Statistical Analysis Plan

PROTOCOL TMI-13-01 (ALCON PROTOCOL GLD122-P001) / NCT02448875

Protocol Title: **RANDOMIZED PROSPECTIVE CLINICAL EVALUATION OF THE SAFETY AND EFFECTIVENESS OF VISCO-ASSISTED CYPASS IMPLANTATION IN PATIENTS WITH OPEN ANGLE GLAUCOMA**

Project Number: A02974

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Template Version: Version 4.0, approved 16MAR2015

Approvals: See last page for electronic approvals.

Job Notes:

This is the first revision (Version 2.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version F of the study protocol, dated 2016-09-07.

Executive Summary:

Key Objectives:

The purpose of this research study is to assess the safety and effectiveness of visco-assisted CyPass Micro-Stent implantation for the lowering of intraocular pressure (IOP) in patients with open angle glaucoma (OAG).

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List of Abbreviations

ADE	Adverse device effect
AE	Adverse event
BCVA	Best corrected visual acuity
CER	Clinical evaluation report
CI	Confidence interval
CSR	Clinical study report
FAS	Full analysis set
ICF	Informed consent form
IOP	Intraocular pressure (mmHg)
ITT	Intent-to-treat
OAG	Open angle glaucoma
OD	Right eye
OS	Left eye
OU	Both eyes
SADE	Serious adverse device effect
SAE	Serious adverse event
SAS®	Statistical analysis system
SD	Standard deviation
TEAE	Treatment emergent adverse event

1 Study Objectives and Design

1.1 Study Objectives

The purpose of this research study is to assess the safety and effectiveness of visco-assisted CyPass Micro-Stent implantation for the lowering of intraocular pressure (IOP) in patients with open angle glaucoma (OAG).

1.2 Study Description

This is a prospective, randomized, controlled, multicenter, interventional study performed in two phases, as stated below. Up to 150 eyes meeting subject eligibility criteria listed in Section 6 of the protocol will be randomized to study treatment at up to 10 investigational sites.

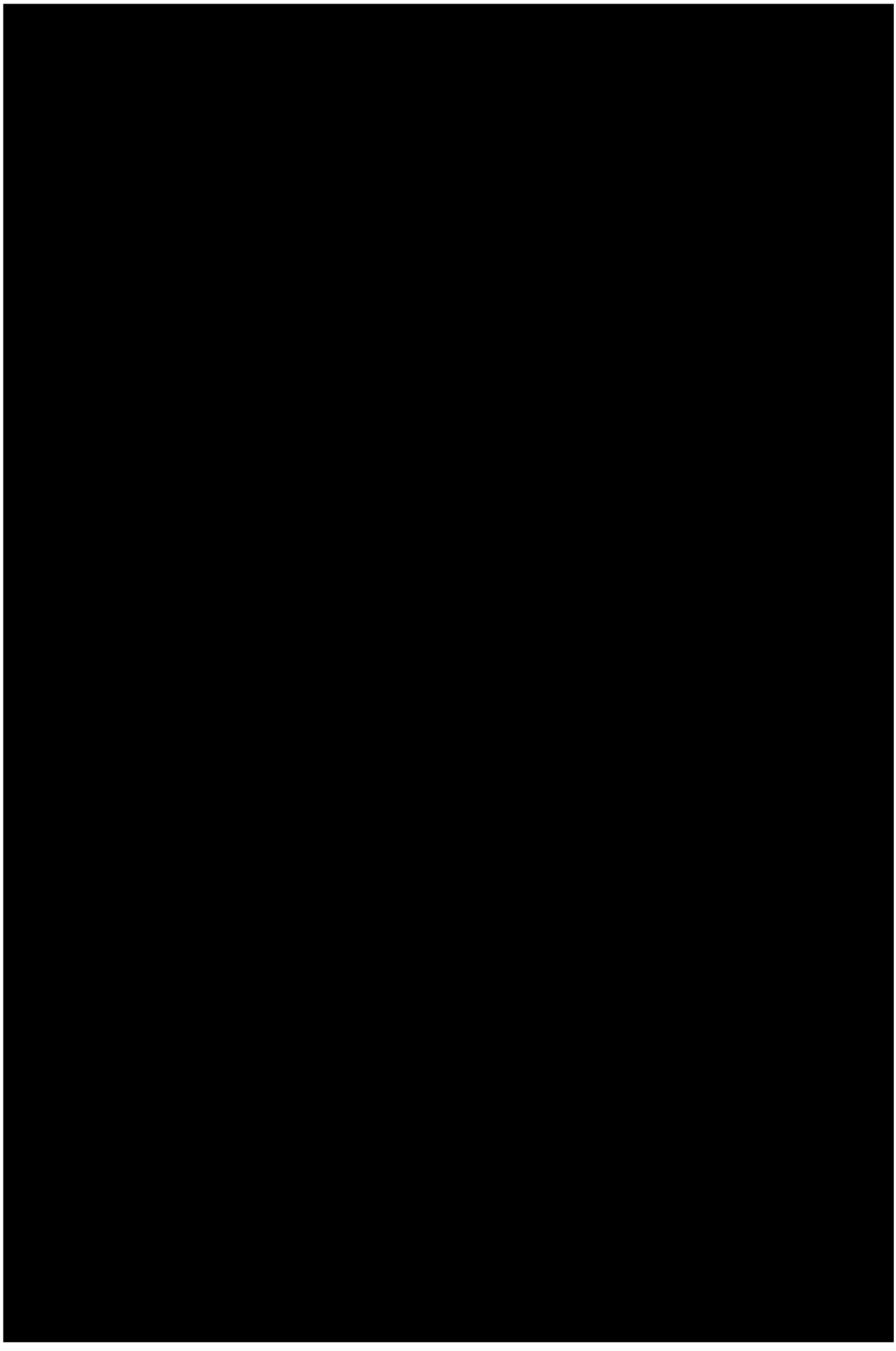
Note, only one eye per subject may be treated under the study protocol. If both eyes qualify for the study, the study investigator will choose which eye will be the study eye. Unless specified otherwise, ocular results refer to the study eye only. Therefore, throughout this SAP and corresponding tables and data listings, the number of subjects and eyes are synonymous.

