Statistical Analysis Plan

Clinical Investigation of the Bacterially-Derived Healon EndoCoat PRO Ophthalmic Viscosurgical Device (OVD)

PROTOCOL NUMBER: VSCO-110-LOKE

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STATISTICAL ANALYSIS PLAN

Clinical Investigation of the

Bacterially-Derived Healon EndoCoat PRO Ophthalmic Viscosurgical Device (OVD)

IDE Number: G220153

PROTOCOL NUMBER: VSCO-110-LOKE

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Table of Contents

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	Title Page	1	Updated with IDE number	IDE number assigned by FDA
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	Appendix I	19-23	• Updated analyses populations to the tables/listings for demographic information, primary endpoints, site heterogeneity, and other covariates	• To align the list of tables with the rest of the SAP document
	Various	Various	• Added table of contents • Restructured the sections and subsections order • Minor editorial changes like section titles and order	Clarifications and improved flow
[redacted]				
	Various	Various	Minor editorial changes	Clarifications
6.0	5.1	12, 13	Edited the description to the IOP primary endpoint	To improve clarity

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
	[redacted]	[redacted]	[redacted]	[redacted]
	5.3	16, 17	Editorial changes to align the section with previous sections 5.1 and 5.2	To improve consistency

1 INTRODUCTION

This document summarizes the statistical methods for the safety and effectiveness analyses of the VSCO-110-LOKE study, comparing the Healon EndoCoat PRO ("EndoCoat PRO") OVD with the EndoCoat OVD. This study is a 3-month, prospective, multicenter, paired-eye, randomized, subject/evaluator-masked clinical trial conducted at up to 10 sites in the USA. Subjects will be randomly assigned to receive the study OVD in one eye and the control OVD in the fellow eye. [redacted]

1.1 STUDY OBJECTIVES

The purpose of this clinical trial is to evaluate the safety and effectiveness of the EndoCoat PRO OVD as compared to the EndoCoat OVD. All study endpoints will be evaluated at 3-months postoperative.

1.2 STUDY ENDPOINTS

PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the cumulative rate of IOP spike (30mmHG or greater) at 3 months.

PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is the mean percent ECC change from preoperative to 3 months postoperative.

[redacted]

1.3 STUDY HYPOTHESES

Safety: The Healon EndoCoat PRO OVD is statistically non-inferior to Healon EndoCoat OVD with regard the cumulative rate of IOP spikes ≥ 30 mmHg at 3 months postoperatively, by a non-inferiority margin of 10%.

Effectiveness: The Healon EndoCoat PRO OVD is statistically non-inferior to Healon EndoCoat OVD as measured by the mean endothelial cell count (ECC) change from preoperative to 3 months postoperatively, by a non-inferiority margin of 5%.

1.4 RANDOMIZATION AND MASKING

A randomization list stratified by investigational sites was created by a JJSV biostatistician who is independent and not involved in the study activities. Subjects are randomly assigned to receive either the Healon EndoCoat PRO or the Healon EndoCoat control in the first operative eye in a 1:1 ratio; subjects then receive the OVD not used in the first-eye surgery in the fellow eye. Randomization will take place after the subject has signed the informed consent document, has met all inclusion and exclusion criteria, and the investigator has documented which eye will be the first to undergo surgery.

The subjects, investigators, and the study technicians performing the postoperative exams are to be masked through study completion. To maintain subject/technician-masking through the 3-month study exams, a masking plan will be tailored for each site to detail how OVD assignment information will be concealed from masked technicians. Recommended steps to maintain masking include ensuring that all items pertaining to OVD assignment and records are kept separately from all other study documents and subject medical records until after completion of the final study visit. For example, OVD logs (indicating the OVD model used in each eye) may be kept in the operating room study notebook until completion of the final study visit, at which time they may be placed in the subject medical charts.

2 GENERAL STATISTICS

2.1 ANALYSIS POPULATIONS

[redacted]

- mITT: modified ITT population will consist of all randomized subjects who have any investigational or control OVD used. Subjects will be analyzed as per planned randomization schema.
- Safety: Safety Population (SP) will consist of all subjects who have any investigational or control OVD used or attempted use (defined as either OVD system coming into contact with the eye) and analyzed per treatment received.

- Per-Protocol: Per-Protocol Population will include subjects with an investigational or control OVD used, evaluated within the proper study interval and without clinically relevant protocol deviations (deviations that could potentially impact the primary or secondary endpoints) in both eyes as determined prior to database lock.

