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

PROTOCOL

NCT04629521

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

Protocol Number:	GLD122-P004
Development Stage of Project:	N/A
Sponsor Name and Address:	Alcon Research, LLC and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	CyPass® Micro-Stent

Investigator Agreement:

- I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practice (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, all applicable regulatory authority regulations, and conditions of approval imposed by the reviewing IRB or regulatory authority.
- I will supervise all testing of the device involving human subjects and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met in accordance with applicable local and governmental regulations.
- I have read and understand the appropriate use of the investigational product(s) as described in the protocol, current Investigator's Brochure, product information, or other sources provided by the Sponsor.
- I understand the potential risks and side effects of the investigational product(s).
- I agree to maintain adequate and accurate records in accordance with government regulations and to make those records available for inspection.
- I agree to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements of the Sponsor and government agencies.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

Have you ever been disqualified as an Investigator by any Regulatory Authority? ☐ No ☐Yes
Have you ever been involved in a study or other research that was terminated? ☐ No ☐Yes If yes, please explain here:

Principal Investigator:

Signature Date

Name and professional position:

Address:

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[redacted]

[redacted]

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1 GLOSSARY OF TERMS

Names of test product(s)	Throughout this document, test product(s) will be referred to as CyPass or CyPass Micro-Stent
Name of Control Product(s)	N/A
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (test product) or control product. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the test product or control product.*
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (test product). *Note: For subjects, this definition includes events related to the test product, the control product, or the procedures involved. For users or other persons, this definition is restricted to events related to the test product.* Requirements for reporting Adverse Events in the study can be found in Section 11.
Anticipated Serious Adverse Device Effect	Serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the risk management file.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequate labeling.* Requirements for reporting Device Deficiencies in the study can be found in Section 11.

Enrolled Subject	Any subject who signs an informed consent form for participation in the study.
Investigational Product (IP)	Is defined as a preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or control product in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Malfunction	Failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.
Non-interventional Study	A non-experimental (observational) study meeting all of the following conditions: • The intervention is provided according to current clinical practice and marketing authorization; • The assignment of a participant to a particular treatment strategy is not decided in advance by a protocol but falls within current practice; • The decision to provide an intervention is separate from the decision to include the participant in the study; and • The diagnostic and monitoring procedures fall within normal clinical practice, consistent with the standard of care. Interviews, questionnaires, and procedures that do not change or influence treatment may be considered normal clinical practice.
Non-serious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.

Randomized Subjects	This is a single arm study; therefore, subjects will not be randomized.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in the health of the subject that either resulted in: a. a life-threatening illness or injury. *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* *b.* any potentially sight-threatening event or permanent impairment to a body structure or a body function.

	c. in-patient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.* *d.* a medical or surgical intervention to prevent a) or b). *e.* any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, or a congenital abnormality or birth defect. *Refer to Section 11 for additional SAEs.*
Unanticipated Serious Adverse Device Effect	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk management file.
Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note: This definition includes slips, lapses, and*

	mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

2 LIST OF ACRONYMS AND ABBREVIATIONS

Table 2–1 List of Acronyms and Abbreviations Used in This Protocol

Abbreviation	Definition
AC	Anterior chamber
ADE	Adverse device effect
AE	Adverse event
BCDVA	Best corrected distance visual acuity
BCVA	Best corrected visual acuity
CCT	Central corneal thickness
C:D	Cup to disc (ratio)
CECD	Central endothelial cell density
CRF	Case report form
CyPass	CyPass Micro-Stent
dB	Decibel
ECD	Endothelial cell density
ECL	Endothelial cell loss
eCRF	Electronic case report form
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GPCMS	Global Product Complain Management System
ICF	Informed consent form
ICH	International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IRB	Institutional review board
[redacted]	[redacted]
IP	Investigational product
ISO	International Organization for Standardization
MD	Mean deviation
mm	Millimeter
[redacted]	[redacted]
MOP	Manual of procedures
N/A	Not applicable
OCT	Optical coherence tomography
PAS	Post-approval study
POAG	Primary open angle glaucoma
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SITA	Swedish Interactive Testing Algorithm
SLE	Slit-lamp examination
SOP	Standard operating procedure

