Statistical Analysis Plan

Title: Clinical Investigation of the Bacterially-Derived Healon5 Ophthalmic Viscosurgical Device (OVD)

NCT02782676

Document Date: 1/22/2016

Uploaded: 4/13/2018

STATISTICAL ANALYSIS PLAN

CLINICAL INVESTIGATION OF THE BACTERIALLY-DERIVED HEALON 5 OPHTHALMIC VISCOSURGICAL DEVICES (OVD)

PROTOCOL NUMBER: VSCO-109-HLN5

SPONSOR
Abbott Medical Optics, Inc.
1700 E. St. Andrew Place
Santa Ana, CA 92705
714-247-8200

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	1, 2, 6, 7 Appendix I	3, 5, 8, 9 13	Study endpoints updated to move adverse events, inflammation, IOP spikes over time, and mean change in IOP from baseline from other endpoints to secondary safety endpoints.	To address FDA considerations in letter dated January 6, 2016.
	5	6, 7	Primary study endpoints specifically identified as safety or effectiveness.	
	5	8	Non-parametric test will be used to evaluate mean percent ECC change if normality assumption is not met.	

1 INTRODUCTION

This document summarizes the statistical methods to be implemented during the analysis of data for the bacterially-derived Healon5 ophthalmic viscosurgical device (OVD) VSCO-109-HLN5 study. This study will be a 3 month, prospective, multicenter, paired-eye, randomized, masked clinical trial. Subjects will be randomized to receive bacterially-derived Healon5 OVD in one eye and currently-available animal-derived Healon5 OVD in the other eye according to a centralized electronic randomization system. It is expected that there will be 200 evaluable subjects at the 3 month timeframe.

There are two primary endpoints for this study: cumulative rate of intraocular pressure (IOP) spikes 30 mmHg or greater postoperative and mean percent change of endothelial cell count (ECC) preoperatively vs. postoperatively at 3 month.

The secondary safety endpoints are rates of serious and/or device-related adverse events, distribution of the grade of inflammation, IOP spikes of 30 mmHg or greater at 6 hours, 1 day, 1 week, 1 month and 3 months postoperatively, and mean change in IOP from baseline.

Additional endpoints are optical/visual symptoms (non-directed), medical findings/adverse events (non-serious, non-device related), monocular best corrected distance visual acuity (BCDVA) 20/40 or better vs. ISO SPE rate, and uncorrected distance visual acuity (UCDVA).

2 ANALYSIS POPULATIONS

2.1 ANALYSIS POPULATIONS/HANDLING OF MISSING DATA

Four different populations will be presented for the primary endpoints (cumulative IOP spike, and mean percent ECC change): Intent-to-Treat (ITT), sensitivity analysis, safety population, and per-protocol population. The ITT population will be the primary analysis population for the primary endpoints and will include all subjects who were randomized and had surgeries using the test OVD in one eye and the control OVD in the other eye (i.e., paired OVDs were used). Sensitivity analysis will include all subjects who were randomized regardless of OVD use; i.e., include subject that had no study OVD, one study OVD or paired OVDs used. The safety population will include available subjects who had one or both study OVDs. The per-protocol population will include available subjects who had surgeries with paired OVDs, were evaluated within the proper study interval and were without clinically-relevant protocol deviations

For the secondary safety endpoints and other additional study endpoints, only data from the safety population will be presented.

INTENT-TO-TREAT ANALYSIS

The ITT population will include all subjects who were randomized and had surgeries using a test OVD in one eye and a control OVD in the other eye (i.e., paired OVDs). For randomized subjects who had study OVDs but did not have data available at a specific postoperative visit, (e.g. they missed a visit, were lost to follow-up), data will be imputed for the ITT analyses using a planned multiple imputation method. The planned imputation method is the MCMC full-data imputation as described in Little & Rubin[1]. Data imputation and analysis will be performed using the MI and MIANALYZE procedures[2] in SAS®.

