Statistical Analysis Plan

PROTOCOL TMI-13-01 (ALCON PROTOCOL GLD122c-C001)
NCT03273907

Protocol Title:	Post Approval Study of the CyPass System in Patients with Primary Open Angle Glaucoma Undergoing Cataract Surgery
[redacted]	[redacted]
Protocol TDOC Number:	TDOC-0052735
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
Approvals:	See last page for electronic approvals.

Job Notes:

This is the original (Version 1.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 4.0 of the study protocol.

Executive Summary:

Key Objectives:

The primary objective of this study is to demonstrate that the rate of clinically relevant complications associated with CyPass Micro-Stent placement and stability using the CyPass 241-S applier, as determined at 36 months in the post-market setting, is less than the pre-specified performance target, which is based on experience with the CyPass Model E applier in the COMPASS (TMI-09-01) Trial.

Decision Criteria for Study Success:

This study is considered a success if the observed rate of clinically relevant complications associated with CyPass Micro-Stent placement and stability, as determined at 36 months, is less than the pre-specified performance target.

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List of Tables

Table 1-1 List of Abbreviations

ADE	Adverse device effect
AE	Adverse event
BCDVA	Best corrected distance visual acuity
CER	Clinical evaluation report
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
ICF	Informed consent form
IOP	Intraocular pressure (mmHg)
ITT	Intention to treat
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA®	Medical Dictionary for Regulatory Activities
MRSE	Manifest refraction spherical equivalent
OAG	Open angle glaucoma
OD	Right eye
OS	Left eye
OU	Both eyes
PAS	Post approval study
POAG	Primary open angle glaucoma
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SSI	Secondary surgical intervention
TEAE	Treatment emergent adverse event
WHO	World Health Organization

1 Study Objectives and Design

This statistical analysis plan (SAP) describes the statistical analysis outlined in Section 15 of the study protocol (Version 4.0) along with any additional analyses planned before database lock (DBL).

1.1 Study Objectives

To demonstrate that the rate of clinically relevant complications associated with CyPass Micro-Stent placement and stability using the CyPass System (Model 241-S) as determined at 36 months in the post-market setting is less than the pre-specified performance target, which is based on experience with the CyPass Model E applier in the COMPASS (TMI-09-01) trial.

1.2 Study Description

This study is a prospective, non-randomized, multicenter, single arm, post approval study of the CyPass System. Following routine cataract surgery, one CyPass Micro-Stent will be implanted into one study eye of each qualified subject. If both eyes qualify for the study, the eye with the worse BCDVA will be the study eye. If BCDVA in both eyes is the same, then the study investigator will choose which eye will be the study eye. Unless specified otherwise, ocular results refer to the study eye only. Therefore, throughout this SAP and corresponding tables and data listings the number of subjects and eyes are synonymous.

Subject participation in this study is expected to last up to 37.5 months and include 10 study visits. Within 42 days of screening, qualified subjects will receive cataract surgery followed by implantation of the CyPass Micro-Stent in one eye (the study eye) at the surgery visit. Eight postoperative follow-up visits are planned to occur at 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, 24 months, and 36 months after surgery. Further details are provided in Appendix A: Schedule of Visits and Appendix B: Study Design. Upon completion of the 36-month follow-up visit, subjects will be exited from the study.

This post-approval study is designed to provide continued reasonable assurance of the safety and effectiveness of the device.

1.3 Masking

This is a post-approval, open-label study. Treatment is known to the investigators, subjects, and Alcon personnel involved with the planning and execution of the study.

1.4 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 two years, starting from the date of approval, and will continue to be submitted annually thereafter, until study completion.

For each interim report, the number of subjects enrolled and implanted with the CyPass device will be reported. In addition, the number of clinically relevant complications associated with CyPass Micro-Stent placement and stability (events toward the primary safety endpoint) will be reported, and a listing and summary table with the number of adverse events, and number and proportion of subjects experiencing all such events will be provided. A listing of all ocular SAEs will also be provided. A summary of the secondary effectiveness endpoints will be reported once 50% of the subjects in the intention to treat analysis set have completed Visit 5 (6 Month Follow-up Visit).

2 Analysis Sets

All subjects will be considered enrolled once they have signed the informed consent form.

2.1 Intention to Treat Analysis Set

The intention to treat (ITT) analysis set will be defined as the set of study eyes for which a CyPass Micro-Stent implant is attempted. The ITT analysis set will serve as the primary set for the safety and effectiveness summaries and analyses, as well as for all demographics, baseline, surgery, and study conduct summaries.

3 General Reporting Conventions

- ≠ All study eyes will receive the same treatment consisting of CyPass Micro-Stent implantation following uncomplicated cataract surgery. Therefore, summary tables will be presented for all subjects combined across all investigative centers.
- ≠ Available data at each assessment time point will be presented. No imputations will be made for missing data.
- ≠ Appropriate descriptive statistics will be computed and displayed (by assessment time point and other key variables as appropriate for both continuous and categorical variables as described below.

