIAL FREQENCIES 3, 6, 12 AND 18 CPD

Spatial frequency testing is to be performed twice under each lighting condition. The average of the two log testing scores will be used for the analysis. If a subject cannot detect the reference pattern in one test and can detect the reference pattern or better in the other test, the score of the other test will be used. For eyes that cannot see the reference pattern for a spatial frequency, the corresponding reference patch scores will be assigned. The number and percentage of eyes unable to see the reference patterns (scores of “0”) will be tabulated and presented. Means and medians will be labeled as “<” with the standard deviation labeled as “>” to the reported values as appropriate. A non-parametric analysis of the paired change in contrast sensitivity from

preoperative to the refractive stability point will be conducted in which medians will be provided as valid, unbiased estimates of the center of the distribution; additionally, the 25th and 75th percentile values will be provided to show non-parametric measures of variability. The 95% confidence interval of the median change will also be provided.

6.2 BINOCULAR UCVA

The frequency and proportion of subjects with each acuity line of binocular UCVA (20/16 or better, 20/20 or better, 20/25 or better, 20/40 or better, 20/100 or better and worse than 20/100) will be summarized over time.

6.3 POSTOPERATIVE UCVA VS. PREOPERATIVE BSCVA

The frequency and proportion of eyes with acuity line changes of UCVA compared to preoperative BSCVA (decreases of >2 lines, =2 lines, =1 line, no change, increases of =1 line, =2 lines and > 2 lines) will be reported over time.

6.4 MANIFEST SPHERE VS. CYCLOPLEGIC SPHERE

Mean, standard deviation, minimum and maximum for manifest and cycloplegic spheres and the paired difference between the manifest and cycloplegic spheres at the pre-operative and at the stability time point will be presented.

The difference between the manifest and cycloplegic refractions is calculated as follows:
Cycloplegic and Manifest Sphere Difference = Cycloplegic Sphere - Manifest Sphere

6.5 MANIFEST CYLINDER ANALYSIS

Summary statistics (mean, standard deviation, median, minimum and maximum) will be reported over time for MRC.

6.5.1 NON-VECTOR ANALYSES

Accuracy of Cylinder to Target (Emmetropia)

The accuracy of MRC will be summarized over time. The summary will include the frequency and proportion of eyes MRC within $\pm$ 0.50 D and with $\pm$ 1.00 D. In addition, mean and standard deviation of attempted correction and achieved correction and the percent of achieved correction for MRC will be calculated as follows at each evaluation time point:

- Mean Attempted Correction = Mean of - (Preop MRC)
- Mean Achieved Correction = Mean of (Postop MRC – Preop MRC)
- % Achieved = [Mean of (Postop MRC - Preop MRC)/ Mean of - (Preop MRC)] *100

Reduction of Absolute Cylinder at Stability Time Point

The reduction of absolute cylinder for astigmatic eyes (preop |MRC| > 0.50 D) will be calculated as follows at the stability time point.

- % Reduction= [Mean of (Preop MRC - Postop MRC)/ Mean of (Preop MRC)] *100

The mean, minimum and maximum of the percent of reduction of absolute cylinder will be presented by preoperative MRC categories (>0.00 D to ≤0.50 D, >0.50 D to ≤1.00 D, >1.00 D to ≤2.00 D, >2.00 D to ≤3.00 D, >3.00 D to ≤4.00 D).

Absolute Shift in Axis at Stability Time Point

For astigmatic eyes (preop |MRC| > 0.05 D), the frequency and proportion of eyes with absolute shift in axis (0º, > 0 to ≤ 5°, > 5 to ≤ 10°, > 10 to ≤ 15°, > 15 to ≤ 30°, > 30°) will be presented by residual cylinder magnitude categories (0.00 D, >0.00 D to ≤0.50 D, >0.50 D to ≤1.00 D, >1.00 D to ≤2.00 D, >2.00 D to ≤3.00 D, >3.00 D to ≤4.00 D etc.) at the stability time point.