SENSITIVITY ANALYSIS

Sensitivity analysis will include all subjects who were randomized whether they had none, one OVD or both OVDs. For missing data in the sensitivity analysis, different imputation approaches (e.g. worst-case scenario, best-case scenario and tipping point) will be used. For the difference between eyes, a worst-case scenario will be performed with the worst difference score (that favoring the control the most) assigned to the missing data. For the best-case scenario, the difference score favoring the control OVD the most will be assigned to missing data. If more than 10 percent of randomized subjects have missing data at the primary analysis time point then a tipping point analysis will also be performed.

SAFETY (SF) ANALYSIS

The safety population will consist of all subjects who had any study OVD used and with data available at the time of analysis (i.e., no data imputation). For endpoint analyses using the safety population, if a subject receives only one study OVD then their data will be reported separately since they will not have any between eye difference values. However, if only one eye had a study OVD, then data for that eye will be included in reporting of adverse events and complications. Reporting of cumulative complications (occurring at any time postoperative) will include data from all eyes that had a study OVD.

PER-PROTOCOL (PP) ANALYSIS

The PP population will only include subjects who had surgeries with paired OVDs used, were evaluated within the proper study interval and were without clinically-relevant protocol deviations (deviations that could potentially impact the primary or secondary endpoints for either eye as determined prior to database lock). PP tables will include available data at the time of analysis with no data imputation performed**.**

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 (both eyes), Operative, 6 hour, 1 day and 1 week for each eye, and 1 month and 3 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. In this study, unless otherwise indicated, paired t-tests will be used for continuous data, Wilcoxon signed-rank test for ordinal data and McNemar's test for dichotomous data.

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.

2.4 RANDOMIZATION

Randomization will be done for each investigational site according to a centralized electronic randomization system. Once the surgeon has determined that the subject has met all specific criteria and selected which will be the first operative eye for a given subject, the randomization can occur indicating which OVD is to be used in the first eye surgery and the alternate OVD is to be used in the fellow eye surgery.

If mis-randomization occurs in the study, the subject's study data will be analyzed according to the randomization schedule in the ITT and sensitivity populations and will be analyzed according to the OVDs received in the safety population. The subject will be excluded in the Per-Protocol population analysis.

2.5 MULTIPLICITY ADJUSTMENT

No multiplicity adjustment is planned for the primary endpoints since both endpoints are required to meet statistical significance. No multiplicity adjustment is planned for the secondary safety endpoints as these are safety endpoints not intended for claims. Please see Section 6 for more details regarding the planned analysis of secondary safety endpoints.

2.6 SITE DIFFERENCES

For the primary endpoints, data will be reported by site using the safety population. To evaluate site differences, a mixed model analysis will be performed taking paired eyes into account. The model will include OVD group as a fixed variable with site and site by OVD group interaction as random variables. If the interaction term is significant at the 0.15 level, then further examination of effects of site will be evaluated. 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. Subject accountability will be summarized as a frequency distribution by scheduled visits. A frequency table 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, ethnicity and eye color will be presented. 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, ethnicity and iris color will also be tabulated.

4 PREOPERATIVE/OPERATIVE VARIABLES

Preoperative and operative variables will be reported for each OVD group. The frequency and proportion of eyes with selected responses will be tabulated for categorical data. Descriptive statistics will be used for continuous data. Statistical comparisons between OVD groups will be performed using paired analyses as appropriate (e.g., paired t-tests for continuous data; Wilcoxon signed-rank test for ordinal data; McNemar's test for paired binary proportions). Two-sided testing with an alpha level of 0.05 will be used for preoperative and operative variables.

5 POSTOPERATIVE PRIMARY ENDPOINTS

5.1 SAFETY: CUMULATIVE RATE OF IOP SPIKES 30 MMHG OR GREATER MEASURED POSTOPERATIVELY

The cumulative frequency and proportion of eyes with an IOP spike will be reported for both OVD groups for the safety population, PP population and sensitivity analysis. For ITT population (with imputation), only the difference between the OVD groups will be reported. The difference in the cumulative IOP spike rate will be analyzed by the McNemar test using a GLIMMIX procedure taking into account the paired data. The GLIMMIX model will model spike as the dependent variable and OVD group as an independent variable and include the SUBJECT = option for the paired eye data. The

hypothesis testing of non-inferiority for cumulative percentage of IOP spikes will be tested using a 1-sided, McNemar test at an alpha of 0.025 with a delta of 0.10 (10%). The null hypothesis is that the paired difference between eyes is less than or equal to -10%. The alternative hypothesis is that the paired difference between eyes is greater than -10%.