  For continuous variables, descriptive statistics include n (number of subjects/eyes) with non-missing data, mean, standard deviation (SD), median, minimum and maximum values. The following number of decimal places will be used: mean and

median values to one more decimal place than the raw data; minimum, and maximum to the same number of decimal places as the raw data and SD to two more decimal places than the raw data.

For categorical parameters, the number and percentage of subjects/eyes within each category will be presented. The denominator for percentages will be based on the number of subjects/eyes with non-missing data appropriate for summary purposes. If a count of zero is obtained for categorical data, the zero count and percentage will still be displayed. Unless otherwise noted, percentages will be presented to one decimal place.

With the exception of the primary study endpoint, that is a one-sided test (alpha=0.05), all other applicable confidence intervals (CI) will be at the alpha = 0.05 (two-sided) level.

≠ Baseline is defined as the last assessments obtained prior to CyPass implantation surgery on Day 0.
≠ Change from baseline (pre-surgery) (where relevant) will only be summarized for subjects with both screening (pre-surgery) and post-op data for the relevant visit
≠ Study day: Study day will be calculated relative to the date of CyPass implantation surgery (Day 0) as: Date of event – date of surgery. This formula will be used when calculating days to a specific event (i.e., ocular medications and/or AE start date). A negative study day indicates an event prior to surgery.
≠ Individual listings of data represented on the eCRF will be provided to facilitate investigation of the tabulated values and to allow for clinical review of key variables. All data listings will be sorted by site-subject number, visit, and assessment time points where appropriate. Data from unscheduled visits will be excluded from the summary tables (except for adverse events) but included, chronologically, in the data listings.

4 Study Conduct, Subject Baseline, and Surgical Summaries

All summaries in this section will be presented for the ITT analysis set, unless otherwise specified.

4.1 Subject Disposition

A subject disposition table will be presented that displays the number of subjects enrolled in addition to the number of screen failures as well as the number subjects treated, completed, and discontinued. This table will also contain counts for each reason for premature study discontinuation. Furthermore a listing of reasons for early study discontinuation will also be provided.

An accountability table as per ANSI Z80.27-2014 (revision of ANSI Z80.27-2001 (R2011)), Annex G will be provided.

4.2 Protocol Deviations

A listing of protocol deviations will be provided.

4.3 Demographic and Baseline Characteristics

Subject demographics to be summarized include age, sex, race, and ethnicity. Baseline summaries will include study eye (OD, OS) and baseline IOP .

4.4 General Medical and Ophthalmic History

All general medical history and ophthalmic history findings will be presented in separate data listings.

4.5 Implantation Surgery

CyPass implantation information regarding the placement of the device and surgical procedural data will be presented in the listings.

5 Effectiveness Analysis Strategy

5.1 Effectiveness Endpoints

5.1.1 Primary Effectiveness Endpoint

There is no primary effectiveness endpoint for this study.

5.1.2 Secondary Effectiveness Endpoints

All secondary effectiveness endpoints will be evaluated at 36 months postoperatively.

≠ Mean change in IOP

- Change in IOP from baseline is defined as, for each subject,

$$Change = PostOp\ IOP - Baseline\ IOP$$

≠ Proportion of subjects with IOP reduction ≥ 20% while using the same or fewer topical ocular hypotensive medications

The outcome of ≥ 20% decrease in IOP from baseline up to 36 months post-operatively, while using the same or fewer topical ocular hypotensive medications, is determined as follows,

- Percent change in IOP from baseline is defined as, for each subject,

$$Percent\ Change = \frac{PostOp\ IOP - Baseline\ IOP}{Baseline\ IOP} \text{ x } 100$$

such that negative percent changes represent a favorable effect, while positive percent changes represent an unfavorable effect. Therefore, IOP response is achieved if the percent change is ≥ 20% lower than baseline (i.e. the percentage change is ≤ −20%), while the subject is using the same or fewer topical ocular hypotensive medications compared to baseline.

- IOP response rate: Proportion of eyes meeting the effectiveness outcome is defined as the number of eyes with occurrence of ≥ 20% decrease from baseline, while the subject is using the same or fewer topical ocular hypotensive medications compared to baseline, divided by the number of eyes having non-missing postoperative and baseline IOP measurements and non-missing postoperative and baseline hypotensive medication information.