[redacted]

[redacted]

2.2 MISSING DATA HANDLING RULE

The primary analysis will be based on the multiple imputation approach for all primary endpoints. [redacted]

The observed case data (i.e., no imputation for missing values) will be used to supplement the inspection of the impact of missing data on the primary endpoints. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3 VISIT WINDOWS

All subjects will undergo a minimum of 11 visits: Preoperative for both eyes; 1st eye operative; postoperative for 1st eye at 8 hours, 1 day, 1 week; 2nd eye operative; postoperative for 2nd eye at 8 hours, 1 day, and 1 week; postoperative for either each eye individually or both eyes together at 1 month and 3 months (depending on gap between surgery of 1st and 2nd eye). The exact number of days allowed 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.

2.4 DATA CONVENTIONS

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

2.5 TYPE I ERROR RATE

The overall study Type I error rate is 0.025 one-sided. No multiplicity adjustment is necessary for testing non-inferiority of the 2 primary endpoints (1 safety and 1 effectiveness) since both endpoints are required to meet statistical significance. No additional multiplicity adjustment is planned for other effectiveness or safety endpoints.

3 ACCOUNTABILITY/ENROLLMENT

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 counts and proportions will be computed.

3.1 ACCOUNTABILITY

All summaries will be by OVD and total overall. 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.

[5] Holladay, J.T., Visual Acuity Measurements, J. Cataract Refract. Surg. Vol 30, Feb, 2004.

[6] 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

4 DEMOGRAPHICS AND PREOPERATIVE/OPERATIVE PARAMETERS

Subject level parameters such as demographic variables will be reported by subject. Eye level parameters such as monocular preoperative and/or operative variables will be reported by OVD. For comparison between the OVDs, two-sided alpha of 0.05 will be used. As demographic variables analysis is only exploratory in nature and related to baseline and demographic characteristics to show adequate balance between OVD groups induced by randomization, there will be no multiplicity adjustment. 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.

Subject demographic data including age, sex, race, ethnicity, and iris 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, continuous age will be summarized with descriptive statistics. The frequency distributions of sex, race, and iris color will also be tabulated. Baseline demographic data will also be reported by site.

[redacted]

Please see Appendix I for list of preoperative and operative parameters to be analyzed.

5 POSTOPERATIVE ANALYSES – PRIMARY ENDPOINTS

The safety population will be the primary analysis set for the primary safety endpoint; the mITT population will be the primary analysis set for the primary effectiveness endpoint.

[redacted]

5.1 PRIMARY SAFETY ENDPOINT

An IOP spike is defined as an IOP of 30 mmHg or greater. The cumulative rate of IOP spikes (count and proportion of eyes with an IOP spike) at 3 months will be reported by

OVD groups. An eye with an IOP spike is an eye which experienced one or more IOP spikes during the postoperative 3-month follow-up.

Hypothesis Testing

The null and alternative hypotheses for testing the non-inferiority of the test Healon EndoCoat PRO OVD compared to the control Healon EndoCoat OVD with respect to cumulative IOP spike rate at 3 months (p) are as follows:

$$H_0: p_{test-control} \geq \delta$$
$$H_A: p_{test-control} < \delta$$

[redacted]

Success Criteria: the upper bound of the 2-sided 95% confidence interval (CI) for $p_{test-control}$ is less than 10%.

[redacted]

[redacted]

5.2 PRIMARY EFFECTIVENESS ENDPOINT

The percent change in ECC from preoperative to 3 months postoperative will be reported by descriptive statistics by OVD groups. The percent change in ECC from preoperative to postoperative is calculated as followed:

Percent change in ECC = (Postop ECC minus Preop ECC)/Preop ECC *100%

Hypothesis Testing

The null and alternative hypotheses for testing the non-inferiority of the test Healon EndoCoat PRO OVD compared to the control Healon EndoCoat OVD with respect to percent change in ECC at 3 months (μ) are as follows:

$$H_0: \mu_{test-control} \leq \delta$$
$$H_A: \mu_{test-control} > \delta$$

[redacted]

[redacted]

Success Criteria: the lower bound of the 2-sided 95% confidence interval (CI) for $\mu_{test-control}$ is greater than -5%.