Absolute shift in axis is determined as follows:

- If postoperative axis - preoperative axis > 90, then axis shift = |postoperative axis – preoperative axis - 180|.
- In other cases, if postoperative axis - preoperative axis <-90, then axis shift = 180 + postoperative axis – preoperative axis.
- In other cases, axis shift = |postoperative axis - preoperative axis|.
- Shifts are defined to be zero for eyes with zero residual cylinder magnitude.

A listing of eyes with residual astigmatism of greater than 0.50 D and an axis shift of >30° will be provided.

6.5.2 VECTOR ANALYSES

Vector analysis will be conducted in accordance with Eydelman 2006[3] for eyes with astigmatism (magnitude of preoperative MRC >0.50 D).

Vector Stability of MRC

Vector stability of MRC will be evaluated for two cohorts: a “consecutive cohort” (eyes with data at two consecutive visits) and a “consistent cohort” (eyes with data at all periodic visits through the point of stability and the confirmatory time point).

The frequency, proportion and 95% confidence intervals of eyes with vector MRC change ≤1.00 D, as well as ≤0.50 D, between visits will be reported. Mean, standard deviation and 95% confidence

[3] Eydelman M, Drum B, Holladay J etc (2006). Standardized analyses of correction of astigmatism by Laser systems that reshape the cornea. Journal of Refractive Surgery 22: 81-95.

intervals of the mean magnitude of MRC vector change between visits and the mean MRC vector change per year and mean MRC vector change per month will be calculated and reported.

Vector Analysis Summary at Stability Time Point

The mean and standard deviation of intended refractive change (|IRC|), surgically induced refractive change (|SIRC|), error vector (|EV|), correction ratio (CR) and error ratio (ER) will be presented by preoperative MRC categories (>0.50 D to ≤1.00 D, >1.00 D to ≤ to 2.00 D, >2.00 D to ≤ to 3.00 D, >3.00 D to ≤ 4.00 D).

Error of Magnitude (EM) at Stability Time Point

The mean and standard deviation of EM will be presented by preoperative MRC categories (>0.50 D to ≤1.00 D, >1.00 D to ≤2.00 D, >2.00 D to ≤3.00 D, >3.00 D to ≤4.00 D). The frequency and proportion of eyes for each preoperative MRC category will be reported.

Error of Angle (EA) at Stability Time Point

The mean and standard deviation of EA will be presented by preoperative MRC categories (>0.50 D to ≤1.00 D, >1.00 D to ≤2.00 D, >2.00 D to ≤3.00 D, >3.00 D to ≤4.00 D). The frequency and proportion of eyes for with |EA| ≤ 15°, EA>+15° and EA≤15° will also be reported.

6.6 KERATOMETRIC ANALYSIS

Summary statistics (mean, standard deviation, median, minimum and maximum) will be reported over time for the Average Keratometry (AVK). Stability of average keratometry will be evaluated for two cohorts: a “consecutive cohort” (eyes with data at two consecutive visits) and a “consistent cohort” (eyes with data at all periodic visits through the point of stability and the confirmatory time point). The frequency, proportion and 95% confidence intervals of eyes with AVK changes ≤1.00 D, as well as ≤0.50 D, between visits will be presented.

The following formulas will be used:

- Average Keratometry (AVK) = (Flat + Steep) / 2
- |current AVK – previous AVK| ≤ 0.5 and ≤ 1.00 D.

Additionally, summary statistics (mean, standard deviation, minimum and maximum) of mean keratometric cylinder magnitude (Kmax – Kmin) differences from preoperative to the stability time point will be presented. The absolute keratometric steep meridian axis shift (<15° and ≥15°) between preoperative and the stability time point stratified by keratometric cylinder magnitude (0.00 D, >0 D to ≤0.50 D, >0.50 D to ≤1.00 D, >1.00 D to ≤1.50D etc.) at the stability time point will also be reported. A listing of eyes with absolute keratometric axis shift ≥15° from preoperative to the stability time point will be provided.

