Statistical Analysis Plan

Clinical Investigation of the iDesign Advanced WaveScan Studio System with 1Design 1.3-PRESBY treatment and STAR S4 IR™ Excimer Laser System

NCT Number: NCT02806726

Document Date: 10 Nov 2015

STATISTICAL ANALYSIS PLAN

CLINICAL INVESTIGATION OF THE

IDESIGN ADVANCED WAVESCAN STUDIO SYSTEM (SOFTWARE VERSION 1.2) WITH IDESIGN 1.3-PRESBY TREATMENT AND STAR S4 IR™ EXCIMER LASER SYSTEM

PROTOCOL NUMBER: STAR-116-TOPS

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1 INTRODUCTION

This document summarizes the statistical methods and tables to be implemented during the analysis of data for this feasibility study of a new treatment algorithm (iDesign 1.3-PRESBY) to increase depth of focus after wavefront-guided LASIK correction of myopic refractive errors. This study will be a 9-month, prospective, multi-center, non-randomized, contralateral clinical trial.

All endpoints will be evaluated at 6 months. The primary endpoint is monocular distance corrected intermediate visual acuity (DCIVA). The secondary endpoint is monocular distance corrected near visual acuity (DCNVA). The safety endpoints include monocular best corrected visual acuity (BSCVA), rates of induced manifest astigmatism and rates of serious and device-related adverse event rates.

Other endpoints include monocular and binocular UCDVA and BSCVA, monocular and binocular UCIVA and UCNVA, binocular DCIVA and DCNVA, monocular low contrast BSCVA, monocular mesopic DCNVA, monocular depth of focus, iDesign aberrometry measurements, pupil size, manifest refraction, keratometry, anterior segment evaluation, ocular and visual symptoms.

Table listings are included in Appendix I.

2 ANALYSIS POPULATIONS AND VISIT SCHEDULE

2.1 ANALYSIS POPULATIONS

The safety population will be the primary analysis population for all endpoints and will consist of all eyes that receive study treatment.

2.2 VISIT SCHEDULE

All eyes will be examined preoperatively and at 1 day, 1 week, 1 month, 3 months, 6 months and 9 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.

Unless otherwise indicated, alpha will be set to 0.05 for two-sided statistical testing.

For visual acuity data, 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.

3 STATISTICAL METHODS

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 PRIMARY ENDPOINT

MONOCULAR DISTANCE CORRECTED INTERMEDIATE VISUAL ACUITY (DCIVA)

The primary endpoint is mean monocular DCIVA under photopic conditions at 67 cm. Results will be reported by CustomVue combined with iDesign 1.3-PRESBY treatments (test) group versusCustomVue (control) group and compared using a one-sided, paired t-test with alpha level of 0.025. The null hypothesis is that the mean difference between eyes (control minus test) for LogMAR DCIVA is less than or equal to zero (ie, test acuity is the same as or worse than that of control). The alternative hypothesis is that the mean difference between eyes for DCIVA is greater than zero (ie, test acuity is better than that of control).

H_o: $\mu_{diff} \leq 0$ (test is worse than (higher LogMAR) or equal to control)

H_1: $\mu_{diff} > 0$ (test is better (lower LogMAR) than control)

where

μ_{diff} = the mean difference in LogMAR DCIVA between control eyes and test eyes (control minus test)

Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean DCIVA for test compared to control (p ≤ 0.025).

In addition, clinical significance will be achieved if the mean DCIVA for the test group is at least one line better than that for the control group.

3.4 SECONDARY ENDPOINT

MONOCULAR DISTANCE CORRECTED NEAR VISUAL ACUITY (DCNVA)

Mean monocular DCNVA at 40 cm will be reported by CustomVue combined with iDesign 1.3-PRESBY treatments (test) group versus CustomVue treatments (control) group and compared using a one-sided, paired t-test with an alpha level of 0.025. The null hypothesis is that the mean difference between eyes (control minus test) for logMAR DCNVA is less than or equal to zero. The alternative hypothesis is that the mean difference between eyes for DCNVA is greater than zero.

H_o: $\mu_{diff} \leq 0$ (test is worse than (higher logMAR) or equal to control)

H_1: $\mu_{diff} > 0$ (test is better (lower logMAR) than control)

where

μ_{diff} = the mean difference in logMAR DCNVA between control eyes and test eyes (control minus test)

Reject the null hypothesis if one-sided p-value ≤ 0.025.

The success criterion is a statistically significantly lower mean logMAR value for test compared to control eyes (p ≤ 0.025).

Clinical significance is achieved if the mean DCNVA for the test group is at least 1.5 lines better than that for the control group.

3.5 SAFETY ENDPOINTS

1. MONOCULAR BSCVA

Mean monocular BSCVA will be reported by test and control groups with the mean difference between postoperative and preoperative BSCVA evaluated using a two-sided, 90% confidence interval (CI). The null hypothesis is that the mean difference (postoperative minus preoperative) in logMAR BSCVA is greater than or equal to 0.1 logMAR. The alternative hypothesis is that the mean difference in BSCVA is less than 0.1 logMAR.

H_o: $\mu_{diff} \geq 0.1$

H_1: $\mu_{diff} < 0.1$

where

μ_{diff} = the mean difference in logMAR BSCVA between postoperative and preoperative eyes (postoperative minus preoperative).

The success criterion is achieved if the upper limit of the 90% CI of the differences in mean logMAR BSCVA for postoperative compared to preoperative eyes is < 0.1 logMAR for both test and control groups.

Clinical significance is achieved if the mean postoperative BSCVA is no more than one line worse than preoperative BSCVA for both test and control groups.