H_o: $p_c - p_t \leq \delta$

H_a: $p_c - p_t > \delta$

where…

p_t = Test rate of IOP spikes 30 mm Hg or greater

p_c = Control rate of IOP spikes 30 mm Hg or greater

δ = non-inferiority margin: -10%

Success Criteria: If the lower 2-sided 95% confidence interval (equivalent to the 1-sided 97.5% CI) for the difference between the proportions is greater than -10% [3].

5.2 EFFECTIVENESS: MEAN PERCENT ECC CHANGE PREOPERATIVELY VS. POSTOPERATIVELY

The mean percent change in ECC from preoperative to 3 months postoperative will be reported by descriptive statistics for both OVD groups for safety population, PP population and sensitivity analysis. For ITT (with imputation), only the mean difference between the two OVD groups will be reported. The percent change in ECC from preoperative to postoperative is calculated as followed:

Percent change in ECC = (Postop ECC minus Preop ECC)/Preop ECC

The difference in mean percent change in ECC will be analyzed by a paired t-test. The hypothesis testing of non-inferiority for mean percent ECC change will be tested using a 1-sided, paired t-test at an alpha of 0.025 and a delta of 5%. The null hypothesis is that the paired mean difference for mean percent change in ECC is equal to or less than -5%. The alternative hypothesis is that the paired mean difference in percent change between eyes is greater than -5%.

H_o: $\mu_{test} - \mu_{control} \leq \delta$

H_a: $\mu_{test} - \mu_{control} > \delta$

where…

μ_{test} = ECC percent change in test OVD

$\mu_{control}$ = ECC percent change in control OVD

δ = non-inferiority margin: -5%

Success Criteria: If the lower 2-sided 95% confidence interval (equivalent to 1-sided 97.5% CI) for the mean difference between eyes in percent change for ECC is greater than -5%.

If the percent ECC change does not meet normality assumption, a non-parametric test will be performed to evaluate the non-inferiority of ECC endpoint. A similar alpha level of 0.025 and a delta of 5% will be used for the 1-sided non-parametric test.

In addition, ECC for preoperative, 3 months postoperative and the difference between preoperative and 3 months will also be reported as supportive data using the safety population.

6 SECONDARY SAFETY ENDPOINTS

6.1 SERIOUS AND/OR DEVICE-RELATED ADVERSE EVENTS

Serious and/or device related adverse event rates will be tabulated with the frequency and proportion of eyes with these events reported over time and cumulatively by OVD group. The AE rates will be compared to the ISO SPE rate[4]. Comparison of the ISO SPE rates will be performed using an exact test based on the binomial distribution. The null hypothesis is that the study rate for test OVD is equal or lower than the ISO SPE rate, and the alternative hypothesis is that the study rate for test OVD is greater than the ISO SPE rate.

H_o: $p_t \leq p_i$
H_a: $p_t > p_i$
where
p_t = proportion of test OVD eyes with the AE
p_i = ISO SPE rate with the AE
Success Criteria: If one-sided p-value ≥ 0.025.

6.2 DISTRIBUTION AND GRADE OF INFLAMMATION

The grades of inflammation (for epithelial and stromal edema, cells and flare, anterior and posterior synechiae, and fibrin presence) will be tabulated with frequency and proportion of eyes with each grading for each event presented over time and cumulatively for both OVD groups.

6.3 RATE OF IOP SPIKES 30 MMHG OR GREATER AT 6 HOURS, 1 DAY, 1 WEEK, 1 MONTH AND 3 MONTHS POSTOPERATIVELY

The rate of IOP spike 30 mmHg or greater at 6 hour, 1 day, 1 week, 1 month and 3 months postoperatively will be tabulated with frequency and proportion by OVD group and analyzed using the McNemar test.

6.4 MEAN CHANGE OF IOP FROM BASELINE

The mean change of IOP at 6 hour, 1 day, 1 week, 1 month and 3 months will be compared to baseline. Descriptive statistics will be presented by OVD group.