Abbreviation	Definition
SSI	Secondary surgical intervention
UBM	Ultrasound biomicroscopy
US	United States

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Non-interventional
Investigational products	Test Product: CyPass Micro-Stent The CyPass Micro-Stent is a polyimide tube with a fenestrated lumen. The stent has a single piece design and is 0.25" (6.35 mm) long. The inner diameter of the stent is 0.012" (0.30 mm) and the outer diameter is 0.017" (0.43 mm). The CyPass Micro-Stent is designed for placement in the angle of the eye, with the proximal end extending from the angle into the anterior chamber (AC) and the distal end residing in the supraciliary space. When properly implanted, the CyPass Micro-Stent is intended to allow outflow of aqueous fluid from the AC, where the device proximal end resides, through and around the fenestrated lumen and distal end of the tube into the supraciliary and suprachoroidal space via the uveoscleral pathway.
Purpose and rationale	The purpose of this 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.
Objective(s)	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.
Endpoint(s)	Safety • 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/mm^2) • Assessment of stabilization of ECL • Corneal sequelae associated with ECL

	• Association between peripheral and central ECD count and number of observed rings • Secondary surgical interventional (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) $\geq$ 10 letters • Change in visual field mean deviation (MD) • Change in central corneal thickness [redacted]
Assessment(s)	Safety • Ocular medical history • Ocular surgical history • Ocular hypotensive medications • Monocular Best Corrected Distance Visual Acuity (BCDVA) via ETDRS • IOP • Pachymetry central corneal thickness (CCT) • Gonioscopy (with goniophotography) • Ultrasound biomicroscopy (UBM)/Optical coherence tomography (OCT; if available at the site) • Slit-lamp examination • Visual field

	• Fundus examination with C:D ratio • Specular microscopy (central and peripheral [nasal] endothelial cell density) • Ocular adverse events (these include but are not limited to corneal haze/edema, device malposition, device explantation, device trimming, device repositioning) occurring since exit visit from COMPASS or COMPASS XT (whichever was the last study visit) will be captured as ocular history
Study Design	Prospective; non-interventional, non-randomized; unmasked; observational; single-arm; total duration of subject's participation in the study is follow-up visits scheduled annually and an exit visit when the subject has reached 10 years post-CyPass implantation; duration of study is up to 4 years. 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] 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.
Subject population	Subjects who were implanted with a CyPass Micro-Stent in the COMPASS trial. Planned number of subjects enrolled/consented: Up to 374 (total number implanted with a CyPass Micro-Stent in the COMPASS trial) Planned number of completed subjects: Up to 374
Key inclusion criteria	• Any subject who was implanted with a CyPass Micro-Stent as a participant in the COMPASS trial.

(See Section 8.1 for a complete list of inclusion criteria)	• Able to understand the requirements of the study and willing to follow study instructions, provide written informed consent, and agree to comply with all study requirements, including the required study follow-up visits.
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	• Inability to comply with the protocol or required follow-up visit/procedures.
Data analysis and sample size justification	The analysis set for both the safety and effectiveness analyses will be the set of all enrolled subjects. No hypothesis testing is planned. All study endpoints will be described with summary statistical appropriate to scale. No missing data imputation is planned. 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. Sample size is based on the number of subjects who were implanted with a CyPass Micro-Stent in the COMPASS trial (374) and 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.
Key words	Prospective; non-interventional, observational, multi-center study; being conducted in the US only; up to 374 enrolled and up to 374 complete annual follow-up visits; 10 years post-CyPass implantation
Associated materials	N/A

Table 3–1 Schedule of Study Procedures and Assessments

Procedure	84-Month Visit (2555±120 days)[1]	96-Month Visit (2920±120 days)[1]	108-Month Visit (3285±120 days)[1]	120-Month Visit/ Exit Visit (3650±120* days)[1]
Informed Consent[2]	X	X	X	X
Demographics[2]	X	X	X	X
Inclusion/Exclusion[2]	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.

