An Observational Multicenter Clinical Study to Provide Additional Long-Term Follow-up Beyond 60 Months for Subjects Implanted with a CyPass Micro-Stent in the COMPASS Trial

STUDY ID

GLD122-P004

STATISTICAL ANALYSIS PLAN

NCT04629521

Short Title:

Statistical Analysis Plan
GLD122-P004

Full Title:

Statistical Analysis Plan
GLD122-P004

Protocol Title: An Observational Multicenter Clinical Study to Provide Additional Long-Term Follow-up Beyond 60 Months for Subjects Implanted with a CyPass Micro-Stent in the COMPASS Trial

[redacted] [redacted]

Protocol TDOC Number: TDOC-0056258

[redacted] [redacted]

[redacted]

Template Version: Version 4.0, approved 16MAR2015

Approvals: See last page for electronic approvals.

Job Notes:

This is the second (Version 3.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 3.0 of the study protocol.

Executive Summary:

Key Objectives:

The primary objective is to assess long-term (10 years post-CyPass implantation) status of the corneal endothelium in subjects who were implanted with the CyPass Micro-Stent in the COMPASS trial.

Table of Contents

List of Tables

1 Study Objectives and Design

1.1 Study Objectives

The objective of the study is to assess long-term (10 years post-CyPass implantation) status of the corneal endothelium in subjects who were implanted with the CyPass Micro-Stent in the COMPASS trial.

1.2 Study Description

This is a prospective, non-interventional, observational, non-randomized, multicenter, single arm clinical study. Up to 374 subjects who were implanted with a CyPass Micro-Stent in the COMPASS trial will be enrolled. Subjects will be considered enrolled in the study after informed consent is obtained during the first study visit.

Subject participation in this study is variable depending on the number of follow-up visits expected. Annual follow-up visits will be scheduled for each subject based on the date of CyPass implantation and an exit visit will occur when the subject has reached 10 years post-CyPass implantation. For some subjects, the first visit will be at or after 10 years post-CyPass implantation, and therefore the first visit may coincide with the 120 Month/Exit visit. [redacted] The study is expected to be completed in approximately 4 years. Because collection of ECD is not part of standard of care, retrospective data collection will not be attempted for visits that occurred prior to subject enrollment. The one exception will be ocular adverse events data, which will be collected for all visits, wherever available.

1.3 Randomization

This study is not randomized, but the original COMPASS trial was randomized, and all subjects who are eligible for this trial were randomized to receive the CyPass device in the COMPASS trial.

1.4 Masking

Not Applicable

1.5 Interim Analysis

Interim reports pertaining to the progress of the post-approval study will be submitted to the FDA for review every 6 months for the first 2 years and annually thereafter, starting from the date of FDA approval of the protocol, until study completion.

2 Analysis Sets

2.1 Enrolled

The analysis set for both the safety and effectiveness analyses will be the set of all enrolled subjects. Only subjects enrolled in this study will be summarized.

3 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, demographics table (including age, gender, and race). Counts and percentages will be presented for categorical variables such as sex, age, race, and study eye. Baseline ECD will be summarized overall with the mean, standard deviation, median, minimum, and maximum.

4 Safety Analysis Strategy

4.1 Safety Endpoints

The primary objective of the study is to assess long-term (10 year post CyPass implantation) status of the corneal endothelium in subjects who were implanted with the CyPass Micro-Stent in the COMPASS trial.

The safety endpoints are:

- Rate of occurrence of sight-threatening adverse events (AEs)
- Rate of occurrence of ocular AEs
- Central and peripheral (nasal) ECD measurements
- Analyses of rate of loss and rate of low ECD (ie, ≤1000 cells/mm2)
- Assessment of stabilization of ECL
- Corneal sequelae associated with ECL
- Association between peripheral and central ECD count and number of observed rings
- Secondary surgical interventions (SSIs) to modify the device position (eg, repositioning, trimming, explanation)
- Effects of SSIs on central and peripheral ECD

- CyPass Micro-Stent movement and/or malposition
- Corneal AEs (eg, corneal decompensation, tube corneal touch, corneal edema, etc.) caused by CyPass Micro-Stent
- Losses in Best Corrected Visual Acuity (BCVA) ≥10 letters
- Change in visual field mean deviation (MD)
- Change in central corneal thickness

4.2 Safety Hypotheses

There are no safety hypotheses planned in this study. The focus of the safety analysis will be to assess the long-term status of the corneal endothelium and a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters.