7 ADDITIONAL ENDPOINTS

7.1 OCULAR VISUAL SYMTPOMS (NON-DIRECTED)

The ocular visual symptoms (non-directed) will be tabulated with the frequency and proportion of eyes with these events reported over time and cumulatively by OVD group.

7.2 MEDICAL FINDINGS/ADVERSE EVENTS (NON-SERIOUS, NON-DEVICE RELATED)

The medical findings and other adverse events (non-serious, non-device related) will be tabulated with the frequency and proportion of eyes with these events reported over time and cumulatively by OVD group.

7.3 MONOCULAR BEST-CORRECTED VISUAL ACUITY (BCDVA)

The proportion of test OVD eyes achieving 20/40 or better BCDVA will be compared to the ISO SPE rates. The null hypothesis is that the proportion of test OVD eyes achieving 20/40 is greater than or equal to the ISO SPE values and the alternative hypothesis is that the proportion of test OVD eyes achieving 20/40 or better BCDVA is less than the ISO SPE values.

The proportion of eyes achieving each BCDVA acuity line equivalent will also be reported over time by OVD group.

7.4 UNCORRECTED DISTANCE VISUAL ACUITY (UCDVA)

The proportion of eyes achieving each UCDVA acuity line equivalent will be reported over time by OVD group.

8 SAMPLE SIZE CALCULATIONS

Cumulative IOP spikes are defined as an IOP of 30 mm Hg or greater at any visit. The percentage of eyes with IOP spikes will be assumed to be 30% (15798:2001(E), Annex D), and a correlation of 0.5 (medium strength). Using a one-sided, McNemar test and assuming an alpha of 0.025, power = 0.80, and a minimum detectable difference of δ=0.10 yields a sample size of n=195 eyes per group. Adding 20% for lost-to-follow-up and screen failures yields a sample size of 241 subjects (482 eyes total with contralateral control).

Assuming a 1-sided, non-inferiority, paired t-test with alpha=0.025, a common standard deviation of 305 cells[5], and a correlation of 0.50 (medium strength), a sample of n=195 subjects (390 eyes) provides over 99% power to detect a minimum clinically significant decrease in mean Endothelial Cell Count (ECC) of at least δ =125 cells. This corresponds to a 5% decrease using a standard deviation of 12% from a baseline ECC of 2500 cells.

Since the sample size required to detect a minimum clinically significant effect for IOP spikes also provides over 99% power to detect a minimum clinically significant effect for ECC loss, the sample size for the study will be based on the number calculated for IOP spikes. Therefore, the sample size required is 195 subjects. Adding 20% for lost-to-follow-up and screen failures yields a sample size of 241 subjects (482 eyes).

9 REFERENCES

1. Little, R. and Rubin, D. Statistical Analysis with Missing Data, John Wiley & Sons, Inc. New York, Second Edition, (2002)
2. SAS Institute. The MI and MIANALYZE Procedures. SAS/STAT 9.2 User Guide. and SAS/STAT User Guide for the MI Procedure: Imputation Methods. Cary, N.C.
3. Liesegang TJ. Viscoelastic substances in ophthalmology. Surv ophthalmol 1990; 34:268-293
4. ISO 11979-7:2006I. International Standard for Ophthalmic Implants – Intraocular Lenses – Part 7: Clinical Investigations, (2006). Amendment 1 to Annex B (2012).
5. Nichols JJ, Kosunick M, Bullimore MA. Reliability of Corneal Thickness and Endothelial Cell Density Measures. J Cataract Refract Surg 2003 ;19:344-352