4 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be created by the Study Sponsor and must be approved by the IRB/IEC and global and regional Health Authorities, as applicable, prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent (re-consent), as required by the IRB/IEC.

5 INTRODUCTION

5.1 Rationale and Background

The COMPASS trial was a prospective, randomized, comparative multicenter study to assess the safety and effectiveness of the CyPass Micro-Stent in subjects with primary open angle glaucoma who were undergoing cataract surgery. In the study, a total of 505 subjects were randomized to one of two treatment groups, as follows: the CyPass group underwent cataract surgery and received the CyPass Micro-Stent, while the Control group underwent cataract surgery alone. All subjects randomized were followed for 24 months postoperatively, Vold 2016.

The study was performed in 2 phases. During the initial phase, 75 subjects were randomized. After FDA review of 3-month or longer postoperative data on these subjects, approval was granted for enrollment and randomization of the remaining 430 subjects in the study expanded phase. Enrollment in the initial study phase began in September 2009 and ended in August 2010. Enrollment in the expanded phase of the study began in July 2011 and the last study subject was randomized in March 2013.

The COMPASS XT trial was designed to collect safety data beyond 24 months postoperatively for subjects who completed the COMPASS trial until 60 months. Study enrollment was initiated April 2016 and the last subject visit occurred in April 2018, Ianchulev 2019, and Reiss 2019.

5.2 Purpose of the Study

The purpose of this 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.

At the end of the study, a clinical study report will be prepared in accordance with applicable regulatory requirements and standards.

Results of the study are intended for publication on the databases in which they are registered. Results may be offered for additional publication if they are of scientific interest.

5.3 Risks and Benefits

There may also be unknown risks to use of CyPass Micro-Stent. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, clinical oversight and monitoring.

Refer to the product label for additional information.

6 STUDY OBJECTIVES

6.1 Safety Objective(s)

Table 6–1 Safety Objective(s)

Objective(s)	**Endpoint(s)**
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	• 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, $\leq$ 1000 cells/mm^2) • Assessment of stabilization of ECL • Corneal sequelae associated with ECL • Association between peripheral and central ECD count and number of observed rings • Secondary surgical interventional (SSIs) to modify the device position (eg, repositioning, trimming, explantation) • 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) $\geq$ 10 letters • Change in visual field mean deviation (MD) • Change in central corneal thickness

[redacted]

7 INVESTIGATIONAL PLAN

7.1 Study Design

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.

7.2 Rationale for Study Design

This study is designed in accordance with Alcon's agreement with the United States Food and Drug Association (FDA) in order to evaluate the long-term safety of subjects who had been implanted with CyPass Micro-Stent.

7.2.1 Purpose and Timing of Interim Analyses and Resulting Design Adaptations

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.

7.3 Rationale for Duration of Treatment/Follow-Up

The follow-up period is aligned with Alcon's agreement with the United States FDA.

7.4 Rationale for Choice of Control Product

Not applicable.

7.5 Data Monitoring Committee

Not applicable.

7.6 Milestones

The study milestone timeline presented below is based upon the expectation that, following initiation of the first site, the remaining study sites will be activated at a rate of approximately 4 per month. The enrollment rate at activated sites will be approximately 4 subjects per month per site. Timelines for the activation of sites and subject enrollment will vary greatly due to the time that has elapsed since these subjects were observed in previous studies. Enrollment will continue throughout the study and new subjects will be enrolled up until the completion of the study. The IRB approval rate is expected to be 4 sites per month, until all sites are IRB-approved.

Table 7-1 Study Milestones

Key Milestone	**Target Date**
First Site Activated	May 2020
First Subject First Visit	May 2020
Last Subject First Visit	June 2021
Last Subject Last Visit	August 2023

Database Lock	September 2023
Submit PAS Final Report	December 2023

8 STUDY POPULATION

The study population consists of any subject who was implanted with a CyPass Micro-Stent as a participant in the COMPASS trial. It is aimed to enroll (consent) up to 374 subjects in up to 24 sites in the United States. Subjects who participated in the COMPASS trial will be enrolled for the duration of the study.