Dose Selection Phase: During this phase, the first cohort (Cohort 1) of 63 subjects was randomized (1:1:1) to receive either a CyPass Micro-Stent with 30 µl adjunct Healon 5 viscoelastic, a CyPass Micro-Stent with 60 µl of adjunct Healon 5 viscoelastic, or a CyPass Micro-Stent without adjunct viscoelastic. After completion of at least 3 months follow-up on all subjects in this phase, an interim review of safety and efficacy data was performed to determine the optimum dose of adjunct viscoelastic for the study expansion phase.

Expansion Phase: After the dose selection phase, the study was expanded to include a second cohort (Cohort 2) of up to 90 additional subjects who were randomized 1:1 to either the CyPass Micro-Stent without adjunct viscoelastic or to the CyPass Micro-Stent with 60 µl adjunct viscoelastic (the dose selected based on Dose Selection Phase results).

Visit Schedule and Visit Windows: Enrolled study subjects are expected to participate in the study from Screening/Baseline through 12 months postoperatively in accordance with Table 1 – Study Examinations and Procedures (Appendix 1 in the study protocol) below.

Note, prior to protocol version D, Amendment dated 07Oct2014, the 12 Month Washout visit was not required for mainly the initial dose selection phase subjects who were on IOP lowering medication. All Cohort 2 patients were enrolled under protocol version D or a later version.



1.3 Randomization

Subjects were randomized to their assigned treatment on the day of their surgical procedure. Randomization lists were provided for each study site.

During the Dose Selection Phase of the study, subjects were randomized in Cohort 1 using a 1:1:1 schedule to receive either CyPass Micro-Stent with 30 µl of adjunct Healon viscoelastic, CyPass Micro-Stent with 60 µl of adjunct Healon viscoelastic, or the CyPass Micro-Stent with no adjunct Healon viscoelastic.

During the Expansion Phase of the study, subjects were randomized in Cohort 2 using a 1:1 schedule to receive either CyPass Micro-Stent without adjunct Healon viscoelastic or the CyPass Micro-Stent with 60 µl of adjunct Healon 5 viscoelastic.

1.4 Masking

This study was not masked. Treatment assignment may be known to the investigators, subjects, or Alcon personnel involved with the planning and execution of the study.

2 Analysis Sets

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

2.1 Full Analysis Set

The full analysis set (FAS) will serve as the primary set for the efficacy analyses. The FAS includes all randomized subjects who undergo CyPass implantation surgery.

All primary and secondary endpoint summaries will be carried out using the FAS analysis set; that is, subjects assigned to the treatment to which they were randomized.

