Next Generation Cataract and Vitreoretinal Surgery Study

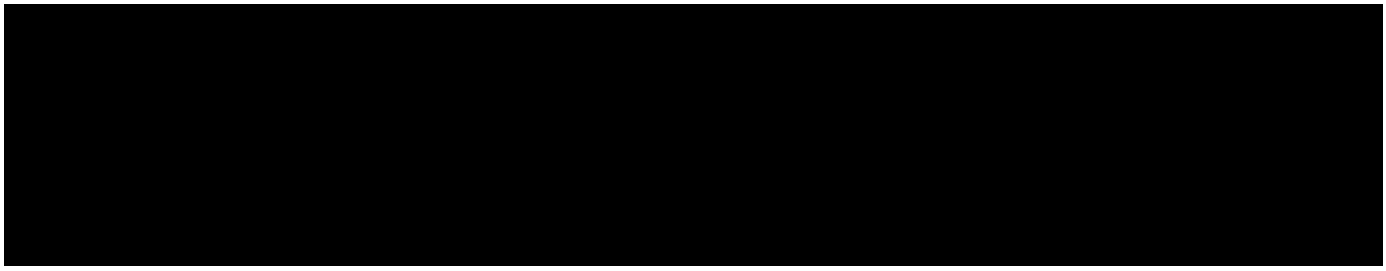
STUDY ID

CTV678-E001

STATISTICAL ANALYSIS PLAN

NCT06165744

Statistical Analysis Plan for CTV678-E001
Title: Next Generation Cataract and Vitreoretinal Surgery Study



Executive Summary:

Key Objectives:

The objective of this study is to obtain device-specific safety and performance clinical data to support marketability in Europe and to collect formal user feedback.

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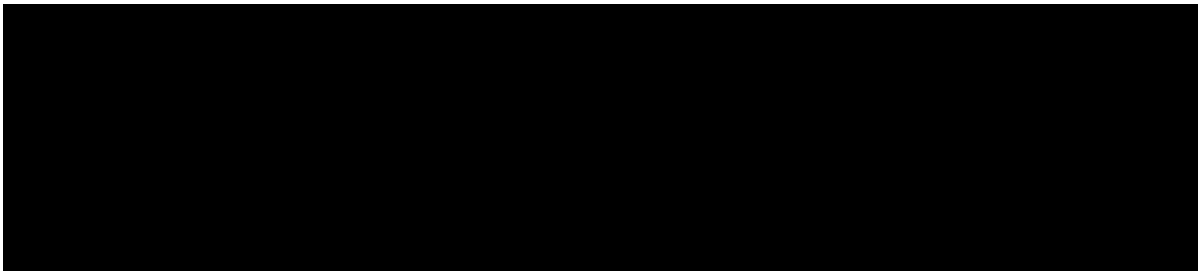

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1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

The objective of this study is to obtain device-specific safety and performance clinical data to support marketability in Europe and to collect formal user feedback.

1.2 Study Description

This is a prospective, single arm, nonrandomized, multicenter study of adults with clinically documented diagnosis of vitreoretinal disease(s) with or without cataract and who meet the inclusion/exclusion criteria.

The investigational device, the UNITY VCS, is intended to facilitate management of fluid and gases, as well as removal, grasping, cutting, illumination, and coagulation of ocular materials. The target patient population for this study are those undergoing vitreoretinal surgery with or without simultaneous cataract surgery.

Planned study visits will include screening/enrollment, surgery using UNITY VCS, follow-up at 1 day, 1 week, 1 month, and 3 months. Unscheduled visit data will be included as appropriate.

The schedule of study procedures and assessments can be found in the appendix.

1.3 Randomization

Not applicable.

1.4 Masking

This is an open-label study.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 ANALYSIS SETS

All eligible subjects will be screened to determine if they meet all inclusion and no exclusion criteria. Subjects who provide informed consent will be considered enrolled in the study.

2.1 Full Analysis Set

The primary analysis set for the effectiveness outcomes will be the full analysis set. The full analysis set includes all eyes with successful completion of surgery.

2.2 Safety Analysis Set

The safety analysis set will include all eyes with attempted use of the UNITY VCS (successful or aborted after contact with the eye) and will be used for the safety outcomes. Attempted use of the UNITY VCS is defined as any time the device makes contact with the eye.

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Subject characteristics and study conduct summaries will include subject disposition, demographics, and reason for surgery. Summaries will be presented for subjects in the safety and full analysis sets indicating the count receiving posterior segment (i.e., vitreoretinal) only or a combined (i.e., vitreoretinal and simultaneous cataract) procedure. Additionally, procedures will be summarized by simple and complex. Listings will be provided for medical history, screen failures by reason, protocol deviations, baseline medications, and for subjects included in the safety analysis set but excluded from the full analysis set. All descriptive summary statistics will be displayed with count and percent for categorical data such as sex, age, race, and ethnicity. Count (n), mean, standard deviation, median, minimum, and maximum will be presented for continuous variables such as age.

Subject characteristics and study conduct summaries will be presented for the full analysis set unless the safety analysis set is different, in which case they will be presented for both.