8.1 Inclusion Criteria

Written informed consent must be obtained before any study specific assessment is performed. Upon signing informed consent, the subject is considered enrolled in the study.

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Subject must be able to understand and sign an IRB/IEC approved Informed Consent form (ICF).
2. Any subject who was implanted with a CyPass Micro-Stent as a participant in the COMPASS trial.
3. Able to understand the requirements of the study, willing to follow study instructions, and agree to comply with all study requirements, including the required study follow-up visits.

8.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for participation in this study.

1. Inability to comply with the protocol or required follow-up visit/procedures.

8.3 Rescreening of Subjects

Due to the nature of the study, any subject implanted under the original COMPASS trial that presents for enrollment will be considered whether the subject has been previously screened for this protocol or not.

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s): CyPass Micro-Stent

Control Product(s) (If applicable): Not applicable

Table 9–1 Test Product

Test Product	CyPass Micro-Stent
Manufacturer	Alcon Vision, LLC 6201 South Freeway Fort Worth, Texas 76134-2099 USA
Indication for use and intended purpose in the current study	The CyPass system is indicated for use in conjunction with cataract surgery, or in a standalone procedure in pseudophakic subjects, for the reduction of IOP in adult subjects with mild to moderate POAG.
Product description and parameters available for this study	Test Product: CyPass Micro-Stent The CyPass system consists of the CyPass Micro-Stent, which is contained in a loading device (loader tip), and the CyPass applier. The CyPass Micro-Stent is a polyimide tube with a fenestrated lumen. The stent has a single piece design and is 0.25" (6.35 mm) long. The inner diameter of the stent is 0.012" (0.30 mm) and the outer diameter is 0.017" (0.43 mm). The CyPass Micro-Stent is designed for placement in the angle of the eye, with the proximal end extending from the angle into the AC and the distal end residing in the supraciliary space. When properly implanted, the CyPass Micro-Stent is intended to allow outflow of aqueous fluid from the AC, where the device proximal end resides, through and around the fenestrated lumen and distal end of the tube into the supraciliary and suprachoroidal space via the uveoscleral pathway.

	The CyPass applier is the hand-held surgical instrument used to implant the CyPass Micro-Stent. The applier consists of a medical-grade polymer handpiece with a guidewire assembly. The guidewire assembly includes a nitinol implant delivery guidewire extending from inside the handpiece through and beyond the distal end of a stainless steel tube (guidewire tube) that supports the guidewire. The guidewire is 0.011" (0.28 mm) in diameter and formed with a 0.48" (12 mm) radius of distal curvature and a blunt distal tip to facilitate location and blunt dissection of the plane between the ciliary body and sclera. The CyPass applier delivers the CyPass Micro-Stent to the desired location within the eye. Once the guidewire has positioned the CyPass Micro-Stent at the desired location within the eye, the implant is released from the guidewire using the front button on the CyPass applier. This action withdraws the guidewire back into the guidewire tube, leaving the CyPass Micro-Stent in position in the eye.
Formulation	N/A
Usage	N/A
Packaging description	N/A
Labeling description	N/A
Storage conditions	N/A
Supply	N/A

More information on the test product can be found in the CyPass Micro-Stent Package Insert.

9.2 Other Medical Device or Medication Specified for Use During the Study

No other medical devices or medications are required to be used in conjunction with the treatments during the clinical study.

9.3 Treatment Assignment / Randomization

In this non-interventional, observational follow-up study, there is no treatment assignment.

A subject will be assigned a subject number that will be captured in the electronic data capture system. The subject number will be linked to the subject number previously assigned under the COMPASS protocol. Subjects will not be randomized in this study.

9.4 Treatment masking

Not applicable.