6.7 HIGHER ORDER ABERRATIONS (HOA)

Analyses of higher order aberrations (HOA) from iDesign aberrometry measurements will include root mean square (RMS) values for total higher order aberrations and key specific components: coma, trefoil, and spherical aberration. Analyses will be performed for 5 mm wavefront diameters. HOA summary statistics (mean and standard deviation) will be reported over time.

A paired analysis will be done for HOA change between preoperative visit and at the stability time point. Mean change and 95% confidence interval will be provided for each HOA.

6.8 INTRAOCULAR PRESSURE (IOP)

Summary statistics (mean, standard deviation, minimum and maximum) will be reported over time for IOP. The frequency and proportion of eyes with changes in IOP from preoperative visit (decrease >10 mmHg, decrease 6 to 10 mmHg, decrease 1 to 5 mmHg, no change, increase 1 to 5 mmHg, increase 6 to 10 mmHg, increase >10 mmHg) will be presented over time.

6.9 ANTERIOR SEGMENT EVALUATION

Rates of postoperative medical findings noted from the biomicrocopy slit lamp examination, including degree of corneal clarity, will be tabulated with the frequency and proportion of eyes with findings reported over time.

6.10 NEI-RQL-42 QUESTIONNAIRE DATA

Analysis of the National Eye Institute Refractive Quality of Life *(NEI-RQL-42)* patient-reported outcomes instrument will be done according to the NEI-RQL-42 User's Manual, Version 1.0 (see Appendix IV). Items that are left blank (missing data) are not taken into account when calculating the scale scores.Scores represent the average for all items in the scale that the respondent answered. For items 36b to 42b, each has four response levels, but is expanded to five levels using items 36a to 42a, respectively. If 'a'=2, then 'b' should be left blank. If there is a discrepancy between 'a' and 'b', ignore the response to 'a' and go with the response to 'b'. The 13 sub-scales of the NEI-RQL-42 will be analyzed and reported over time. The mean of each of the sub-scales will be calculated at preoperative visit and at the time point of refractive stability. The paired difference of each of the sub-scales between preoperative visit and the time point of refractive stability will be reported.

6.11 OSDI QUESTIONNAIRE

The OSDI mean total score will be calculated and dry eye symptoms categorized as normal (0-12 points), mild (13-22 points), moderate (23-32 points) and severe (33-100 points) will be reported preoperatively and postoperatively over time.

6.12 OCULAR VISUAL SYMPTOMS

The frequency and proportion of eyes with spontaneously reported ocular visual symptoms (non-directed) will be presented. Additionally, the frequency and proportion of eyes with different levels of severity of specific visual symptoms based on the Patient Reported Visual Symptom Questionnaire (PRVSQ PRO) will be reported. No imputations for missing values should be used for PRVSQ-LASIK/PRK item responses; that is, any item with a missing response will be maintained as a missing value for analysis. However, any patient that provides a written-in limitation to question F, but fails to explicitly answer “Yes” to the item will be considered as having provided a “Yes” response to question F. To conservatively classify severe visual symptoms, any patient that reports an extreme level of bother (i.e., “Extremely bothered” to question E) and limitations due to that symptom (i.e., “Yes” to question F) will be considered having a severe symptom, regardless of missing responses on any other item. Note that results from the PRSVQ questionnaires completed following the 3-month study visit will be used for reliability validation purposes for the PRSVQ only and will not be analyzed in this study or used for AE reporting).

6.13 COMPLICATIONS/ADVERSE EVENTS/NON-REFRACTIVE RETREATMENT PROCEDURE

The frequency and proportion of eyes with specific complications and adverse events following the ANSI Guidance Document for Corneal Reshaping, Z80.11-2012) will be presented over time. A listing of all serious and/or device-related adverse events will also be provided. Additionally, non-refractive retreatment procedures will be tabulated and summarized.