- Combination ocular hypotensive medications will be counted as two medications. In particular, all combination medications will be programmatically counted as two medications:
  - ≠ Bimatoprost / Timolol
  - ≠ Brimonidine Tartrate / Timolol
  - ≠ Brinzolamide / Timolol
  - ≠ Dorzolamide HCl / Timolol Maleate
  - ≠ Latanoprost / Timolol
  - ≠ Travaprost / Timolol
  - ≠ Brinzolamide / Brimonidine Tartrate

  Any subjects who are using the following oral medications will be excluded from the analysis of this endpoint.
  - ≠ Acetazolamide
  - ≠ Methazolamide

≠ Proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg

$$Proportion = \frac{\#\ of\ subjects\ not\ using\ ocular\ hypotensive\ medications\ having\ 6\ mmHg \le IOP \le\ 18\ mmHg\ at\ the\ postoperative\ visit}{\#\ of\ subjects\ in\ ITT\ set}$$

5.1.2.1 Effectiveness Hypotheses

There are no statistical hypotheses for the secondary effectiveness endpoints; these endpoints will be summarized descriptively.

5.1.3 Prior and Concomitant Ocular Medication Usage

Start and stop dates of ocular hypotensive medications/treatments will be compared to the date of CyPass implantation surgery (Day 0) to allow medications/treatments to be classified as either *prior* or *concomitant*.

All medications recorded from enrollment and prior to surgery will be classified as *prior* medications. If a medication has either (1) start date before the date of surgery and a stop date on or after the date of surgery or (2) a start date on or after the date of surgery, then the medication will be classified as *concomitant*. Concomitant medications with a start date on the date of surgery will be classified as *intraoperativ*e medications, while concomitant medications with a start date after surgery will be classified as *postoperative* medications.

For summarization, combination ocular hypotensive medications will be counted as two medications, as specified in section 5.1.2.

Summary statistics for the average number of ocular hypotensive medications used per subject at each visit will be presented. In addition, a categorical summary of the number of ocular hypotensive medications (None, 1, 2, 3, or >3) reported at each visit will be presented. Shift tables cross tabulating hypotensive medication usage at 12, 24, and 36 months postoperatively versus baseline will be presented. Frequencies of use by medication name will be created.

6 Safety Analysis Strategy

6.1 Safety Endpoints

6.2 Primary Safety Endpoint

The primary endpoint is the rate of clinically relevant complications associated with CyPass Micro-Stent placement and stability as determined at 36 months.

$$Rate = \frac{\#\ of\ subjects\ who\ experience\ clinically\ relevant\ complications\ associated\ w/\ CyPass\ placement\ \&\ stability}{\#\ of\ subjects\ in\ ITT\ set}$$

As described in the protocol, Section 8.2.2.1, the specific device-related complications included in this primary endpoint are:

- ≠ Failure to implant CyPass, defined as inability to successfully deploy or insert the CyPass.
- ≠ Clinically significant CyPass malposition, defined as CyPass positioning after deployment such that:
    - The device is not in the supraciliary space, or

- There is a clinical sequela resulting from device position including, but not limited to:
  - ≠ Secondary surgical intervention to modify device position (eg, repositioning, proximal end trimming or explantation)
  - ≠ Corneal endothelial touch by device
  - ≠ Corneal edema leading to loss of BCDVA > 2 lines at the last postoperative visit, in comparison with preoperative BCDVA
  - ≠ Progressive ECL, defined as ongoing reduction in endothelial cell count of 30% or more relative to the screening ECD value, where 'ongoing reduction in endothelial cell count' is defined as losses continuing after Visit 5 (6 Month Follow-up)
  - ≠ Erosion of device through sclera
  - ≠ Device obstruction requiring secondary surgical intervention.

6.2.1 Safety Hypothesis

The primary null hypothesis to be tested is that the observed rate of clinically relevant complications associated with CyPass Micro-Stent placement and stability is greater than or equal to the performance target rate of 7%. The corresponding alternative hypothesis to be tested is that the observed rate of complications is less than the performance target rate. These hypotheses are expressed formulaically as:

$$H_0: p_c \geq 7\%$$
$$H_1: p_c < 7\%$$

where p_c is the population proportion of eyes experiencing a complication event at 36 months.

6.2.2 Analysis Methods

The primary safety hypothesis will be tested with an exact one-sided binomial test with type I error 0.05. This endpoint will be summarized by numerator (number of eyes meeting the endpoint), denominator (number of eyes in the ITT set), and the rate of ITT eyes meeting the endpoint. In addition, a summary of each individual complication type included in the primary safety endpoint (and a listing of these complications) will be provided.

Otherwise, no formal statistical hypothesis testing is planned for this study.

6.3 Secondary Safety Endpoints

All secondary safety endpoints will be evaluated at 36 months postoperatively.