[redacted]

[redacted]

[redacted]

5.3 SITE HETEROGENEITY AND OTHER COVARIATES

The analysis of site heterogeneity and of the impact of key covariates on the primary endpoints will be performed using the safety population observed case data for the primary safety endpoint and using the mITT population observed case data for the primary effectiveness endpoint.

When a model approach will be used, any interaction term will be tested at 0.15 significance level.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

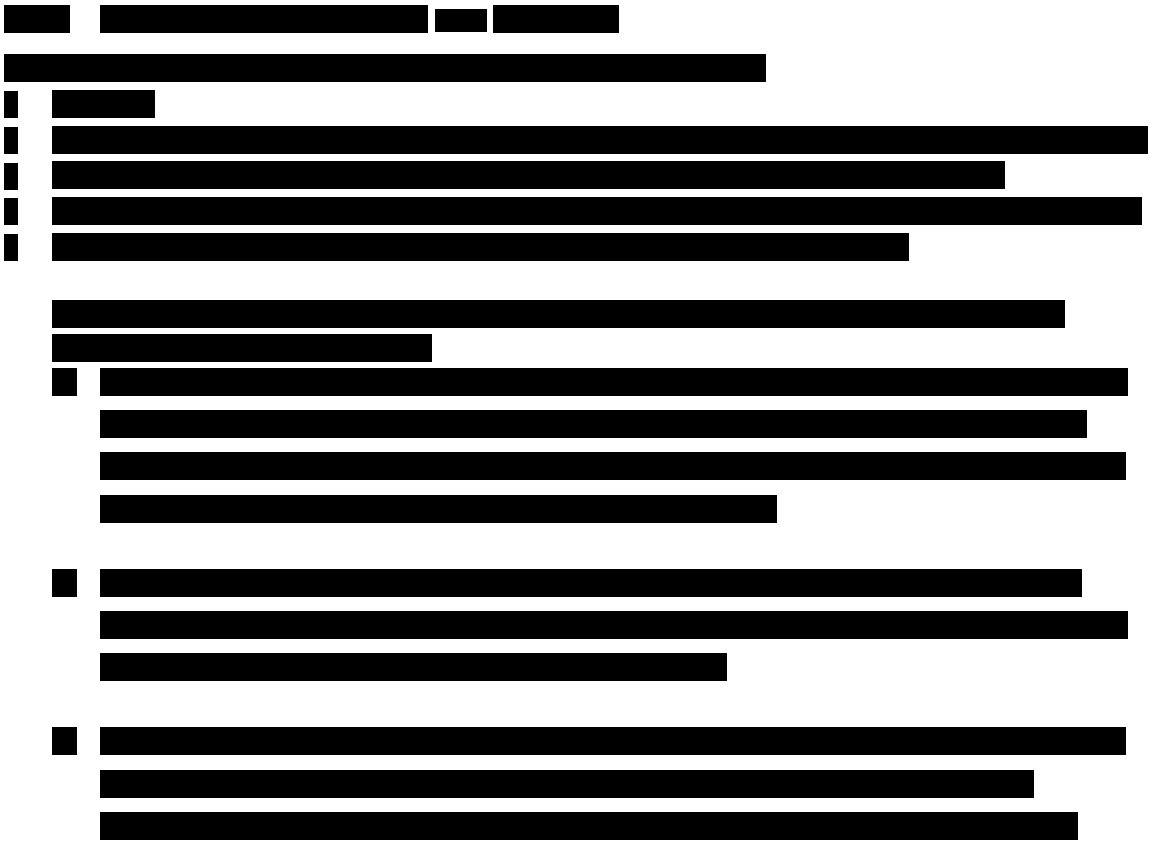
6 POSTOPERATIVE ANALYSES – OTHER ENDPOINTS

The safety population will be used for the analyses of all other endpoints.

6.1 OTHER IOP RELATED ENDPOINTS

The percentage of IOP spikes at 8 hours, 1 day, 1 week, 1 month and 3 months postoperatively will be summarized by OVD and the corresponding 95% CI of the paired-eye difference in proportions will be presented using same method as primary safety endpoint described above. No adjustment in the confidence level for multiple CIs will be made. The count and percentage of IOP spike for the 8-hour visit will also be stratified in 2-hour intervals (6-8 hour and 8-10 hour).

The continuous IOP value and change in IOP from preoperative will be presented by descriptive statistics for the 8-hour (separated by measurements done at 6-8 hours and 8-10 hours), 1-day, 1-week, 1-month and 3-month postoperative time points by OVD. The 8-hour visit will also be stratified in 2-hour intervals (6-8 hour and 8-10 hour).