6.14 SCHIRMER I TEAR TEST (WITH ANESTHETIC)

The mean scores of Schirmer I Tear Test at preoperative visit and at the stability time point will be presented. The mean paired change in Schirmer I Tear Test score will be reported.

6.15 EXPLORATORY SATISFACTION QUESTIONNAIRES

The frequency and proportion of patients with satisfaction about the study procedure from the non-validated questionnaires designed to collect patient satisfaction data prior to and following refractive corneal surgery will be summarized.

7 OUTCOME STRATIFICATIONS

To evaluate the consistency of results, the primary effectiveness endpoints (MRSE within 0.50 D, MRSE within 1.00 D, UCVA 20/40 or better) and safety endpoints (BSCVA worse than 20/40, loss of >2 lines of BSCVA) will be stratified by key factors at the stability point. These factors will include age group, gender, race, site, preoperative contact lens wear, preoperative iDesign spherical equivalent (<-9.00 D to ≥-10.00 D, <-8.00 D to ≥-9.00 D, <-7.00 D to ≥-8.00 D. etc.), preoperative iDesign sphere (<-7.00 D to ≥-8.00 D, <-6.00 D to ≥-7.00 D. etc.), preoperative iDesign cylinder (IDC magnitude of ≥0.00 D to ≤0.50 D, >0.50 D to ≤1.00 D, >1.00 D to ≤ 2.00 D, >2.00 D to ≤3.00

D, >3.00 D to ≤4.00 D), wavefront capture diameter, iris registration status, and clinically significant protocol deviations that may affect key study outcomes. Stratification of outcomes by preoperative refractive error (IDSE, IDS and IDC) will provide evaluation of results across the treatment range. The frequency, proportion and 95% confidence intervals of eyes with each factor group will be presented.

For comparisons across categories, a Mantel-Haenszel chi-square test for ordinal data and a Cochran-Mantel-Haenszel test for non-ordinal data will be used to compare the observed percentages across categories. Additionally, the results for each category will be compared to the target criterion for each study endpoint using chi-square goodness-of-fit test. All statistical tests and p-values will be reported as 2-sided and a significance level of 0.15 will be used to assess homogeneity of the primary safety and effectiveness endpoints for baseline and demographic variables.

Statistical significant factors will be further investigated.

8 INTERIM ANALYSES

Up to four interim analyses may be conducted to determine the point of refractive stability when 90% of treated subjects have reached the 3, 6, 9 and 12 month visits, respectively. These analyses will only include refractive stability criteria evaluation.

9 SAMPLE SIZE CALCULATIONS

Per ANSI Z80.11-2012, Annex E, the sample size calculation is to be based on the probability of observing an adverse event at a rate greater than or equal to the expected rate but less than or equal to an acceptable target. This study will be powered to detect the percentage of eyes losing 2 or more lines of BSCVA at 3 months. In the approved indication for the original STAR S4 IR System Myopia clinical study (PMA P930016-S016, approved 05/23/03), the percentage of eyes losing 2 or more lines of BSCVA at 3 months was 0.3% (1/318, 95% exact CI (0.00%, 1.7%)). The target rate will be chosen to assure that the proposed study will be able to detect at least the upper limit of the exact 95% confidence interval.

The hypothesis is

$\boldsymbol{H_0}$: $p_{trt} \leq p_{\text{target}}$

$\boldsymbol{H_1}$: $p_{\text{trt}} > p_{\text{target}}$

where

p_{trt} = Estimate of the percentage of eyes losing 2 or more lines of BSCVA at 3 months using the STAR S4 IR and iDesign System

p_{target} = Expected percentage of eyes losing 2 or more lines of BSCVA at 3 months per previously approved PMA P930016-S016

Using the binomial distribution with an alpha of 0.05, 80% power and a sample size of n=300 eyes, a rate of at least 1% can be detected. Therefore, a sample size of 300 evaluable eyes at the time point of stability is required.