≠ Rate of occurrence of sight-threatening adverse events including,

- Persistent (at time of study exit) BCDVA loss of 3 or more lines compared to best BCDVA achieved during the course of study
- Endophthalmitis
- Corneal decompensation
- Retinal detachment
- Severe choroidal hemorrhage or detachment
- Aqueous misdirection

$$Rate = \frac{\#\ of\ subjects\ who\ experience\ any\ sight-threatening\ adverse\ events}{\#\ of\ subjects\ in\ ITT\ set}$$

≠ Rate of ocular secondary surgical interventions (SSI)

$$Rate = \frac{\#\ of\ subjects\ with\ any\ ocular\ SSIs}{\#\ of\ subjects\ in\ ITT\ set}$$

≠ Rate of ocular SSIs associated with CyPass placement and stability

$$Rate = \frac{\#\ of\ subjects\ with\ any\ ocular\ SSIs\ associated\ with\ CyPass\ placement\ and\ stability}{\#\ of\ subjects\ in\ ITT\ set}$$

6.3.1 Secondary Safety Hypotheses

There are no statistical hypotheses for the secondary safety endpoints.

6.3.2 Analysis Methods

These endpoints will be summarized by numerator (number of eyes meeting the endpoint), denominator (number of eyes in the ITT set), and the rate of ITT eyes meeting the endpoint.

6.4 Other Safety Outcomes

The following safety outcomes will be summarized by numerator (number of eyes experiencing the outcome), denominator (number of eyes in the ITT set), and the rate of ITT eyes experiencing the outcome.

≠ Increase from baseline IOP of 10 mmHg or greater at any time at/after 30 days postoperative

- Change in IOP from baseline at/after 30 days postoperative is defined as,

$$Change = PostOp\ IOP - Baseline\ IOP$$

- Note: for subjects having IOP change ≥ 10 mmHg at any time at/after 30 days postoperative, a subject will be counted only once for reporting this outcome across all postoperative visits..

≠ BCDVA loss of 2 or more lines compared to screening (Visit 0)

- Change in BCDVA from screening to any postoperative visit is defined as,

$$Change = PostOp\ BCDVA - Screening\ BCDVA$$

≠ BCDVA loss of 2 or more lines in comparison with best recorded BCDVA at any postoperative visit.

Note: for subjects with BCDVA loss of 2 or more lines to any visit, a subject will be counted only once for reporting this worsening across all postoperative assessments.

≠ Device movement, defined as a change by at least 1 in the number of CyPass rings visible (e.g., from 1 ring to 2 rings or from 3 rings to 2 rings) that does not result in clinical sequelae (e.g., secondary surgical intervention to modify device position, corneal endothelial touch by device, corneal edema leading to loss of BCDVA > 2 lines at the last postoperative visit in comparison with preoperative BCDVA, progressive endothelial cell loss, erosion of device through sclera, or device obstruction requiring secondary surgical intervention), and that is not attributable to any one or more of the following:

- variations in gonioscopic viewing angle or illumination
- changes in angle anatomy due to concomitant findings such as resolution of hyphema
- changes in anterior chamber depth
- development of focal peripheral anterior synechiae

6.5 Additional Safety Assessments

6.5.1 Adverse Events

The applicable definition of an Adverse Event (AE) can be found in the study protocol Section 13 Device Deficiencies and Adverse Events. All AEs occurring from when a subject signs informed consent to when a subject exits the study will be accounted for in the reporting. Timing of the adverse event is specified by the investigator on the case report

form when the "Description of Adverse Event" category is selected. *Systemic* adverse events include non-ocular events and events in the fellow eye.

An overall summary of treatment emergent adverse events will be provided including the number and percentage of unique subjects/eyes with at least one AE, AE in the study eye, serious AE in the study eye, systemic AE, serious systemic AE, device related AE (ADE), serious device related AE (SADE), and AE leading to withdrawal.

Descriptive summaries (subject counts and percentages, event counts) for AEs will be presented by primary SOC and PT of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 19.0 or a more recent version). The SOCs will be presented in alphabetical order. PTs will be ordered in decreasing proportion. The following summary tables and corresponding subject listings will be provided:

- ≠ Non-serious AEs in the study eye (TEAE only)
- ≠ Serious AEs in the study eye (TEAE only)
- ≠ Non-serious systemic AEs for all enrolled subjects (includes non-ocular events and events in the fellow eye)
- ≠ Serious systemic AEs for all enrolled subjects (includes non-ocular events and events in the fellow eye)
- ≠ Adverse device effects (ADE) for all study eyes(TEAE only)
- ≠ Serious adverse device effects (SADE) for all study (TEAE only)
- ≠ All adverse events occurring in the study eye prior to surgery

Both subject and event counts will be presented for AEs. Subject counts refer to the number of subjects with the respective AE of interest. Subjects who experience multiple AEs for a PT will be counted once, similarly for subjects with multiple AEs per SOC, for subject counts. Event counts refer to the number of occurrences of the respective AE of interest, regardless of whether a subject already had this event.

Additionally, individual subject listings provided will include:

- ≠ Deaths for all enrolled subjects
- ≠ Withdrawals due to AE(s) for all enrolled subjects

All reported adverse events will be detailed in the data listings. These listings will also include AEs, where appropriate, that occur after signing the ICF but prior to surgery.