2.2 Safety Analysis Set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. The safety analysis set will include all enrolled subjects who undergo CyPass implantation surgery. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual treatment received. Therefore, subjects/eyes exposed to an incorrect study treatment will be included in the group corresponding to the actual treatment received. All listings of safety data will use the Safety Set.

3 Statistical Methods

Statistical analyses will be performed to summarize the primary and secondary efficacy endpoints as well as key safety evaluations. Additionally, within each treatment, changes from baseline will be assessed where appropriate.

3.1 General Reporting Conventions

- Only one eye per subject may be treated under the study protocol. If both eyes qualify for the study, the study investigator will choose which eye will be the study eye. Unless specified otherwise, all 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.

- Available data at each assessment time point will be presented. No imputations will be made for missing data.

- [redacted]

- Appropriate descriptive statistics will be computed and displayed by assessment time point for both continuous and categorical variables. For continuous variables, descriptive statistics include n (number of subjects/eyes) with non-missing data, mean, standard deviation (SD), median, minimum and maximum values. 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 with non-missing data appropriate for summary purposes. Unless otherwise noted, percentages will be presented to one decimal place. Any confidence intervals (CI) will be at the alpha = 0.05 (two-sided) level.

- Summary tables will be presented by treatment and overall, as appropriate, for both phases/cohorts combined.

- Study day: Study day will be calculated relative to the date of stent 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 data listings of select 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 Treatment (i.e., CyPass, CyPass with 30 µl, and CyPass with 60 µl), Cohort (1 or 2), 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.

- Analyses will be generated using SAS® version 9.2 or higher.

3.2 Baseline References

For reporting IOP results relative to ocular hypotensive medication use, two baseline references will be used as follows:

- Baseline1 = The pre-surgery assessments obtained at the scheduled **Screening** visit that are *prior to washout* (if necessary) for enrolled subjects regardless of whether the subject is taking any ocular hypotensive medications. Also referred to as 'Medicated' or 'Regardless of medications'.

- Baseline2 = The pre-surgery assessments obtained at the scheduled **Baseline** visit that are *after washout* of subject's ocular hypotensive medications for those subjects taking hypotensive medications; if a subject is not medicated at Screening, then Baseline2 = Baseline1 (i.e., per protocol Section 7.1, "Subjects who are medication naïve at screening may have the screening and baseline testing performed on the same day."). Also referred to as 'Unmedicated' or 'Without medications'.

All other data will reference only one baseline, designated "Baseline", defined as the last assessments obtained prior to CyPass implantation surgery on Day 0.

3.3 Prior and Concomitant Ocular Medications/Treatments

Start and stop dates of ocular medications/treatments will be compared to the date of stent 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 *intraoperative* medications, while concomitant medications with a start date after surgery will be classified as *post-operative* medications.

3.4 Adverse Events

The onset date of an adverse event will be compared to the date of stent implantation surgery (Day 0) to determine if the adverse event is treatment emergent or not. Adverse events with an onset date on or after the date of surgery will be classified as treatment emergent adverse events (TEAEs). Adverse events with an onset date on the date of surgery will be classified as *intraoperative* adverse events, while adverse events with an onset date after surgery will be classified as postoperative adverse events.

3.5 Coding Dictionaries

Verbatim adverse events will be coded into internal, non-dictionary, standardized terms for presentation. Further, the relationship of each adverse event to study device or implantation procedure will be determined.

General medical and ocular histories will be categorized by body system for presentation.

4 Study Conduct and Patient Baseline Summaries

4.1 Subject Disposition

Subject accountability will be summarized per ANSI Z80.27-2014 (revision of ANSI Z80.27-2001 (R2011)), Annex G. The number and percentage of subjects enrolled in the study will be presented by site for each treatment and overall; similar tables will display the total subjects in each analysis set (e.g., FAS, Safety) by site for each treatment and overall. Finally, a table will be constructed to present the number and percentage of subjects in each of the analysis sets (i.e., FAS and Safety) by treatment and overall.

A listing of subjects discontinued from the study will also be presented and the primary reason for discontinuation will be provided for those subjects.

4.2 Protocol Deviations

A listing of protocol deviations will be provided.

4.3 Demographic and Baseline Information, and General Medical and Ophthalmic History

Demographic and baseline information will be summarized using the FAS by treatment and overall. Subject demographics include age, sex, race, and ethnicity. Baseline information includes study eye (OD, OS) and lens status (phakic, pseudophakic).

General medical history findings and ophthalmic medical/surgical history findings will be presented separately in the data listings.