CONTRAST SENSITIVITY SUBSTUDY SAMPLE SIZE

The sample size calculation for the substudy is based on ANSI guidance (ANSI Z80.11) using non-inferiority approach. With a sample size is 65, a paired t-test with a 0.05 one-sided significance level will have over 90% power to detect the paired difference mean contrast sensitivity is no less than 0.15 below zero when the expected mean difference is 0, assuming the non-inferiority margin equals 0.15 and the standard deviation of the difference is 0.40.

APPENDIX I TABLE LISTING FOR STAR-115-MIPS

Variable	Subject	Eye
ENROLLMENT/PREOP/OP		
Accountability/Enrollment		
eyes/subjects by investigational site (n)	**x**	**x**
Accountability table over time – (Available for analysis, Missing data –Forms not received, Active, Missed visit, Lost to follow-up, Discontinued) (n and % of eyes)		**x**
Out of Interval listing		**x**
Demographics		
Demographic – Age in years (N, Mean, SD, Min., Max), race, sex, contact lens wear history(soft, rigid, none) (n and %) by site and overall	**x**	
Preoperative Characteristics		
iDesign Refractions (IDSE, IDS, IDC) - (N, Mean, SD, Min, Max) Manifest refractions (MRSE, MRS, MRC) – (N, Mean, SD, Min, Max)		**x**
IDSE/IDS by IDC dioptric bins (n and % of eyes).		**x**
Site poolability analysis		**x**
Operative Data		
Iris registration used or not (n and % of eyes)		**x**
Operative complications (n and % of eyes)		**x**
PRIMARY ENDPOINTS		
Monocular UCVA - (n, % and 95%CI for each acuity line:20/16 or better, 20/20 or better, 20/25 or better, 20/40 or better, 20/100 or better and worse than 20/100)		**x**
MRSE predictability – MRSE over time(N, Mean, SD, Min., Max) MRSE accuracy(n, % and 95% CI of eyes wthin±0.5D and within ±1.0D; n and % of eyes with overcorrection or undercorrection of more than 1D or 2D)		**x**
MRSE stability – two sets of tables (consecutive/consistent cohorts) MRSE change between visits (n, % and 95% CI of eyes of within ±0.5D /±1.0D change), mean rate of change per year, SD and the 95% CI, mean rate of change per year divided by 12 to get the mean rate of change per month		**x**
MRC stability – two sets of tables (consecutive/consistent cohorts) MRC change between visits (n, % and 95% CI of eyes of within ±0.5D /±1.0D change), mean rate of change per year, SD and the 95% CI, mean rate of change per year divided by 12 to get the mean rate of change per month		**x**
BSCVA over time at each acuity line (20/20 or better, 20/25 or better etc.) – (n, % and 95% CI of eyes) BSCVA line change from preop (decrease > 2 lines, = 2 lines, =1 line, no change, increase =1 line, =2 lines, > 2 lines) – (n and % of eyes)		**x**

Induced manifest astigmatism (absolute change in MRC from preop, by 0.25D step increment) – (n, %, 95% CI of eyes)		**x**
Serious device-related AEs (N and % of eyes cumulatively)		**x**
OTHER ENDPOINTS		
Contrast sensitivity (photopic without glare at 3,6,12 and 18cpd; mesopic with and without glare at 3, 6, 12 and 18cpd) - (change from preop: median, 25th and 75th percentiles, 95% CI of the median, and tabulation of eyes unable to see reference patterns)		**x**
Binocular UCVA over time - (n, % and 95%CI for each acuity line:20/16 or better, 20/20 or better, 20/25 or better, 20/40 or better, 20/100 or better and worse than 20/100)	**x**	
Postop UCVA vs Preop BSCVA - (n and % of eyes with each line change: decrease > 2 lines, =2 lines, =1 line, no change, increase =1 line, =2 lines, > 2 lines)		**x**
MRS vs CRS – Mean of MRS and CRS and paired difference (N, Mean, SD, Min., Max)		**x**
Manifest Cylinder Analysis – Nonvector and Vector Nonvector – MRC overtime (N, Mean, SD, Min., Max) Nonvector – MRC accuracy (n, %, 95% CI of eyes wthin±0.5D and within±1.0D; mean and SD of attempted and achieved correction; % achieved) Nonvector – reduction of absolute cylinder (N, mean, min, max by preop MRC categories) Nonvector – absolute shift in axis (n and % of eyes with axis shift by residual cylinder magnitude categories) Vector- MRC stability– two sets of tables (consecutive/consistent cohorts) MRC vector change between visits (n, %, 95% CI of eyes of within ±0.5D /±1.0D change), mean rate of vector change per year, SD and the 95% CI, mean rate of vector change per year divided by 12 to get the mean rate of vector change per month. Vector – vector analysis summary (mean and SD of |IRC|, |SIRC|, |EV|, CR and ER by preop MRC categories) Vector – EM (mean and SD by preop MRC categories) Vector – EA (mean and SD by preop MRC categories)		**x**
Keratometric analysis Average K (defined as (flat+steep)/2) - (N, mean, SD, min, max) Stability of Average K - two sets of tables (consecutive/consistent cohorts) Average K change between visits (n, %, 95% CI of eyes of within ±0.5D /±1.0D change)		**x**