9.5 Accountability Procedures

Not applicable.

9.6 Changes to Ocular Hypotensive Medications, Treatments/ Procedures

After the subject is enrolled into the study, the Investigator must instruct the subject to notify the study site about:

- Any new medications
- Alterations in dose or dose schedules for current medications,
- Any medical procedure or hospitalization that occurred or is planned
- Any non-drug therapies (including physical therapy and blood transfusions).

The Investigator must document this information in the subject's case history source documents.

10 STUDY PROCEDURES AND ASSESSMENTS

10.1 Informed Consent and Screening

The Investigator or delegate must explain the purpose and nature of the study, and have the subject read, sign, and date the IRB/IEC-approved informed consent document. The subject must sign the ICF BEFORE any study-specific procedures or assessments can be performed, including study-specific screening procedures. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the informed consent document.

The Investigator or delegate must provide a copy of the signed document to the subject and place the original signed document in the subject's chart, or provide documentation as required by local regulations.

Every effort should be made to locate the subjects who were implanted with a CyPass Micro-Stent in the COMPASS trial so that as much study information as possible may be obtained. The Investigator, or designee, must document at least 3 attempts to contact the subject within a reasonable timeframe to locate the subject.

10.2 Description of Study Procedures and Assessments

Detailed descriptions of assessments and procedures are provided in the MOP. The Investigator is responsible for ensuring responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

10.2.1 Demographics

Obtain demographic information including age, race, and sex at the first study visit.

10.2.2 Inclusion/Exclusion Criteria

Evaluate inclusion/exclusion criteria at the first study visit.

10.2.3 Ocular Medical History

Collect ocular medical history information. These may include but are not limited to corneal haze/edema and device malposition.

10.2.4 Ocular Surgical History

Collect ocular surgical history information. These may include but are not limited to device explantation, device trimming, and/or device repositioning.

[redacted]

10.2.6 Best Corrected Visual Acuity: Safety Assessment

Perform monocular BCVA testing using ETDRS for the study eye at all study visits (84-Month Visit [±120 days] to 120-Month Visit [±120 days]) prior to any assessment

requiring administration of eye drops to dilate the eyes, or any assessment requiring contact with the eye. This assessment must be performed study personnel who have successfully completed the training required to conduct the assessment.

[redacted]

10.2.8 Pachymetry CCT: Safety Assessment

Measure central corneal thickness for the study eye at all study visits (84-Month Visit [±120 days] to 120-Month Visit [±120 days]) using a standalone pachymeter or the Konan specular microscope.

10.2.9 Gonioscopy: Safety Assessment

Perform gonioscopy for the study eye at all study visits (84-Month Visit [±120 days] to 120-Month Visit [±120 days]) using a gonioprism and a slit-lamp microscope. Assess both Shaffer Grade in all four quadrants and the number of CyPass rings visible and document per PI judgement. Take gonio photographs to document CyPass position at all study visits (84-Month Visit [±120 days] to 120-Month Visit [±120 days]).

10.2.10 UBM/OCT: Safety Assessment

If available, perform imaging with UBM or OCT for the study eye at all study visits (84-Month Visit [±120 days] to 120-Month Visit [±120 days]). The same instrument should be used throughout the study.

10.2.11 Slit-Lamp Exam: Safety Assessment

SLE of the cornea, iris/anterior chamber and lens must be performed in the study eye before instillation of any diagnostic eye drops at every study visit (84 Month Visit [±120 days] to 120 Month Visit [±120 days]).

10.2.12 Visual Field

All visual fields will be obtained with a Humphrey automated perimeter using the 24-2 SITA standard testing method. The visual fields must be performed with a non-dilated pupil unless, in the opinion of the investigator, the pupil is so miotic that dilation is required (eg, < 3 mm). If dilation was performed at the first study visit's visual field examination(s), it should be performed at all subsequent visual field examinations for that subject.