4.4 Implantation Surgery and Adjunct Treatment Administration

Implantation surgery and adjunct treatment administration details will be presented in the listings.

[redacted]

5 Efficacy Analysis Strategy

5.1 Efficacy Endpoints

Primary Efficacy Endpoint

The outcome of ≥ 20% decrease in IOP from baseline (unmedicated/Baseline2) up to 12 months post-operatively without IOP lowering medications (IOP response) is determined as follows,

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

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

  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%).

- IOP response rate: Proportion of eyes meeting the effectiveness outcome is defined as the number of eyes with occurrence of ≥ 20% decrease from baseline divided by the number of eyes having non-missing post-Baseline and Baseline IOP measurements at each the given visit.

While the IOP response rate at 12 months without IOP lowering medications is the primary endpoint, results will be summarized at each postoperative visit relative to unmedicated baseline. Note, at 12 months for subjects being treated with ocular hypotensive medications, a washout for the 12 month assessment was intended to obtain unmedicated IOP measurements. Note: prior to version D of the protocol, the 12 Month Washout visit was not required for the initial dose selection phase subjects who were on IOP lowering medication

Secondary Efficacy Endpoints

- Rate of intraoperative and post-operative device related ocular adverse events up to 12 months postoperatively

$$Rate = \frac{\#\text{ of subjects who experience } either \text{ an intraoperative } and/or \text{ post} - \text{operative device related ocular AE}}{\#\ of\ subjects}$$

such that device related includes definitely, probably, or possibly.

- Mean change in medicated IOP from baseline (Baseline1) to 12 months postoperatively regardless of medications
    - Computed for subjects having both non-missing baseline medicated IOP and 12 month postoperative regardless of medications measurements.
- Proportion of eyes using ocular hypotensive medications at 12 months postoperatively

$$Proportion = \frac{\#\ of\ subjects\ being\ treated\ with\ ocular\ hypotensive\ medications\ at\ the\ 12\ month\ postoperative\ visit}{\#\ of\ subjects\ at\ the\ 12\ month\ postoperative\ visit}$$

- Mean number of topical IOP lowering medications at 12 months postoperatively as compared with medicated baseline (Baseline1). [redacted]
- [redacted]

[redacted]

[redacted]

A data listing will accompany this summary presenting each subject's Screening, Baseline, 6 month, and 12 month (regardless of medications and/or unmedicated) IOP measurements, number of IOP medications, and corresponding aqueous lake characteristics, where applicable.

[redacted]