K cylinder magnitude difference from preop - (N, mean, SD, min, max) Absolute K cylinder axis shift (<15 °, ≥15°) from preop by K cylinder magnitude(0.00 D, >0 D to ≤0.50 D, >0.50 D to ≤1.00 D, >1.00 D to ≤1.50D etc.) at stability time point		
HOA analysis HOA overtime - (n, mean and SD) HOA paired difference – (n, mean and 95% CI around the mean)		**x**
IOP IOP over time – (N, mean, SD, min, max) Change in IOP(decrease>10mmHg, decrease 6-10mmHg, decrease 1 to 5mmHg, no change, increase 1 to 5mmHg, increase 6-10 mmHg and increase>10mmHg) from preop - (n, %)		**x**
Medical findings from slit lamp examination over time (n and %)		**x**
Corneal clarity ratings over time (from slit lamp exam; n and %)		**x**
Shirmer I Tear Test Test score summary(N, mean, SD, min, max at preop and at the stability time point) and change in the test score (N, mean, SD, min, max)		**x**
OSDI Mean OSDI total score at each visit. N and % of dry eye symptoms categorized as none, mild, moderate and severe.		
NEI-RQL-42 questionnaire data Mean of the 13 scales at preop and at the stability time point. Mean paired difference will be calculated.	**x**	
Ocular visual symptoms N and % of each non-directed, monocular ocular visual symptoms will be tabulated over time.		**x**
Visual Symptoms from PRVSQ PRO questionnaire N and % of severity level for each symptom under different condition	**x**	
Specific Complications and AEs per ANSI Guidance Document for Corneal Reshaping, Z80.11-2012 N and % of eyes will be tabulated overtime and cumulatively.		**x**
Listings of all serious and/or device related adverse events		**x**
Non-ocular adverse events	**x**	
Non-refractive retreatment procedures over time and cumulatively		**x**
Satisfaction questionnaire N and % of patients will be reported	**x**	
OUTCOME STRATIFICATION The primary effectiveness endpoints (MRSE±0.5D, MRSE±1.0D, UCVA 20/40 or better) and safety endpoints (BSCVA worse than 20/40, loss of > 2 lines of BSCVA) stratified by age group, gender, race, site, contact lens wear, preop IDSE, preop IDS, preop IDC, wavefront capture diameter, IR status and clinically significant protocol deviation – (n, % and 95% CI). P-values will be provided		**x**

APPENDIX II LOGMAR CONVERSIONS AND LINE CHANGES

LogMAR score for UCVA and BSCVA	
Category	LogMAR
20/16 or better	≤ -0.06
20/20 or better	≤ 0.04
20/25 or better	≤ 0.14
20/32 or better	≤ 0.24
20/40 or better	≤ 0.34
20/50 or better	≤ 0.44
20/63 or better	≤ 0.54
20/80 or better	≤ 0.64
20/100 or better	≤ 0.74
Worse than 20/100	>0.74