10.2.13 Dilated Fundus Exam: Safety Assessment

Dilated fundus examination includes ophthalmoscopic assessments of the vitreous, retina, macula, choroid, and optic nerve of the study eye at all study visits (84-Month Visit [±120 days] to 120-Month Visit [±120 days]). The C:D ratio will be assessed on both the horizontal and vertical axis.

10.2.14 Specular Microscopy

Perform specular microscopy (central and peripheral ECD) for the study eye at all study visits (84-Month Visit [±120 days] to 120-Month Visit [±120 days]) using the Konan specular microscope. Details regarding imaging methods are contained in the MOP. Analysis will be conducted by a reading center per International Standard Organization (ISO) 11979-7(2018) recommendations.

10.2.15 Adverse Event Collection: Safety Assessment

Assess and record ocular adverse events that are observed or reported, including those associated with changes in concomitant medication dosing since the previous visit. Requirements for reporting adverse events in the study can be found in Section 11.

10.2.16 Device Deficiencies: Safety Assessment

Assess and record any Device Deficiencies that are reported or observed, including those associated with changes in concomitant medication dosing since the previous visit. Requirements for reporting device deficiencies in the study can be found in Section 11.

10.3 Unscheduled Visits

If a subject visit occurs between any regularly scheduled study visits, this visit must be documented as an Unscheduled Visit. During all unscheduled visits, the Investigator must conduct the following procedures:

- Collect ocular Adverse Event information
- Record changes in ocular hypotensive medication
- Follow standard of care procedures and document the results

The Investigator may perform additional procedures for proper diagnosis and treatment of the subject. The Investigator must document this information in the subject’s case history source documents.

If during an Unscheduled Visit the subject is discontinuing from the study, the Investigator must conduct Exit procedures according to Table 3–1 Schedule of Study Procedures and Assessments as possible.

10.4 Discontinued Subjects

10.4.1 Screen Failures

Not Applicable.

10.4.2 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the Investigator after any study-related ophthalmic assessments have been completed.

Subject numbers of discontinued subjects must not be re-used.

Subjects may discontinue from study at any time for any reason. Subjects may also be discontinued from the study at any time if, in the opinion of the Investigator, continuing the study assessments pose a risk to their health.

For subjects discontinuing from the study, the Investigator must complete all Exit procedures according to Table 3–1 Schedule of Study Procedures and Assessments and Section 10.4.3, if the subject is willing and able, and if in the opinion of the Investigator it is safe for the subject to do so.

The Investigator must document the reason for study or treatment discontinuation in the subject's case history source documents.

To ensure the safety of all subjects who discontinue early, Investigators must assess each subject and, if necessary, advise them of any therapies and/or medical procedures that may be needed to maintain their health.

10.4.3 Schedule of Procedures and Assessments for Subjects Discontinued from Investigational Product

Not applicable.

10.5 Clinical Study Termination

The Study Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time.

If the clinical study is prematurely terminated or suspended by the Study Sponsor:

- The Study Sponsor must:
    - Immediately notify the Investigator(s) and subsequently provide instructions for study termination.
    - Inform the Investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The Investigator must:
    - Promptly notify the IRB/IEC of the termination or suspension and of the reasons.
    - Provide subjects with recommendations for post-study treatment options as needed.

The Investigator may terminate the site's participation in the study for reasonable cause.

10.5.1 Follow-Up of Subjects after Study Participation Has Ended

Following this study, the subject will return to their eye care professional for their routine eye care.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device (test article). Refer to the Glossary of Terms for categories of AEs, ADEs, and SAEs.