5.3 Statistical Methods for Efficacy Analyses

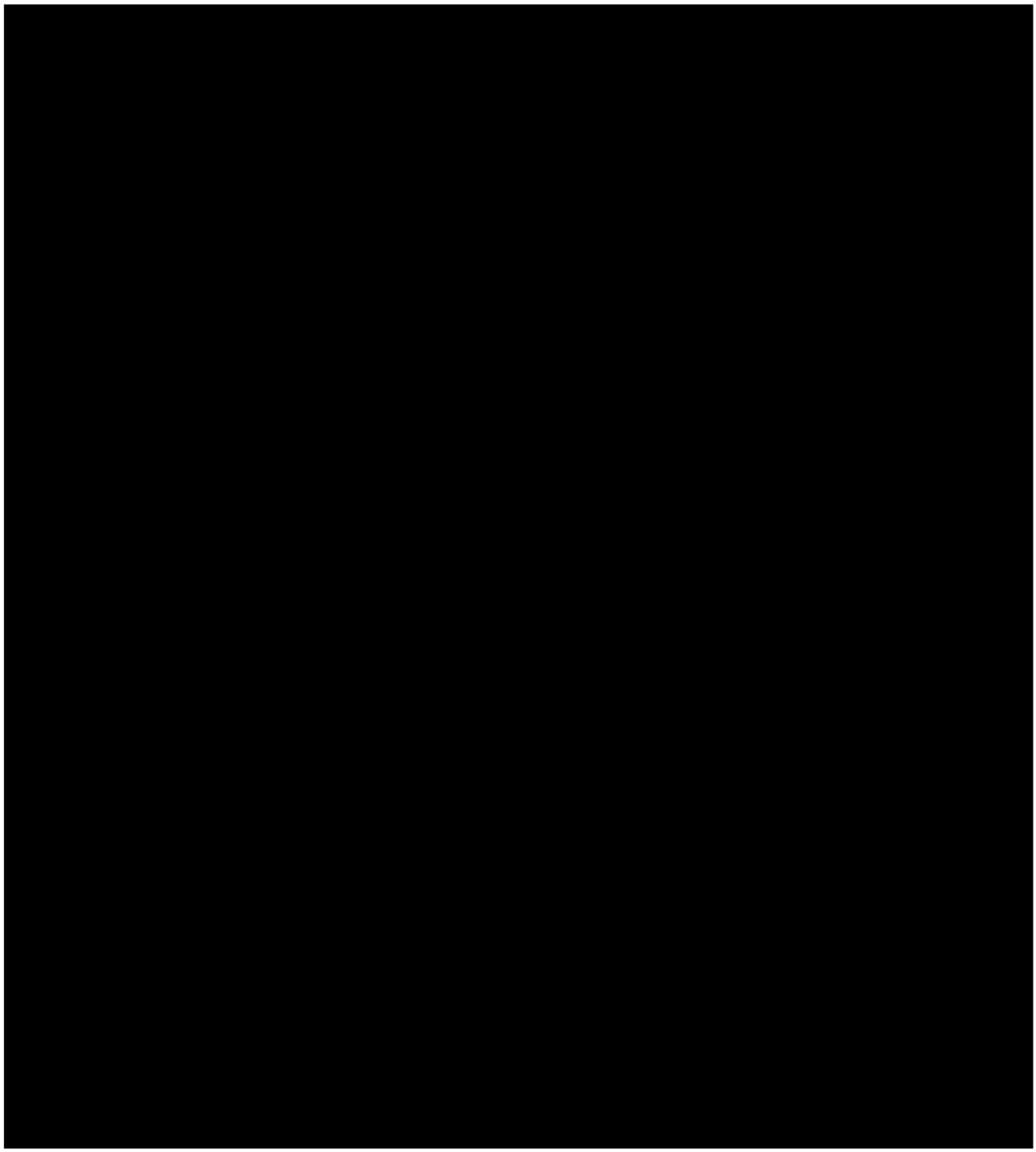
[redacted]

The primary efficacy endpoint, the achievement of a 20% decrease in IOP relative to baseline in the absence of IOP lowering medications up to 12 months post-operatively will be summarized at each post-operative visit by the number and percent of subjects having IOP response and the corresponding 95% confidence interval (CI) based on the exact binomial distribution.

Secondary efficacy endpoints describing proportions meeting given criteria will be summarized at each post-operative visit by the number and percentage of responses and the corresponding 95% CI based on the exact binomial distribution. While descriptive statistics for all continuous parameters for the actual values and change from baseline, including the 95% CI of the actual/observed results (based on a *t*-distribution) and change (based on a paired *t*-distribution), will be provided for each protocol specified visit, the 12 month visit is of most interest.

All efficacy analysis summaries will be produced using the FAS set.

[redacted]



6 Safety Analysis Strategy

6.1 Safety Endpoints

All analyses of safety will be performed on the study eye, with the exception of adverse events, using the Safety Set. Results of safety assessments include the following:

- Adverse events
- Manifest refraction
- Best Corrected Visual Acuity
- Intraocular pressure
- Gonioscopy
- Slit Lamp Examination
- Visual Field
- Dilated fundus examination and C/D ratio
- Secondary Surgical Interventions
- CyPass Explantation and/or Repositioning
- Device deficiencies

6.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment and/or data listings of the safety results listed in Section 6.1.

6.3 Statistical Methods for Safety Analyses

6.3.1 Adverse Events

The applicable definition of an Adverse Event (AE) can be found in the study protocol. All AEs occurring from when a subject signs informed consent to when a subject exits the study will be accounted for in the reporting. A treatment emergent AE (TEAE) is an event on or after the day of surgery.

An overall summary of treatment emergent adverse events will be provided including the number and percentage of unique subjects with at least one AE, serious adverse event (SAE), AE leading to withdrawal, non-ocular or ocular, and study eye ocular event. Further, within study eye ocular events, the number and percentage of eyes with at least one: serious ocular event, intraoperative or postoperative ocular event, device related ocular event (definitely, probably, or possibly), serious device related, and serious device related leading to withdrawal. Additionally, for all eyes in the safety set, summarization of unique counts and percentages of ocular AEs by group will be provided separately for intraoperative or postoperative events by the in-house AE coded terms by descending frequency (sorted using overall group frequencies).