4 EFFECTIVENESS ANALYSIS STRATEGY

4.1 Effectiveness Endpoints

Primary Endpoint

The primary performance endpoint is the percentage of surgeons reporting ‘yes’ to the binary question of: ***“Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?"***

Secondary Endpoints

- Total time in the eye from first entry into eye/first trocar in, to incision closure/last trocar out
- Achievement of anatomical success at 3 months postop, i.e., percent of 'yes' responses to the question "Was anatomical success achieved for intended treatment (e.g., macular hole closure, retinal attachment, etc. as applicable for the patient's condition)?"
- Change in BCDVA at 3 months postop when compared to preop

4.2 Effectiveness Hypotheses

No hypothesis testing will be performed. Analyses will be descriptive only.

4.3 Statistical Methods for Effectiveness Analyses

Standard descriptive statistics will be presented based on the type. Individual subject data listings will also be provided. No imputation of missing data is planned. The full analysis set will be used for all effectiveness analysis and all analyses will be based on the study eye unless otherwise stated.

4.3.1 Analysis of the Primary Endpoint

After each surgery, the surgeon completes a user questionnaire. For subjects in the full analysis set, the rate of 'yes' responses to the question ***"Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?"*** will be presented with a count and percentage and will be accompanied by a two-sided exact binomial 95% confidence interval.

4.3.2 Analysis of the Secondary Endpoints

4.3.2.1 Total Time in Eye

Total time in the eye from first entry into eye/first trocar in, to incision closure/last trocar out will be evaluated. At the surgical visit, the total time in the eye will be recorded as the time from first entry into eye/first trocar in, to incision closure/last trocar out. The total time in eye will be summarized with the number of observations, mean, standard deviation, median, minimum, and maximum times in minute. A 95% confidence interval for the mean based on the t-distribution will be presented. Additionally, a 95% non-parametric confidence interval for the median will be constructed. A listing will accompany this summary.

4.3.2.2 Achievement of Anatomical Success

Achievement of anatomical success at 3 months postop, i.e., percent of 'yes' responses to the question "Was anatomical success achieved for intended treatment (e.g., macular hole closure, retinal attachment, etc. as applicable for the patient's condition)?" will be summarized. At the end of follow-up for each patient, surgeons will evaluate the success of the surgery. For subjects in the full analysis set, the rate of 'yes' responses will be presented with a count and percentage and will be accompanied by a two-sided exact binomial 95% confidence interval.

4.3.2.3 Change in BCDVA

Change in BCDVA at 3 months postop when compared to preop will be calculated. BCDVA will be recorded in Snellen and collected at screening, 1 month, and 3 months. Results will be converted to decimal VA. Observed decimal BCDVA values at each study visit and change from 3 months postoperative visit to screening value for the study eye will be presented descriptively (count, mean, median, standard deviation, minimum, maximum, and a 95% confidence interval for the mean based on the t-distribution). A categorical summary of Snellen values (not converted to decimal VA) will be produced and will include counts and percentages for each category at screening, 1 month, and 3 months. A listing will be provided which presents visual acuity results at each visit, including data from 1 day and 1 week visits, where uncorrected data may be recorded per standard of care.

[redacted]

4.5 Interim Analysis for Effectiveness

Not applicable.

5 SAFETY ANALYSIS STRATEGY

5.1 Safety Endpoints

The safety endpoints are:

- Ocular and nonocular AEs and SAEs
- Device deficiencies
- Secondary surgical interventions
- Unplanned intraoperative procedures

5.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of safety endpoints listed in Section 5.1.

5.3 Statistical Methods for Safety Analyses

All adverse events occurring from the time a subject sign informed consent to study exit will be accounted for in the reporting. Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. Descriptive summaries (counts and percentages) and listings will be presented. Individual subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to IP.

5.3.1 Ocular and Nonocular AEs and SAEs

All adverse events reported to Alcon will be accounted for in the reporting. Descriptive summaries (counts and percentages) and listings will be presented. The type of event (serious, device related, etc.) will be summarized overall and by ocular/non-ocular status. Events will also be summarized by MedDRA preferred term, with the number and percent of subjects and a 95% exact binomial confidence interval, as well as a count of the number of events. The applicable definition of an adverse event is in the study protocol. A listing of all adverse events will be constructed to provide further details.

5.3.2 Device Deficiencies

The applicable definition of a device deficiency is in the study protocol. A frequency table showing counts for each device deficiency category will be presented. In addition, a listing of all device deficiencies will be provided.

5.3.3 Secondary Surgical Interventions

Descriptive statistics (counts, percentages, and two-sided 95% exact binomial confidence intervals) of eyes with secondary surgical interventions (SSIs) will be presented. In addition, a listing of subjects with SSIs will be produced.

5.3.4 Unplanned Intraoperative Procedures

Unplanned intraoperative procedures that occur during surgery will be recorded. Descriptive statistics including the count, percentage, and a two-sided 95% exact binomial confidence interval for the percentage will be produced and will be accompanied by a listing.