Figure 11–1 Categorization of All Adverse Events

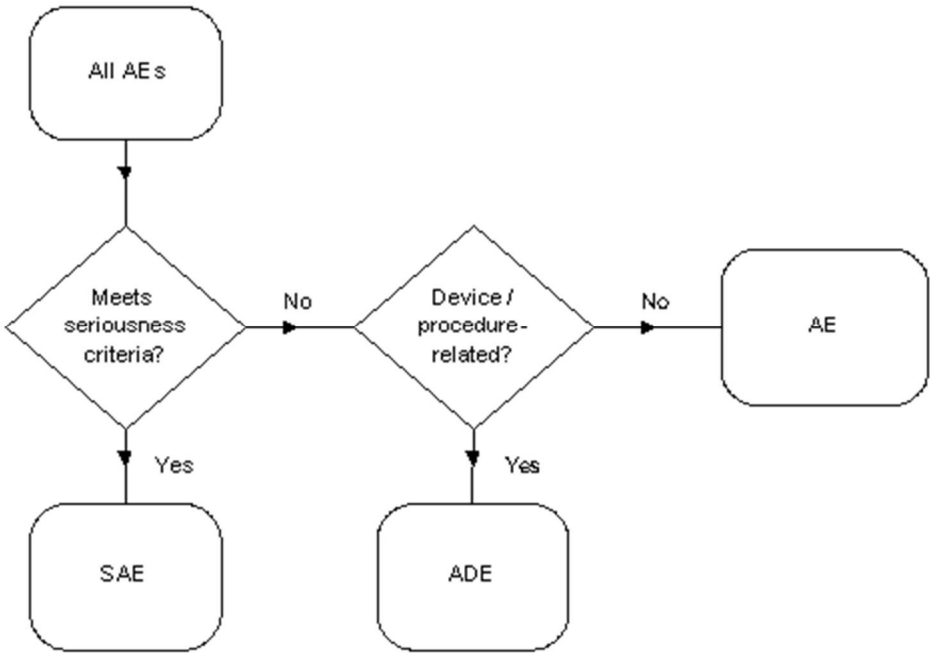
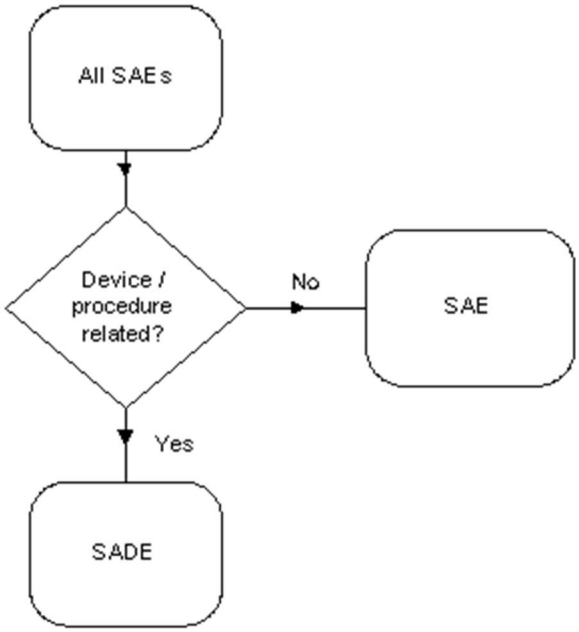


Figure 11-2 Categorization of All Serious Adverse Events



11.1.1 Postoperative Adverse Events

Anticipated postoperative AEs include, but are not limited to, the following complications.

a) BCDVA loss of 2 lines (10 letters) or more on the ETDRS chart in comparison with the best BCDVA reported in COMPASS/COMPASS XT

b) Persistent (at time of study exit) BCDVA loss of 3 or more lines compared to best BCDVA achieved during the course of study, including both the COMPASS trial, and the COMPASS XT trial

c) 2-point worsening to severe on the slit-lamp examination findings (other than cells and flare) not associated with a pre-existing condition

d) Endophthalmitis

e) Flat AC with lens cornea touch

f) Shallow AC with iridocorneal apposition

g) Shallow AC with peripheral iridocorneal apposition

h) Aqueous misdirection

i) Chronic iritis

j) Conjunctivitis

k) Keratitis

l) Corneal edema

m) Corneal opacification

n) Corneal decompensation

o) Hyphema (defined as persistent hyphema of > 2 mm)

p) Vitreous hemorrhage

q) Retinal detachment

r) Other retinal complications (eg, dialysis, flap tears, or proliferative vitreoretinopathy)