All reported adverse events will be detailed in the data listings. Individual subject listings provided will include:

- Ocular AEs for all eyes in the Safety Analysis Set
- Ocular AEs for all eyes not in the Safety Analysis Set
- Non-ocular AEs for all enrolled subjects
- Listing of deaths for all enrolled subjects

These listings will also include AEs that occur after signing the ICF but prior to surgery, if applicable.

6.3.2 Manifest Refraction

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.

6.3.3 Best Corrected Visual Acuity (BCVA)

The number and percentage of responses relative to each Snellen equivalent category (i.e., 20/20 or better, 20/25 or better, etc.) will be presented at each assessment visit. Results will also be included in the data listings. [redacted]

[redacted]

6.3.4 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and reported up to one decimal place. IOP measurements will be summarized relative to both medicated and unmedicated baseline assessments compared to postoperative visits as follows. For medicated baseline IOP, descriptive summaries of observed values, as well as change and percent change from medicated baseline (Baseline1) values will be presented at each postoperative assessment visit compared to medicated baseline. Similarly, descriptive

summaries of observed values, as well as change and percent change from unmedicated baseline (Baseline2) values will be presented at each postoperative assessment visit compared to unmedicated baseline.

Further, IOP measurements over time at the Screening, Baseline, 1 Mo, 3 Mos, 6 Mos, 12 Mos, and 12 Mos unmedicated assessments will be presented graphically using side-by-side box plots to compare results between the CyPass alone and CyPass with 60 µL groups.

6.3.5 Gonioscopy

All gonioscopy results will be included in the data listings.

6.3.6 Slit Lamp Examination

The number and percentage of eyes in each category for assessing corneal edema, anterior chamber cells, anterior chamber flare, and other (slit lamp other specify), as well as lens status and opacity will be presented for each assessment visit.

6.3.7 Visual Field

Visual field measurements will be conducted at Screening and 12 months postop. For subjects having both measurements relative to the Humphrey Visual Field Analyzer 24-2 SITA Standard test, descriptive summaries of observed and change from screening values for visual field mean deviation (dB) will be presented at each assessment visit. Also, a categorical summary of the changes from screening will be presented using the following three categories: Increase ≥ 6.0 dB, No Change (-6.0 dB < to < 6.0 dB), or Decrease ≥ 6.0 dB.

Listings will be provided for all subjects' visual field test results as three subsets below,

- Subjects with matched-pairs relative to Humphrey 24-2 SITA Standard results (This subgroup will match the summary table described above.);
- Subjects with matched-pairs relative to Octopus Normal test results; and
- All other subjects without matched-pairs relative to the same visual field test or missing an assessment for a visit.

6.3.8 Dilated Fundus Examination and C/D Ratio

The fundus examination will be conducted to identify any clinically significant fundus abnormalities, as well as measure the vertical cup to disc ratio (C/D ratio). The C/D ratio will be summarized descriptively at each assessment visit.

A listing will be provided which presents all subjects with any clinically significant fundus abnormalities, as well as present the C/D ratio results.

6.3.9 Secondary Surgical Interventions

A listing detailing subjects with secondary surgical interventions in the study eye will be provided. The listing will include the following variables: treatment, cohort, site-subject, age, sex, race, ethnicity, eye, surgery term, due to AE (if yes, specify), surgery date, study day, and existing condition (Y/N).

6.3.10 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: treatment, cohort, site-subject, age, sex, race, ethnicity, explantation or repositioning event, surgery date, study day, pre-IOP, pre-and post-Shaffer grades, and reason.

6.3.11 Device Deficiencies

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

7 Sample Size and Power Calculations

The primary effectiveness endpoint is the outcome of ≥ 20% decrease in IOP from baseline without IOP lowering medications up to 12 months post-operatively (IOP response). The proportion of eyes meeting the effectiveness outcome, IOP response rate, will be assessed at 12 months. A sample of at least 101 eyes will be enrolled across the two groups (CyPass only control and CyPass + Healon 5 dose selected) with an estimated 86 eyes completing their month 12 visit. Assuming a 30% success rate for the control eyes and a 60% success rate for the visco-assisted eyes, 80% power can be achieved with 43 eyes per arm using a two-tailed alpha of 0.05 that is based on the Likelihood Ratio Chi-square test for two proportions. It is

estimated that approximately 10% of those receiving the CyPass Micro-Stent may be lost to follow-up.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
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05/30/2017 18:23:03	[redacted]	[redacted]
06/05/2017 20:12:51	[redacted]	[redacted]