VA Line Change	
Change (LogMAR Postop VA – LogMar Preop VA)	Category
< -0.24	> 2 lines better
< -0.14 and ≥ -0.24	2 lines better
< -0.04 and ≥ -0.14	1 line better
0.00 ± 0.04	Equal
> 0.04 and ≤ 0.14	1 line worse
> 0.14 and ≤ 0.24	2 lines worse
> 0.24	> 2 lines worse

Key : " * " = multiplication, " - " = subtraction, " / " = division, " ** " = exponent,

log10 = log in base 10, CRF = Case Report Form

Converting ETDRS Letter Scores to LogMAR values When Using Standard Distance for the Chart:

LogMAR value=((ETDRS Letter score for 20/20) – (letter score on CRF))/50

Far VA: LogMAR value = (40-letter score)/50

Converting ETDRS Letter Scores to LogMAR values When NOT Using Standard Distance for the Chart:

LogMAR value=((ETDRS Letter score for 20/20) – (letter score on CRF))/50

+ (log10(standard distance)-log10(actual distance))

Far VA: LogMAR=(40-letter score)/50+(log10(4)-log10(actual distance in M))

Converting from LogMAR to Snellen and Decimal Equivalent:

Snellen Denominator=20*(10**(LogMAR value))

Decimal VA= 20/(Snellen Denominator)

Example

A subject has a letter score of 24 and a test distance of 33 cm.

Converting to LogMAR:

(40 - 24)/50 + (log10(40)-log10(33))=16/50+ (1.602-1.519)=0.32+.083=0.403 LogMAR

The Snellen Denominator is: 20*(10**(0.403) = 20*(2.53) = 50

Decimal VA = 20/50=0.40

APPENDIX III: FORMULAS USED FOR REFRACTIVE DATA

Formulas for Manifest and Cycloplegic Refractive Data

Converting to Minus Cylinder Notation:

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

1. New sphere value=original sphere value + original cylinder value
2. Final cylinder value=change the sign of original cylinder value
3. Final axis value: if the cylinder is equal to 0 then the axis will be set to 0; if the 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 minus cylinder notation) – 0.25

Spherical Equivalent: Spherical equivalent = final sphere + (0.5*final cylinder)

Examples:

Refraction on CRF: sphere: -3.25, cylinder: 0.50, axis: 80

In minus cylinder notation: sphere = -2.75, cylinder = -0.50, axis = 170
Adjusting for infinity: sphere = -3.00, cylinder = -0.50, axis = 170
Spherical equivalent = -3.00 + 0.5*(-0.50) = -3.25

APPENDIX IV:

National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL-42™), Version 1.0:

A Manual for Use and Scoring

Ron D. Hays and Karen L. Spritzer
February 2002

Note that the following citation is suggested when referencing this manual:

Hays, R. D., & Spritzer, K. L. (2002, February). National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL-42™), Version 1.0: A Manual for Use and Scoring. Los Angeles, CA.

SCORING RULES

Scoring the RQL-42 is a two-step process:

First, original numeric values from the survey are recoded following the scoring rules outlined in Table 1. All items are scored so that a high score represents better quality of life. Each item is then converted to a 0 to 100 possible range so that the lowest and highest possible scores are set at 0 and 100, respectively. In this format, scores represent the achieved percentage of the total possible score. For example, a score of 50 represents 50% of the highest possible score.

Second, items within each scale are averaged together to create the 13 scale scores. Table 2 indicates which items contribute to each scale. Scales with at least one item answered can be used to generate a scale score. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Scores represent the average for all items in the scale that the respondent answered.