6.2 OTHER ECC RELATED ENDPOINTS

ECC values at preoperative and 3 months postoperative visits, and within-eye change between preoperative and 3 months postoperative visit will be summarized using descriptive statistics.

[redacted]

Count and percent of eyes at 3-month that show % ECC losses from preoperative levels of ≥0%, ≥10%, ≥20% to 100%, for every 10% interval will be tabulated.

6.3 DISTRIBUTION AND GRADE OF INFLAMMATION

[redacted]

6.4 SERIOUS OR DEVICE-RELATED ADVERSE EVENTS

All SPE types of adverse events reported in the test OVD will be compared to ISO SPE rates using a one-sided 95% Clopper Pearson exact confidence interval. The test AE rate is considered not significantly higher than ISO SPE rate if the lower limit of one-sided 95% confidence interval is less than the SPE rate.

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

Rates of medical findings/adverse events will be tabulated with count and proportion of eyes with these events reported over time by OVD.

Reporting of cumulative complications and cumulative adverse events (occurring at any time postoperative either at standard visits) will include data from all study eyes implanted.

6.6 INVESTIGATOR QUESTIONNAIRE

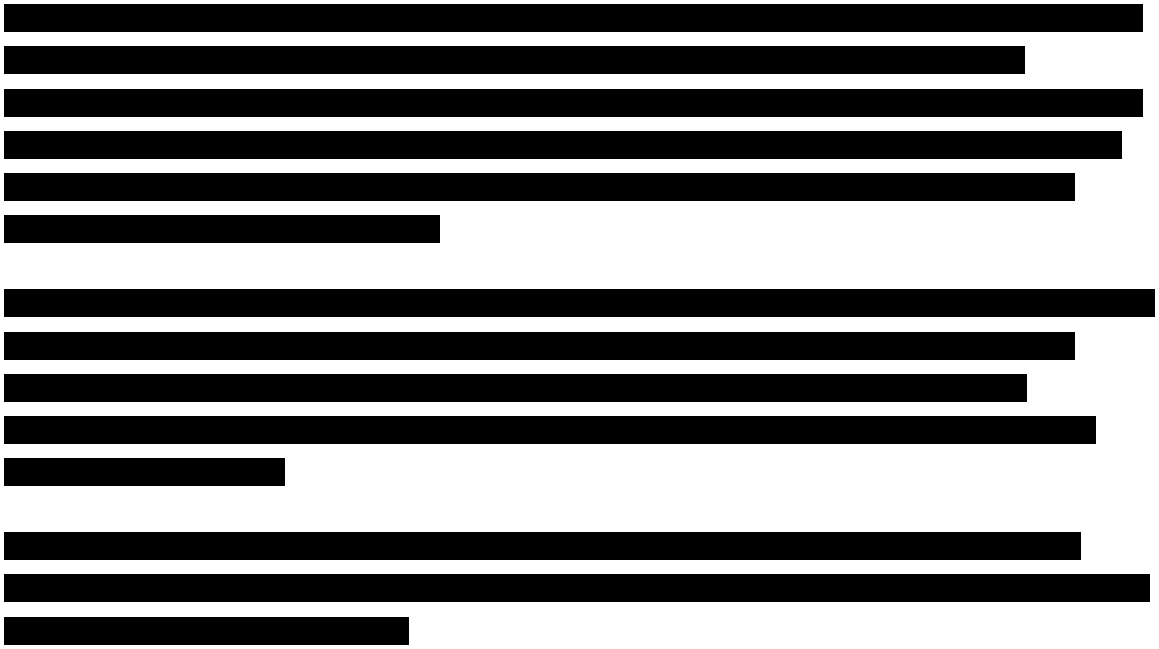
Rates of operative investigator questionnaire will be tabulated with the count and proportion of eyes with these events reported by OVD.

6.7 VISUAL ACUITY ENDPOINTS

The count and proportion of monocular BCDVA will be reported over time by visual acuity line. Percentage of eyes with monocular BCDVA 20/40 or better which received the test OVD will be compared to ISO SPE rate. The test BCDVA rate is considered not significantly lower than ISO SPE rate if the upper limit of one-sided 95% confidence interval is greater than the SPE rate.

The count and proportion of monocular UCDVA at 1 day will be reported by visual acuity line.

7 SAMPLE SIZE CALCULATIONS



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