4.3 Statistical Methods for Safety Analyses

4.3.1 Rate of Occurrence of Sight-Threatening Adverse Events (AEs)

4.3.1.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.1.2 Analysis Methods

Descriptive statistics for sight-threatening adverse events will be presented for study eyes. The rates of all sight-threatening adverse events will be provided with counts and percentages, and these rates will be accompanied by two-sided exact 95% confidence intervals. An eye with multiple ocular adverse events of the same preferred term is only counted once toward the total of this preferred term. The list of adverse events which are considered to be sight-threatening can be found in Section 11.1.2 of the study protocol.

4.3.2 Rate of Occurrence of Ocular AEs

4.3.2.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.2.2 Analysis Methods

Descriptive statistics for ocular adverse events (including SSIs) will be presented for study eyes. The rates of all adverse events will be provided with counts and percentages, and these rates will be accompanied by two-sided exact 95% confidence intervals. An eye with multiple ocular adverse events of the same preferred term is only counted once toward the total of this preferred term.

4.3.3 Central and Peripheral (Nasal) ECD Measurements

4.3.3.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.3.2 Analysis Methods

Central and peripheral (nasal) endothelial cell density will be summarized at each visit. The number of eyes, mean, standard deviation, and the following percentiles will be reported: 0^{th}, 5^{th}, 25^{th}, 75^{th}, 95^{th}, and 100^{th}. A 95% confidence interval based on the t-distribution will be reported for the means at each visit.

The central endothelial cell coefficient of variation and hexagonality will be summarized by visit, in separate tables. The number of eyes, mean, standard deviation, and the following percentiles will be reported: 0^{th}, 5^{th}, 25^{th}, 75^{th}, 95^{th}, and 100^{th}.

4.3.4 Analyses of Rate of Loss and Rate of Low ECD (ie, ≤ 1000 cells/mm^2)

4.3.4.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.4.2 Analysis Methods

Change in central endothelial cell density (within-eye) from baseline and percent change in central endothelial cell density will be summarized by visit. Baseline central endothelial cell density is the data collected at the COMPASS Study baseline visit. All references to baseline endothelial cell density data throughout this protocol refer to data from this visit. The proportion of subjects with central endothelial cell density less than 1000 cells/mm^2, the proportion of subjects with peripheral cell density less than 1000 cells/mm^2, the proportion of subjects with central endothelial cell density less than 500 cells/mm^2, the proportion of subjects with peripheral cell density less than 500 cells/mm^2, and the proportion of subjects

with central endothelial cell loss over 30% from baseline will also be reported at these time points. A 95% exact binomial confidence interval will be presented for the proportions. The following statistics will be presented for change in central endothelial cell density and percent change in central endothelial cell density at each visit: number of eyes, means, standard deviations, and the following percentiles: 0^{th}, 5^{th}, 25^{th}, 75^{th}, 95^{th}, and 100^{th}. A 95% confidence interval based on the t-distribution will be reported for the means at each visit. This analysis will be performed using central endothelial cell density data from visits in the COMPASS, COMPASS XT, and COMPASS XXT studies, where available, and using peripheral cell density data collected in this study. Summary statistics for peripheral (nasal) endothelial cell density will be presented for each study visit.

4.3.5 Assessment of Stabilization of ECL

4.3.5.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.5.2 Analysis Methods

The annualized rate of change and percent rate of change in central endothelial cell density will be summarized at each year of observation. A 95% confidence interval based on the t-distribution will be produced along with the mean, standard deviation, minimum, median and maximum. This analysis will be performed using central endothelial cell density data from visits in the COMPASS, COMPASS XT, and COMPASS XXT studies, where available.