6.5.2 Device Deficiencies

The applicable definition of a device deficiency is found in the study protocol Section 13.1.4. A listing of all device deficiencies, as recorded on the Device Deficiency CRF, will be provided.

6.5.3 Endothelial Cell Count

Endothelial cell count at baseline and at each follow-up visit at which the specular microscopy exam is conducted, will be summarized. In addition, change and percentage change from baseline as well as change between two consecutive visits will also be summarized.

6.5.4 Gonioscopy and Slit Lamp Findings

Gonioscopy and slit lamp results at baseline and at each 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.

6.5.5 Fundus Examination

Fundus examination observations at baseline and at each 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 subject in the ITT cohort (denominator), and the percentage of abnormal findings in each category (numerator / denominator). Also, C/D ratio results will be summarized at each assessment visit for non-missing records. A listing will be provided which presents all subjects with any abnormal fundus exam observations. An additional listing will present the C/D ratio exam results.

6.5.6 Corneal Pachymetry

Central corneal thickness will be summarized at screening, 12, 24, and 36 months postoperatively. This will be measured three times for each subject for each visit, and the median value will be used to calculate summary statistics.

6.5.7 Intraocular Pressure

Descriptive summaries of observed intraocular pressure (IOP) values, as well as change and percent change from baseline values will be presented at each postoperative assessment visit. Subject listings of all IOP measurements along with the number of IOP medications will be presented by visit. IOP is measured twice within the eye. If the values are within 2 mmHg then the average is calculated, otherwise a third measurement is taken and the median of the three is used to represent the IOP at that visit for that eye.

6.5.8 Visual Field Loss Mean Deviation Testing

The visual field mean deviation (dB) testing data collected at screening, 12, 24, and 36 months postoperatively will be summarized. Also, 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).

6.5.9 Manifest Refraction

Sphere, cylinder, and MRSE will be summarized at baseline and at each postoperative visit for which manifest refraction is scheduled.

All manifest refraction results (i.e., sphere (diopters), cylinder (diopters), and axis (degrees)) will be included in the data listings. Note, for cylindrical correction results (i.e., cylinder and axis) recorded in minus-cylinder notation will be converted to plus-cylinder notation for consistency in reporting. Details for this conversion can be found in Appendix D: Cylinder Adjustment Converting Negative to Positive Notation

6.5.10 Best Corrected Visual Acuity (BCDVA)

BCDVA (collected in letters read) will be summarized at baseline and at each post-operative visit at which BCDVA is collected; change from baseline will also be collected at each post-operative visit at which BCDVA is collected. A listing of BCDVA will also be provided. An additional listing of any instances where a loss of BCDVA of two lines or more is reported will also be provided. Data will be collected based on the visual acuity score (letters read). These values will be converted to and reported as Snellen values. Details for this conversion can be found in Appendix E: Conversion of Visual Acuity Score to Snellen Values

6.5.11 CyPass Explantation and/or Repositioning

A listing detailing subjects with CyPass explantation and/or repositioning will be provided. The listing will include the following variables: site-subject, age, sex, race, ethnicity, explantation or repositioning event, surgery date, study day, and reason. The data for this listing will be collected on the adverse events eCRF. Further details can be found in Appendix C: Data Sources.

7 Sample Size and Power Calculations

The performance target for the primary safety endpoint is 7.0%.

An evaluation of COMPASS (TMI-09-01) data showed that through 24 months of follow-up, there were two eyes with failures to implant and eight eyes with CyPass malposition events, respectively, corresponding to the above definitions. In addition, there were four eyes with documentation of three rings visible within the first postoperative week that likely would have undergone early secondary surgical intervention due to anterior CyPass positioning under the approach documented in the Instructions for Use (IFU). Inclusion of these cases would increase the number of observed events from 10 to 14 (3.74%, 95% confidence

interval: 2.1% – 6.2%). Of note, not all investigators documented the number of rings visible in the early postoperative period because this was not a study requirement (data regarding the number of rings is recorded for only 96 subjects at 1 Day and 139 subjects at 1 Week), so this number likely underestimates the number of subjects who would have been candidates for early surgical re-intervention under the new criteria described in the IFU.

Based on these considerations, the "true" event rate is assumed to be 4.0%, and the performance target is set to 7.0%. The following assumptions were used for the sample size calculation:

≠ Type I error = 0.05
≠ one-sided alternative

With a sample size of 360 subjects in the final analysis (unilateral implants only) and a performance target of 7.0%, assuming a true event rate of 4.0%, there is 80% power to reject the null hypothesis based on a one-sided alpha = 0.05-level exact test for a single proportion.

To allow for attrition over this 36-month study, a cumulative rate of up to 20% of subjects lost to follow-up is assumed, corresponding to a targeted implantation of 450 eyes in 450 subjects to achieve at least 360 eyes with 36 months of follow-up.