2. INDUCED MANIFEST REFRACTIVE ASTIGMATISM

The frequency and proportion of eyes with induced manifest refractive astigmatism will be reported at each periodic study visit. The rate of eyes with induced manifest refractive astigmatism of greater than 2.00 diopters will be summarized.

3. SERIOUS AND DEVICE RELATED ADVERSE EVENTS

The number and proportion of eyes with serious and device-related adverse events (non-flap related) will be summarized.

3.6 ADDITIONAL ENDPOINTS

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

The frequency, proportion and 95% confidence intervals of eyes with achieved MRSE within 0.50 D and 1.00 D of intended will be summarized over time. The intended MRSE is defined as " – Preop MRSE". The achieved MRSE is defined as "Postop MRSE - Preop MRSE".

Refractive stability will be evaluated for a consistent cohort (i.e., eyes with data at all periodic study visits). At the point of refractive stability, at least 95% of the eyes in the consistent cohort should have a change ≤1.00 D of MRSE between refractions performed at 1 month and 3 months after surgery or any two refractions performed at least 3 months apart. The mean change (paired differences) in MRSE between pairs of successive refractions will be calculated. The 95% confidence intervals of the mean changes should include zero.

The depth of focus curve data will be presented graphically with mean visual acuity on the vertical axis and defocus points on the horizontal axis for test and control groups. The descriptive statistics of defocus for test and control groups will be reported and compared.

Other visual acuity endpoints (such as UCDVA, UCIVA, UCNVA, DCIVA, DCNVA and low contrast BSCVA) will also be reported by test versus control group with the mean difference between groups also determined.

The mean and standard deviation of iDesign aberrometry measurements (HOA) and keratometry (mean and K cylinder) will be reported over time between test and control gorups.

Manifest cylinder will be analyzed as both non-vector and vector variables (Eydelman, et al, 2006). Non-vector analysis includes the descriptive statistics (mean, SD, minimum and maximum) of MRC over time between test and control groups and the accuracy of MRC will also be summarized over time. Vector analysis summary will be reported by test and control group. 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).

Summary statistics (mean, standard deviation, median, minimum and maximum) will be reported over time for pupil size between test and control groups.

The frequency and proportion of eyes with complications and slit-lamp findings, including corneal clarity, will also be reported over time.

The frequency and proportion of responses to each item from the PRVSQ for PRK/LASIK will be analyzed to compare differences between the test and control groups.

The frequency and proportion of eyes with reported ocular visual symptoms (non-directed) will be presented.

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.

4 SAMPLE SIZE CALCULATIONS

The sample size determination is based on intermediate visual acuity. There is over 80% power to detect a 0.7 line or greater difference in mean visual acuity between the test and control eyes with 34 subjects. This assumes a two-sided paired t-test with an alpha of 0.05 and standard deviation of 1.4 lines.

APPENDIX I TABLE LISTING FOR STAR-116-TOPS

KEY: BSCVA=best corrected distance visual acuity, UCDVA=uncorrected distance visual acuity, DCIVA=Distance corrected intermediate visual acuity, DCNVA=Distance corrected near visual acuity, HOA=higher order aberration

SD=Standard Deviation, D=Diopter, x=tables will be provided – blank indicates table will not be generated

Variable	Test	Control
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**	**x**
Out of Interval listing	**x**	**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 (All subjects only)	**x**	**x**
Preoperative Characteristics		
iDesign Refractions (IDSE, IDS, IDC) - (N, Mean, SD, Min, Max) Manifest refractions (MRSE, MRS, MRC) – (N, Mean, SD, Min, Max)	**x**	**x**
IDSE/IDS by IDC dioptric bins (n and % of eyes).	**x**	**x**
Operative Data		
Iris registration used or not (n and % of eyes)	**x**	**x**
Operative complications (n and % of eyes)	**x**	**x**
Primary endpoint		
Monocular DCIVA in LogMAR (mean, SD, min, max)	**x**	**x**
Secondary endpoint		
Monocular DCNVA in LogMAR (mean, SD, min, max)	**x**	**x**
Safety endpoints		
Monocular BSCVA in LogMAR (mean, SD, min, max,)	**x**	**x**
Induced manifest astigmatism (n and % of eyes)	**x**	**x**
Non-flap related adverse events (n and % of eyes)	**x**	**x**
Other endpoints		

MRSE over time(N, Mean, SD, Min., Max) MRSE accuracy(n, % and 95% CI of eyes wthin±0.50D; n and % of eyes with overcorrection or undercorrection of more than 1D or 2D)	**x**	**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) Vector – vector analysis summary (mean and SD of |IRC|, |SIRC|, |EV|, CR and ER by preop MRC categories)	**x**	**x**
Keratometric analysis Average K (defined as (flat+steep)/2) - (N, mean, SD, min, max) K cylinder(defined as (steep-flat)) magnitude difference from preop - (N, mean, SD, min, max)	**x**	**x**
Monocular 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**	**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**	**x**
HOA analysis HOA overtime - (n, mean and SD) HOA paired difference – (n, mean and 95% CI around the mean)	**x**	**x**
Medical findings from slit lamp examination over time (n and %)	**x**	**x**
Ocular visual symptoms N and % of each non-directed, monocular ocular visual symptoms will be tabulated over time.	**x**	**x**
Visual Symptoms from PRVSQ PRO questionnaire N and % of severity level for each symptom under different condition	**x**	**x**
Serious and/or device related adverse events Listing, n and %	**x**	**x**
Non-refractive retreatment procedures over time and cumulatively	**x**	**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 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