4.3.6 Corneal Sequelae Associated with ECL

4.3.6.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.6.2 Analysis Methods

A listing of corneal sequelae associated with ECL will be provided.

4.3.7 Association between Peripheral and Central ECD Count and Number of Observed Rings

4.3.7.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.7.2 Analysis Methods

Summary statistics for peripheral ECD count will be provided, stratified by visit and by number of rings observed at the visit, for all COMPASS XXT study visits. Summary statistics for central ECD count will be provided, stratified by the number of rings observed at the visit, for all visits with available data from the COMPASS, COMPASS XT, and COMPASS XXT studies.

4.3.8 Secondary Surgical Interventions (SSIs) to Modify the Device Position (eg, Repositioning, Trimming, Explanation)

4.3.8.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.8.2 Analysis Methods

A listing of SSIs to modify the device position will be provided.

4.3.9 Effects of SSIs on Central and Peripheral ECD

4.3.9.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.9.2 Analysis Methods

A listing of central and peripheral ECD measurements will be produced for subjects with SSIs. The date of the SSI will be noted in this listing for each subject.

4.3.10 CyPass Micro-Stent Movement and/or Malposition

4.3.10.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.10.2 Analysis Methods

The rate of all CyPass Micro-Stent movement and/or malposition will be presented with a count and percentage, and will be accompanied by a two-sided exact binomial 95% confidence interval.

4.3.11 Corneal AEs (eg, Corneal Decompensation, Tube Corneal Touch, Corneal Edema, etc.) Caused by CyPass® Micro-Stent

4.3.11.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.11.2 Analysis Methods

A listing of corneal AEs caused by the CyPass Micro-Stent will be provided, which will include central and peripheral ECD measurements, where available.

4.3.12 Losses in Best Corrected Visual Acuity (BCVA) ≥ 10 letters

4.3.12.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.12.2 Analysis Methods

A listing of BCVA loss of 10 letters or more will be provided, and will include all available BCVA data from the COMPASS, COMPASS XT, and COMPASS XXT studies for the subject. BCVA loss of 2 lines (10 letters) or more will be reported as an adverse event, so adverse event data will be the data source for this analysis.

4.3.13 Change in Visual Field Mean Deviation (MD)

4.3.13.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.13.2 Analysis Methods

Change in visual field mean deviation at each visit postoperative as compared to the recorded value at the COMPASS screening visit will be reported. Observed values and change from screening values will be presented descriptively (N, mean, median, standard deviation, standard error, minimum, and maximum) at each study visit for each device.

Counts and percentages of subjects will be presented according to the following categories: increase > 2.0 dB; no change (-2.0 to 2.0 dB); decrease > 2.0 dB. Denominators will consist of the number of subjects with non-missing visual field data at both time points.

4.3.14 Change in Central Corneal Thickness

4.3.14.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

4.3.14.2 Analysis Methods

Change in central corneal thickness from baseline at each follow-up visits will be summarized. A mean, standard deviation, minimum, median, maximum, and a 95% confidence interval based on the t-distribution will be provided for the change and percentage change from baseline at each visit.

4.3.15 Adverse Events

All adverse events reported to Alcon will be accounted for in the reporting. Since some of the data collection for this study will be retrospective, some of the adverse events will have occurred prior to the date of informed consent. Descriptive summaries (counts and percentages) and listings will be presented.

The applicable definition of an Adverse Event (AE) is in the study protocol.

4.3.16 Other Safety Outcomes

4.3.16.1 Best Corrected Visual Acuity (BCVA)

BCDVA (collected in letters read) will be summarized at each post-operative visit at which BCDVA is collected; change from baseline (COMPASS Baseline visit) will also be summarized at each postoperative visit at which BCDVA is collected. Data will be summarized based on the visual acuity score (letters read).