Annex F of ANSI standard Z80.27-2014 refers to ensuring adequate sample size so that any adverse event of a given type that occurs in the population at a rate of 1% or greater is likely to be seen in the study. With 360 subjects, there is at least 97% probability that at least one adverse event will be detected, assuming a true rate of 1.0%. There is at least 95% probability if the true rate is 0.83%.

8 References

American National Standards Institute, Inc. ANSI Z80.27-2014

COMPASS (TMI-09-01) trial CSR.

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 the version of the study protocol with effective date 22-Aug-2017.

10 Appendix A: Schedule of Visits

Table 10–1 Schedule of Visits

Procedure/Assessment	Visit 0 (-42 to -1 days) Screening	Visit 00 (Day 0) Surgery	Visit 1 (+1 day) 1 Day Follow-up	Visit 2 (+5 to 9 days) 1 Week Follow-up	Visit 3 (+21 to 35 days) 1 Month Follow-up	Visit 4 (+70 to 98 days) 3 Month Follow-up	Visit 5 (+150 to 210 days) 6 Month Follow-up	Visit 6 (+330 to 420 days) 12 Month Follow-up	Visit 7 (+690 to 780 days) 24 Month Follow-up	Visit 8 (+1050 to 1140 days) 36 Month Follow-up/Exit/Early Exit
Informed Consent	X									
Demographics	X									
Medical History	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Number of Ocular Hypotensive Medications	X[1]	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[2]	X									
Inclusion/Exclusion	X									
Surgery[3] (with video)		X								
Manifest Refraction	X[1]			X	X	X	X	X	X	X
Monocular BCDVA	X[1,4]		X[5]	X	X	X	X	X	X	X
Specular Microscopy[6]	X[1]					X	X	X	X	X
Visual Field[7]	X[1]							X	X	X
IOP (8:00 – 10:00 am)	X[1]		X	X	X	X	X	X	X	X
Slit Lamp Examination	X[1]		X	X	X	X	X	X	X	X
Gonioscopy (photographed)	X[1]	X	X	X	X	X	X	X	X	X
Fundus Examination	X[1]					X	X	X	X	X
Central Corneal Pachymetry	X[1]							X	X	X
UBM or OCT[8]						(X)	(X)	(X)	(X)	(X)
Adverse Events	X	X	X	X	X	X	X	X	X	X
Device Deficiencies	X	X	X	X	X	X	X	X	X	X

[1] Conduct bilaterally at Visit 0 and in study eye only at postoperative visits, unless otherwise indicated.

[2] In women of child bearing potential only.

[3] An Alcon observer may be present during surgery.

[4] At Visit 0, if BCDVA better than 0.3 logMAR (> 85 letters read), repeat with BAT (Brightness Acuity Meter).

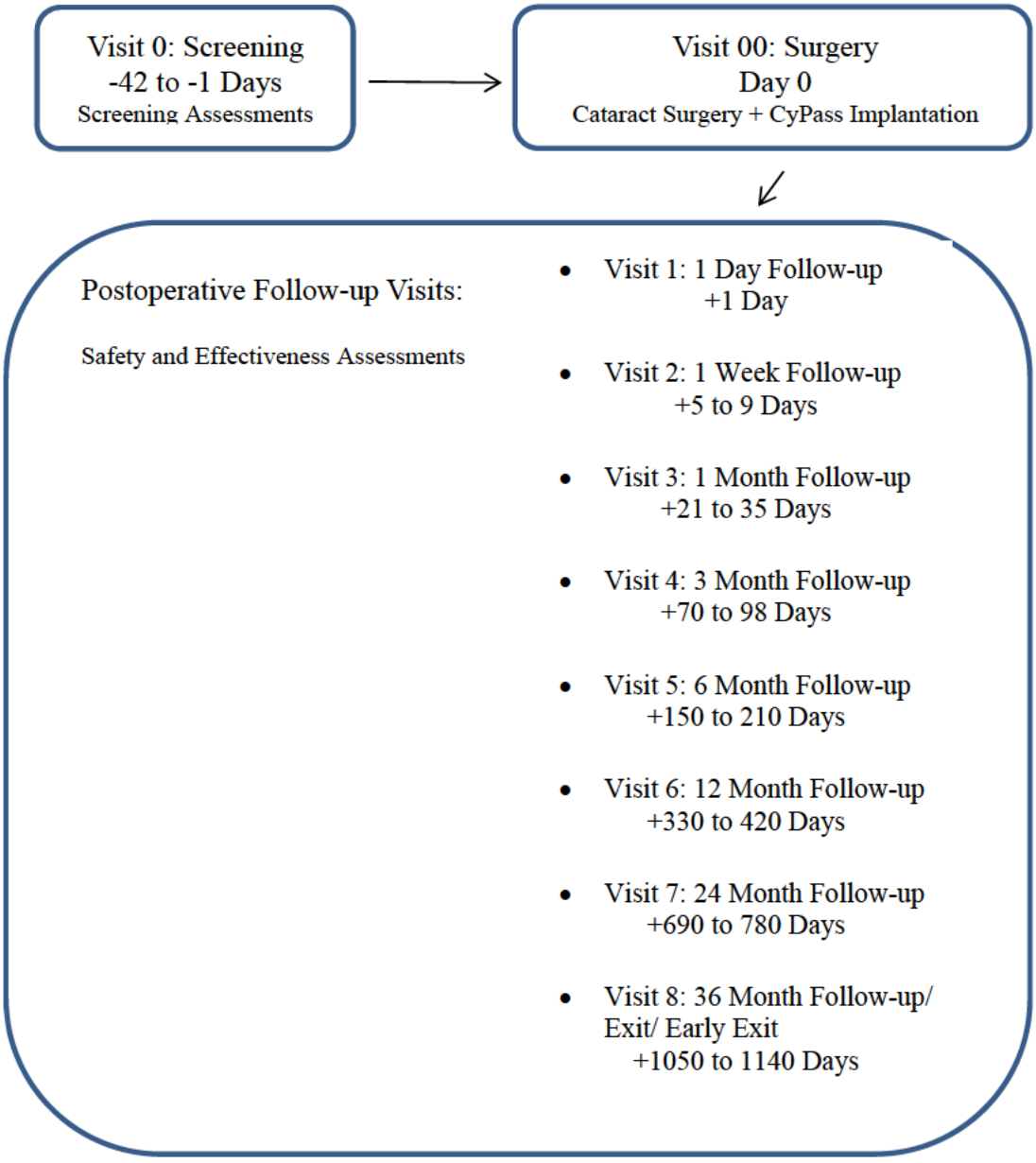
[5] At Visit 1 (Day 1 Follow-up) BCDVA will be conducted as a pinhole test.