5.3.5 Additional Safety Analysis

5.3.5.1 Biomicroscopy Findings/Slit Lamp Examination

A slit-lamp examination will be performed at the screening, 1 day, 1 week, 1 month, and 3 month visits to evaluate the anterior segment of the eye, including eyelids/conjunctiva, cornea, lens, and iris/anterior chamber. A summary of grading at each visit for corneal edema, aqueous cells, and aqueous flare will be presented. Cataract grading and cataract type will be presented for the screening visit. A listing with this information, plus details on any abnormal slit lamp findings, will be provided. Additionally, a listing of postoperative IOL observations will be created.

5.3.5.2 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole mmHg. IOP measurements will be conducted at the screening, 1 day, 1 week, 1 month, and 3 month visits.

Descriptive summaries (count, mean, median, standard deviation, minimum and maximum) of observed values will be presented at each study visit and for the change at 1 day, 1 month and 3 months from baseline. A listing will supplement the summary table.

5.3.5.3 Dilated Fundus Examination

The dilated fundus examination will be conducted at the screening, 1 week, 1 month and 3 month visits. The dilated fundus examination may also be conducted at the 1 day visit as needed. The examination will be performed to evaluate the health of the vitreous, retina including peripheral retina, macula, choroid, and optic nerve. A listing of fundus findings will delineate the results.

[redacted]

7 SAMPLE SIZE AND POWER CALCULATIONS

Based on a sample of 100 surgeries, the expected half-width of the 95% confidence interval for the percentage of surgeons reporting 'yes' to the question ***"Did UNITY VCS using vitreoretinal or combined surgical functionality perform per the intended use as defined in protocol Section 5.1?"*** will be $1.96 \cdot \sqrt{(p(1-p)/100)}$. This half-width is widest at p = 50%. Under this conservative assumption, the expected half-width is < 10% given the sample size of 100.

Allow enrollment for an additional 10% for screen failure and 10% for loss to follow-up to ensure 100 completed subjects.

8 REFERENCES

Base SAS(R) 9.4 Procedures Guide: Statistical Procedures, Second Edition, December 2013

Documentation for calculating non-parametric confidence intervals for quantiles: https://support.sas.com/documentation/cdl/en/procstat/66703/HTML/default/viewer.htm#procstat_univariate_examples10.htm

9 REVISION HISTORY

This is the original (Version 1.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

10 APPENDIX

Table 10-1 Schedule of Study Procedures and Assessments

	Nominal Time ± Window Limits							
	Visit 0 (Screening)	**Visit 00 (Operative)**	**Visit 1 (1 Day)**	**Visit 2 (1 week)**	**Visit 3 (1 month)**	**Visit 4/Exit (3 month)**	**Early Exit[3]**	**Unscheduled Visit[3]**
Procedure/ Assessment	**Day -30 to 0**	**Day 0**	**Day 1 + 2 Days**	**Day 7 ± 3 Days**	**Day 30 ± 14 Days**	**Day 90 ±14 Days**	**N/A**	**N/A**
Eye	Both eyes	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye
Informed Consent	X							
Demographics	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X							
Urine Pregnancy Test[2]	X							
Dilated Pupil Size	X							
Keratometry*	X							
Biometry (ACD, AL)*	X							
Slit lamp exam	X		X	X	X	X	X	
Monocular BCDVA Using Snellen chart[c]	X		X[a]	X[a]	X	X	X	
IOP	X		X	X	X	X	X	

	Nominal Time ± Window Limits							
	Visit 0 (Screening)	**Visit 00 (Operative)**	**Visit 1 (1 Day)**	**Visit 2 (1 week)**	**Visit 3 (1 month)**	**Visit 4/Exit (3 month)**	**Early Exit[3]**	**Unscheduled Visit[3]**
Procedure/ Assessment	**Day -30 to 0**	**Day 0**	**Day 1 + 2 Days**	**Day 7 ± 3 Days**	**Day 30 ± 14 Days**	**Day 90 ±14 Days**	**N/A**	**N/A**
Eye	Both eyes	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye
Dilated Fundus Exam	X		X[b]	X	X	X	X	
Total time in eye		X						
[redacted]								
User Questionnaire		X						
Adverse Events	X	X	X	X	X	X	X	X
Device Deficiencies		X						

[redacted]

[2] Women of child-bearing potential only

[3] Unscheduled/Early Exit Visit – additional study assessments may be performed per investigator's discretion

[redacted]

[a] Visual acuity (VA) to be conducted per site's standard of care using Snellen chart

[b] Optional, to be performed per site's standard of care as needed

[c] BCDVA is done using manifest refraction

*As applicable

Table 10-2 Conversion of Snellen in Feet to Snellen in Meters

	Distance
Snellen Feet 20/	**Equivalent Meter 6/**
10	**3.0**
12.5	**3.8**
16	**4.8**
20	**6.0**
25	**7.5**
30	9.0
32	**9.6**
40	**12.0**
50	**15.0**
60	18.0
63	**18.9**
70	21.0
80	**24.0**
100	**30.0**
114	34.2
125	**37.5**
150	45.0
160	**48.0**
200	**60.0**