Best corrected visual acuity will also be converted to Snellen values and summarized categorically by the following groupings for each scheduled visit: 20/20 or better; 20/25 or better; 20/32 or better; 20/40 or better; worse than 20/40; missing; discontinued. Details for this conversion can be found in Appendix B.

[redacted]

4.3.16.3 Corneal Pachymetry

Central corneal thickness will be summarized at each follow-up visit with n, mean, standard deviation, minimum, median, and maximum. A 95% confidence interval based on the t-distribution will be provided for the change and percentage change from baseline. This will be measured three times for each subject for each visit, and the median value will be used to calculate summary statistics.

4.3.16.4 Gonioscopy

Gonioscopy at baseline (COMPASS Baseline visit) and at each COMPASS XXT follow-up visit at which the exams are conducted will be summarized with counts and percentages of number of rings visible. A listing will accompany this summary.

4.3.16.5 Slit Lamp Findings

Slit lamp results at baseline (COMPASS Baseline visit) and at each COMPASS XXT follow-up visit at which the exams are conducted will be summarized by the number of abnormal findings in each category (numerator), the number of observations with data (denominator). A listing will be provided which presents all subjects with any abnormal slit lamp findings.

4.3.16.6 Visual Field Loss Mean Deviation Testing

The visual field mean deviation (dB) testing data will be summarized for each visit. A categorical summary of changes from screening will be presented using the following three categories: Increase (≥ 2.5 dB), No Change (-2.5 < dB to < 2.5 dB), or Decrease (≤ -2.5 dB).

4.3.16.7 Dilated Fundus Examination

The fundus examination includes ophthalmoscopic assessments of the vitreous, retina, macula, choroid, and optic nerve of both eyes. A frequency table of dilated fundus findings by visit will be presented.

4.3.16.8 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 all device deficiencies, as recorded on the Device Deficiency Form will be provided.

4.4 Interim Analysis for Safety

Interim reports pertaining to the progress of the post-approval study will be submitted to the FDA for review every 6 months for the first 2 years and annually thereafter, starting from the date of FDA approval of the protocol, until study completion.

4.5 Multiplicity Strategy

No statistical testing will be performed so no multiplicity adjustments are necessary.

4.7 Comparison of COMPASS XXT Subjects to Original COMPASS Subjects Implanted with CyPass

Analysis will be conducted to compare subjects followed in this COMPASS XXT study to the full CyPass cohort implanted in the COMPASS trial.