[6] ECD may be requested in the fellow eye at follow-up on a case by case basis.

[7] Visual field testing may be repeated between screening (Visit 0) and surgery (Visit 00), if needed.

[8] UBM or OCT conducted if CyPass is not visible on Gonioscopy at two consecutive visits after Visit 3 (1 Month Follow-up). Images retained at site to demonstrate placement of CyPass.

11 Appendix B: Study Design



12 Appendix C: Data Sources

Endpoint	CRF	Comments
Primary Effectiveness Endpoint		
None		
Secondary Effectiveness Endpoints		
Mean change in IOP	Baseline: Intraocular Pressure_Glaucoma PostOp: Intraocular Pressure_Glaucoma_1	
Proportion of subjects with IOP reduction ≥ 20% while using the same or fewer topical ocular hypotensive medications	Baseline: Intraocular Pressure_Glaucoma PostOp: Intraocular Pressure_Glaucoma_1 Ocular Hypotensive Medications	
Proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg	Baseline: Intraocular Pressure_Glaucoma PostOp: Intraocular Pressure_Glaucoma_1 Ocular Hypotensive Medications	
Primary Safety Endpoint		
Failure to implant CyPass, defined as inability to successfully deploy or insert the CyPass.	Adverse Event(s) SX	Intraop - g) CyPass non-implantation (as defined in the protocol)

Endpoint	CRF	Comments
Clinically significant CyPass malposition, defined as CyPass positioning after deployment such that:		
The device is not in the supraciliary space, or	Adverse Event(s) SX	Postop - bb) CyPass device malposition - positioning after deployment such that the device is not in the supraciliary space (Specify)

Endpoint	CRF	Comments
There is a clinical sequela resulting from device position including, but not limited to: Secondary surgical intervention to modify device position (eg, repositioning, proximal end trimming or explantation) Corneal endothelial touch by device Corneal edema leading to loss of BCDVA > 2 lines at the last postoperative visit, in comparison with preoperative BCDVA Progressive ECL, defined as ongoing reduction in endothelial cell count of 30% or more relative to the screening ECD value, where 'ongoing reduction in endothelial cell count' is defined as losses continuing after Visit 5 (6 Month Follow-up) Erosion of device through sclera Device obstruction requiring secondary surgical intervention.		Postop - cc) CyPass device malposition - positioning after deployment such that there is a clinical sequela resulting from device position (as defined in the protocol) (Specify)
Secondary Safety Endpoints		
Rate of occurrence of sight-threatening adverse events including		