APPENDIX I: TABLE LISTING

	Test Eye	Control Eye	Comments/ Population
ENROLLMENT/PREOP/OP			
Accountability/Enrollment			
No. of eyes by OVD model by investigational site	X	X	SF/PP/ITT/Sensitivity
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	SF/PP/ITT
Out of interval subjects listing – No. of eyes	X	X	SF/PP/ITT
Demographics			
Demographic –Age in years (N, Mean, SD, Min., Max), age in groups (<60,60-69,70-79,>=80), race, ethnicity, sex, iris color			ITT/SF/PP (By Subject)
Age by Site (N, Mean, SD, Min. Max.)			SF (By Subject)
Other demographic data by site (race, ethnicity, sex)			SF (By Subject)
Preoperative Characteristics			
Visual Acuity: No. and percent of eyes for each category Potential Visual Acuity (≤20/40,>20/40) BCDVA (≤20/30, 20/40, 20/50-20/80, 20/100, >20/100) UCDVA (≤20/40, 20/50-20/80, 20/100, >20/100)	X	X	SF
Other Preop Items: No. and percent of eyes for each category Non-clinically significant pathology and/or Medical findings (by finding)	X	X	SF
Operative Data			
General Surgical Parameters: No. and percent with each response IOL model implanted (ZCB00, PCB00, ZKB00, ZLB00, ZMB00) Incision location (Superior, temporal, steep axis, other) Lens placement (Capsular bag, other) Type of Closure (Sutureless, suture) Any concerns/issue with AMO product as part of preparing, performing and/or completing the surgery? (Yes/No) Capsulotomy method (by type) Lens removal method (by method)	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	SF

	Test Eye	Control Eye	Comments/ Population
PRIMARY EFFECTIVENESS ENDPOINTS			
Cumulative IOP 30mmHg spike rate (95% CI.) between OVD groups Cumulative IOP 30mmHG spike rate (No. and percent) by OVD groups	X	X	ITT/Sensitivity/SF/PP Sensitivity/SF/PP
Mean difference between OVD groups in percent ECC change preoperatively vs. 3 months (N, Mean, SD, Median, Min., Max, 95% CI.) Mean percent change of ECC preoperatively vs. 3 months (N, Mean, SD, Median, Min., Max, 95% CI.) by OVD groups	X	X	ITT/Sensitivity/SF/PP Sensitivity/SF/PP
SECONDARY SAFETY ENDPOINTS			
Serious and/or device related adverse event rates (No. and percent) compared to ISO SPE rates Serious and/or device related adverse event rates over time (No. and percent)	X	X	SF
Grades of inflammation (No. and percent) over time and cumulatively (epithelial and stromal edema, cells and flare, anterior and posterior synechiae, fibrin presence)	X	X	SF
IOP 30mmHG spike rate (No. and percent, 95% CI) between OVD groups at 6 hour, 1 day, 1 week, 1 month and 3 months postoperatively	X	X	SF
Change of IOP from baseline at 6-hour, 1-day, 1-week, 1-month, and 3-month postoperatively between OVD groups (N, Mean, SD, Median, Min, Max.)	X	X	SF
ADDITIONAL ENDPOINTS			
Non-directed ocular visual symptoms (No. and percent) over time and cumulatively	X	X	SF
Other AE (non-serious, non-device related)/Medical findings (No. and percent) over time and cumulatively	X	X	SF
Monocular BCDVA by acuity line over time (No. and percent) Percent 20/40 or better vs. ISO SPE rate	X	X	SF
Monocular UCDVA by acuity line at 1 day (No. and percent)	X	X	SF
Other IOP/ECC Tables			
IOP at preoperative, 6 hour, 1 day, 1 week, 1 month and 3 month (N, Mean, SD, Median, Min., Max)	X	X	SF
ECC at preoperative, 3 months and difference between preoperatively vs. 3 months (N, Mean, SD, Median, Min., Max)	X	X	SF
Other Adverse Event Tables			
Non-adverse event/procedures (No. and Percent)	X	X	SF
Listing of serious and/or device-related Adverse Events by event and by OVD type (include site, age, last reported BCDVA, complications)	X	X	SF

KEY:OVD=viscoelastic used, VA=Visual acuity, UCDVA=Uncorrected distance visual acuity, BCDVA=Best corrected distance visual acuity, ITT=Intent to Treat, PP=Per protocol, SF=Safety, SD=Standard deviation, Min.=Minimum value, Max.=Maximum value, C.I.=Confidence interval, X=Tables will be provided – blank indicates table will not be generated for that group, 3M=3-month postoperative visit

TIME FRAME: The 3-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 OVD groups