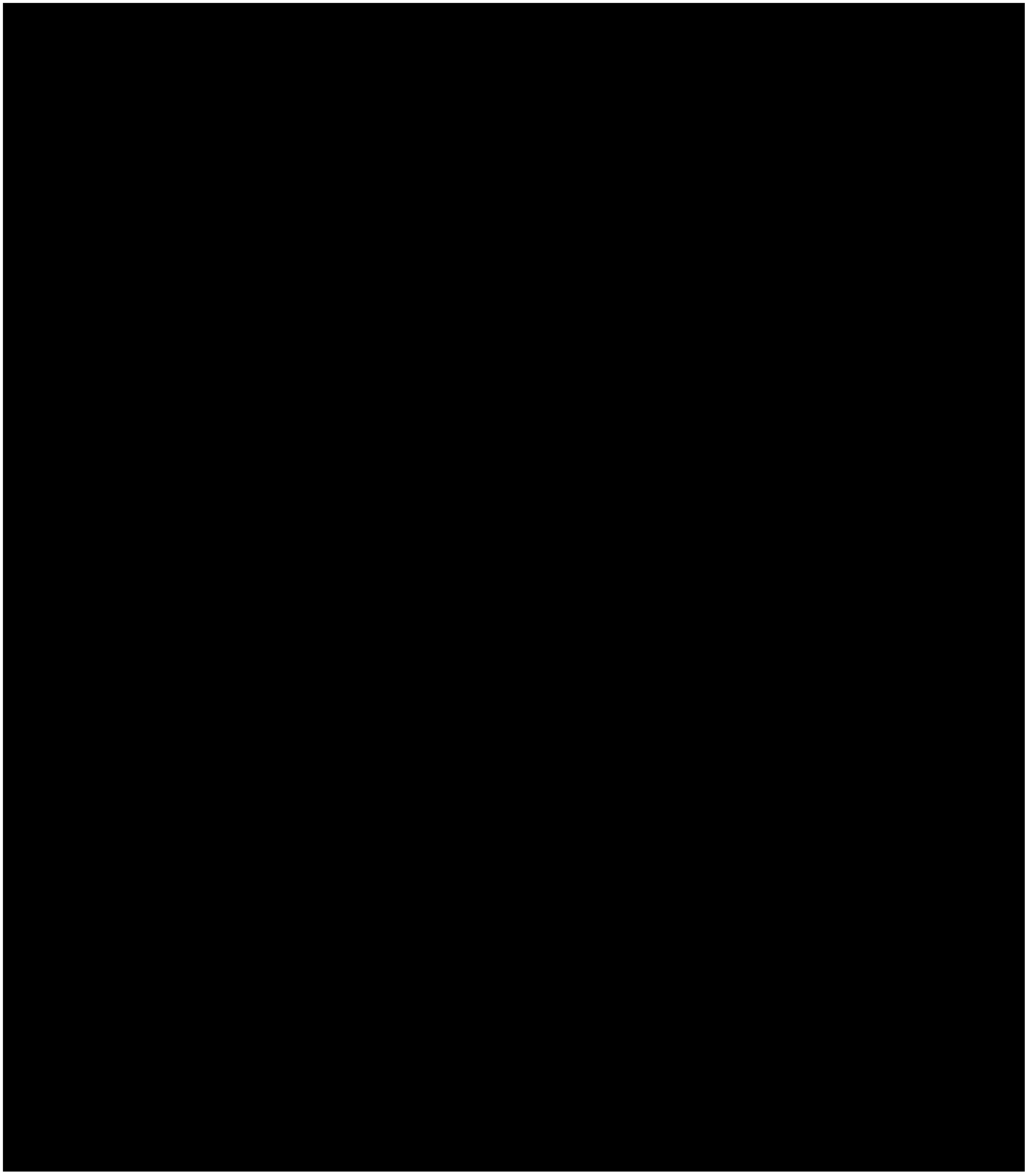
ECD at baseline will be summarized for the two cohorts (COMPASS XXT vs. COMPASS). These summaries will include number of eyes, mean, standard deviation, and the following percentiles: 0th, 5th, 25th, 75th, 95th, and 100th.

The number and percent of eyes having ECD<1000 will be reported for each cohort at 6 months and 24 months.

The within-eye ECD loss from baseline and % ECD loss from baseline at 6 months and 24 months will be summarized for the two cohorts These summaries will include the number of eyes, mean, standard deviation, and the following percentiles: 0th, 5th, 25th, 75th, 95th, and 100th.

The within-eye ECD loss from 6 months to 24 months, and the % ECD loss from 6 months to 24 months will be summarized for the two cohorts. These summaries will include the number of eyes, mean, standard deviation, and the following percentiles: 0th, 5th, 25th, 75th, 95th, and 100th.

The number and percentage (specifying the denominator) of eyes with each level of observed rings at the 24 months visit will be reported for each cohort.



[redacted]

6 Handling of Missing Data

Missing data imputation will not be performed.

7 Sample Size and Power Calculations

Sample size (374) is based on the number of subjects who were implanted with a CyPass Micro-Stent in the COMPASS trial. It is not based on statistical power. 374 subjects were implanted with CyPass in the COMPASS trial. Of these, 215 volunteered to enroll in COMPASS XT. The total enrolled in this trial will be a subset of the 374 COMPASS CyPass subjects, is not restricted to those enrolled in COMPASS XT, and may be above or below the total enrolled in the COMPASS XT trial.