Endpoint	CRF	Comments
Persistent (at time of study exit) BCDVA loss of 3 or more lines compared to best BCDVA achieved during the course of study	Adverse Event(s) SX	Postop - b) Persistent BCDVA loss of 3 lines or more (as defined in the protocol)
Endophthalmitis	Adverse Event(s) SX	Postop - d) Endophthalmitis
Corneal decompensation	Adverse Event(s) SX	Postop - n) Corneal decompensation
Retinal detachment	Adverse Event(s) SX	Postop - p) Retinal detachment
Severe choroidal hemorrhage or detachment	Adverse Event(s) SX	Postop - t) Choroidal hemorrhage or choroidal effusion (as defined in the protocol) lasting longer than 1 month (Specify)
Aqueous misdirection	Adverse Event(s) SX	Postop - h) Aqueous misdirection
The rate of ocular secondary surgical interventions (SSI)	Adverse Event(s) SX	Any one of these four: Postop - ee) CyPass device explantation associated with CyPass placement and stability Postop - ff) CyPass device explantation NOT associated with CyPass placement and stability Postop - gg) Unplanned ocular surgical reintervention associated with CyPass placement and stability Postop - hh) Unplanned ocular surgical reintervention NOT associated with CyPass placement and stability (as defined in the protocol)

Endpoint	CRF	Comments
The rate of ocular SSIs associated with CyPass placement and stability	Adverse Event(s) SX	Either of these two: Postop - ee) CyPass device explantation associated with CyPass placement and stability Postop - gg) Unplanned ocular surgical reintervention associated with CyPass placement and stability
Other Safety Endpoints		
Increase from baseline IOP of 10 mmHg or greater at any time at/after 30 days postoperative	Baseline: Intraocular Pressure_Glaucoma PostOp: Intraocular Pressure_Glaucoma_1	
BCDVA loss of 2 or more lines compared to screening (Visit 0)	Baseline: Visual Acuity_VAS PostOp: Visual Acuity_VAS_1	
BCDVA loss of 2 or more lines in comparison with best recorded BCDVA at any postoperative visit	Baseline: Visual Acuity_VAS PostOp: Visual Acuity_VAS_1	

Endpoint	CRF	Comments
Device movement, defined as a change by at least 1 in the number of CyPass rings visible (eg, from 1 ring to 2 rings or from 3 rings to 2 rings) that does not result in clinical sequelae (eg, secondary surgical intervention to modify device position, corneal endothelial touch by device, corneal edema leading to loss of BCDVA > 2 lines at the last postoperative visit in comparison with preoperative BCDVA, progressive endothelial cell loss, erosion of device through sclera, or device obstruction requiring secondary surgical intervention), and that is not attributable to any one or more of the following:	Adverse Event(s) SX	Postop - dd) CyPass device dislodgement or movement, without sequelae (as defined in the protocol)
variations in gonioscopic viewing angle or illumination		
changes in angle anatomy due to concomitant findings such as resolution of hyphema		
changes in anterior chamber depth		
development of focal peripheral anterior synechiae		

Endpoint	CRF	Comments
Additional Safety Assessments		
Adverse events (ocular and non-ocular)	Adverse Event(s) SX	
Device deficiencies	Device Deficiency	
Endothelial Cell Count	This will come from a dataset provided by the reading center, CIARC	
Slit lamp findings	Baseline: Slit Lamp Observations PostOp: Slit Lamp Observations_1	
Fundus examination (C/D ratio) and fundus findings	Baseline C/D: Fundus Exam PostOp C/D: Fundus Exam_1 Baseline observations: Fundus Observations PostOp observations: Fundus Observations_1	
Corneal pachymetry	Baseline: Corneal Thickness PostOp: Corneal Thickness_1	
Intraocular pressure	Baseline: Intraocular Pressure_Glaucoma PostOp: Intraocular Pressure_Glaucoma_1	
Visual field loss mean deviation testing	Baseline: Automated Perimetry PostOp: Automated Perimetry_1	
Manifest refraction	Baseline: Subjective Refraction PostOp: Subjective Refraction_1	
Monocular BCDVA	Baseline: Visual Acuity_VAS PostOp: Visual Acuity_VAS_1	
Gonioscopy (with Goniophotography) via UBM or OCT	Baseline: Gonioscopy PostOp: Gonioscopy_1	
Secondary Surgical Interventions	Adverse Event(s) SX	
CyPass Explantation and/or Repositioning	Adverse Event(s) SX	

13 Appendix D: Cylinder Adjustment Converting Negative to Positive Notation

Transform cylinder to positive notation (+ notation) using the following:

When CYLINDER_RAW is negative but not missing:

- ≠ Positive notation for sphere: SPHERE_RAW + CYLINDER_RAW
- ≠ Positive notation for cylinder: multiply CYLINDER_RAW by negative one
- ≠ Positive notation for refractive axis: AXIS + 90, if this is greater than 180, then subtract 180 from it.

Otherwise:

- ≠ Use current values of CYLINDER_RAW and SPHERE_RAW, and positive notation for REFRAX is the value of AXIS

Data that is converted to positive notation will have the same level of precision as the original data collected in the database.

14 Appendix E: 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	

LogMar	VAS	Snellen
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	
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	

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

[redacted]