Table 1. Scoring Key: Recoding of Items

ITEM NUMBERS	Original response category	To recoded value of
1, 28	1 ---->	100
	2 ---->	50
	3 ---->	0
	4 ---->	100
2, 9, 10, 12	1 ---->	100
	2 ---->	75
	3 ---->	50
	4 ---->	25
	5 ---->	0
	6 ---->	*
3	1 ---->	100
	2 ---->	100
	3 ---->	200/3
	4 ---->	100/3
	5 ---->	0
4, 5, 6, 11, 23	1 ---->	100
	2 ---->	200/3
	3 ---->	100/3
	4 ---->	0
7, 8, 20, 21, 22, 24, 25	1 ---->	100
	2 ---->	75
	3 ---->	50
	4 ---->	25
	5 ---->	0
13, 14, 34, 35	1 ---->	0
	2 ---->	50
	3 ---->	100
15, 16	1 ---->	100/3
	2 ---->	200/3
	3 ---->	100
	4 ---->	0
	5 ---->	*
17, 18, 31, 32	1 ---->	0
	2 ---->	25
	3 ---->	50
	4 ---->	75
	5 ---->	100
19	1 ---->	100
	2 ---->	100
	3 ---->	75
	4 ---->	50
	5 ---->	25
	6 ---->	0

* Response choice indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Table 1. Scoring Key: Recoding of Items (continued)

ITEM NUMBERS	Original response category	To recoded value of
26, 27	1 ---->	100
	2 ---->	80
	3 ---->	60
	4 ---->	40
	5 ---->	20
	6 ---->	0
29	1 ---->	100
	2 ---->	0
30, 33	1 ---->	0
	2 ---->	100
36b(†), 37b(†), 38b(†), 39b(†), 40b(†), 41b(†), 42b(†)	(b=1) ---->	0
	(b=2) ---->	25
	(b=3) ---->	50
	(b=4) ---->	75
	(a=2 and b=missing) ---->	100

† Items 36b-42b have four response levels, but are expanded to five levels using items 36a-42a, respectively. If a = 2, then b should have been left blank. If there is a discrepancy between a and b, the user needs to decide how to resolve the discrepancy. In many cases, going with the response to b (ignoring a) when there is a discrepancy may be reasonable.

Table 2: Averaging Items to Generate RQL-42 Scales

Scale	Number of Items	After Recoding Per Table 1, Average the Following Items
Clarity of vision	4	23, 37b, 39b, 40b
Expectations	2	1, 28
Near vision	4	2, 7, 8, 11
Far vision	5	4, 5, 6, 9, 10
Diurnal fluctuations	2	3, 20
Activity limitations	4	12, 33, 34, 35
Glare	2	17, 38b
Symptoms	7	18, 19, 24, 25, 36b, 41b, 42b
Dependence on correction	4	13, 14, 15, 16
Worry	2	21, 22
Suboptimal correction	2	31, 32
Appearance	3	27, 29, 30
Satisfaction with correction	1	26

Table 3: Central Tendency, variability (including floor and ceiling effects), and reliability of RQL-42 Scales‡

Measure	Mean	Standard Deviation	% Floor	% Ceiling	Internal Consistency Reliability
Clarity of vision	83.85	18.36	0.1	27.3	0.72
Expectations	43.57	38.22	34.6	22.2	0.90
Near vision	83.94	18.03	0.0	33.5	0.85
Far vision	83.48	15.85	0.0	20.0	0.81
Diurnal fluctuations	74.58	23.13	0.3	30.3	0.73
Activity limitations	85.28	21.92	0.1	53.5	0.76
Glare	76.40	26.41	1.6	40.1	o.75
Symptoms	79.20	16.79	0.0	12.7	0.78
Dependence on correction	42.38	34.75	28.6	15.2	0.74
Worry	61.31	26.04	3.6	10.1	0.80
Suboptimal correction	92.74	17.28	0.8	81.5	0.64
Appearance	79.31	27.00	0.7	31.8	0.66
Satisfaction with correction	74.85	22.55	1.5	28.4	NA

‡ Data is from a cross-sectional study consisting of 665 myopes, 375 hyperopes, and 114 emmetropes recruited from the practices of six medical centers.

NA – Not applicable for a single-item measure.