[redacted]

9 Appendix A: Schedule of Study Procedures and Assessments

Table 9–1 Schedule of Study Procedures and Assessments

Procedure	84-Month Visit (2555±120 days)Error! Reference source not found.	96-Month Visit (2920±120 days)Error! Reference source not found.	108-Month Visit (3285±120 days)Error! Reference source not found.	120-Month Visit/Exit Visit (3650±120* days)Error! Reference source not found.
Informed Consent**Error! Reference source not found.**	X	X	X	X
Demographics**Error! Reference source not found.**	X	X	X	X
Inclusion/Exclusion**Error! Reference source not found.**	X	X	X	X
Ocular Medical History	X	X	X	X
Ocular Surgical History	X	X	X	X
[redacted]				
Monocular BCVA (ETDRS)	X	X	X	X
[redacted]				
Pachymetry CCT	X	X	X	X
Gonioscopy and Gonio photography[3]	X	X	X	X
UBM/OCT[4]	X	X	X	X
Slit-Lamp Exam	X	X	X	X
Visual Field	X	X	X	X
Fundus Exam with C:D Ratio	X	X	X	X
Specular Microscopy (central and peripheral ECD)	X	X	X	X
Ocular AE Assessment[5]	X	X	X	X
Device Deficiencies	X	X	X	X

1. Annual visits are required until 10 years post-CyPass implantation is reached. Not all visits are required for every subject. The number of study visits required to be completed will coincide with the number of months following CyPass implantation. Note: All subjects from COMPASS have surpassed the 72-month follow-up period.
   *For subjects who have reached the 10 years post-CyPass implantation at the time of study initiation, the +120-day visit window does not apply.

2. Informed consent, demographics, and inclusion/exclusion criteria assessments are only required at the first study visit.
3. Gonio photography to be assessed objectively for evaluating device position.
4. Optional – if available at the site.
5. Any ocular AEs occurring since the Exit visit from COMPASS or COMPASS XT (whichever was last study visit) will be captured. These include but are not limited to corneal haze/edema, device malposition, device explantation, device trimming, and/or device repositioning.

6.

10 Appendix B: Conversion of Visual Acuity Score to Snellen Values

LogMar	VAS	Snellen
2.00	0	20/2000
1.98	1	
1.96	2	
1.94	3	
1.92	4	
1.90	5	20/1600
1.80	10	20/1250
1.70	15	20/1000
1.60	20	20/800
1.50	25	20/630
1.40	30	20/500
1.30	35	20/400
1.20	40	20/320
1.10	45	20/250
1.00	50	20/200
0.98	51	
0.96	52	
0.94	53	
0.92	54	
0.90	55	20/160
0.88	56	
0.86	57	
0.84	58	
0.82	59	
0.80	60	20/125
0.78	61	
0.76	62	
0.74	63	
0.72	64	
0.70	65	20/100
0.68	66	
0.66	67	
0.64	68	
0.62	69	

LogMar	VAS	Snellen
0.60	70	20/80
0.58	71	
0.56	72	
0.54	73	
0.52	74	
0.50	75	20/63
0.48	76	
0.46	77	
0.44	78	
0.42	79	
0.40	80	20/50
0.38	81	
0.36	82	
0.34	83	
0.32	84	
0.30	85	20/40
0.28	86	
0.26	87	
0.24	88	
0.22	89	
0.20	90	20/32
0.18	91	
0.16	92	
0.14	93	
0.12	94	
0.10	95	20/25
0.08	96	
0.06	97	
0.04	98	
0.02	99	
0.00	100	20/20
-0.02	101	
-0.04	102	
-0.06	103	
-0.08	104	
-0.10	105	20/16
-0.12	106	
-0.14	107	
-0.16	108	
-0.18	109	
-0.20	110	20/12.5
-0.22	111	
-0.24	112	
-0.26	113	

LogMar	VAS	Snellen
-0.28	114	
-0.30	115	20/10

[redacted]