s) Increase in C:D ratio of ≥ 0.3 units on slit-lamp biomicroscopic examination

t) Confirmed worsening in the visual field mean deviation (MD) of ≥ 2.5 dB compared to the MD determined at the exit of the COMPASS trial or the COMPASS XT trial

u) Choroidal hemorrhage or choroidal effusion, defined as a choroidal effusion or detachment with at least a partially hemorrhagic component that obstructs vision or causes pain (including both peripheral and "kissing" choroidal detachments) lasting longer than 1 month

v) Peripheral anterior choroidal effusion

w) Maculopathy associated with hypotony

x) Maculopathy associated with cystoid edema

y) Hypotony (defined as IOP < 6 mmHg)

z) Clinically significant hypotony, defined as IOP < 6 mmHg with any of the following findings:

   i. Maculopathy

   ii. Flat AC chamber requiring reformation

   iii. Corneal folds

   iv. Worsening of with-the-rule astigmatism by ≥ 1 diopter, or rotation of against-the-rule astigmatism to ≥ 1 diopter of with-the-rule astigmatism

   v. Choroidal effusion requiring surgical drainage

   vi. Suprachoroidal hemorrhage

   vii. BCDVA loss of ≥ 2 lines from the best postoperative BCDVA

aa) Elevated mean IOP ≥ 10 mmHg than the qualifying baseline mean IOP at or after 1 month postoperative

bb) CyPass device obstructed by iris, vitreous, lens, fibrous overgrowth, fibrin, or blood

cc) CyPass device malposition – positioning after deployment such that there is a clinical sequelae resulting from device position including, but not limited to:

   i. Secondary surgical intervention to modify device position (eg, repositioning, proximal end trimming or explantation)

   ii. Corneal endothelial touch by device

   iii. Corneal edema leading to loss of BCDVA > 2 lines in comparison with preoperative BCDVA

iv. 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 6 Months

v. Erosion of device through sclera

vi. Device obstruction requiring secondary surgical intervention

dd) CyPass device dislodgement or movement, without sequelae, where device movement is defined as a change by at least 1 in the number of CyPass rings visible that is not attributable to variations in gonioscopic viewing angle or illumination, changes in angle anatomy due to concomitant findings such as resolution of hyphema, change in AC depth, or development of focal peripheral anterior synechiae

ee) CyPass device explantation associated with CyPass placement and stability

ff) CyPass device explantation NOT associated with CyPass placement and stability

gg) Unplanned ocular surgical reintervention associated with CyPass placement and stability

hh) Unplanned ocular surgical reintervention NOT associated with CyPass placement and stability (other than posterior capsulotomy)

ii) Significant ptosis

jj) Atrophy/phthisis

kk) Wound dehiscence/leak (persistent aqueous leak or fistula formation)

ll) Subconjunctival hemorrhage

mm) Chronic pain in the study eye

nn) Significant foreign body sensation

oo) IOL subluxation

11.1.2 Sight Threatening Adverse Events

Of the postoperative AEs listed in Section 11.1.1, the following are pre-defined as sight threatening and must therefore be reported as SAEs per the guidelines for reporting in Section 11.3:

- 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

Other AEs may also be considered potentially sight threatening, or may meet other seriousness criteria. Any AE meeting any SAE seriousness criterion, as defined in the Glossary of Terms, must be reported as an SAE per Section 11.3.

11.1.3 Device Deficiencies

A device deficiency includes malfunctions, use errors, and inadequate labeling and may or may not be associated with subject harm (ie, ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The Investigator should determine the applicable category for the identified or suspect device deficiency and report any subject harm separately. Any AE resulting from device deficiencies including device malfunction will be captured and reported in the case report form. Only AEs related to the device will also be captured as an ADE on a separate case report form. Examples of device deficiencies include, but are not limited to the following:

- CyPass Micro-Stent issues
    - CyPass Micro-Stent damage
    - Defective CyPass Micro-Stent surface or interior lumen
- Other device issues

11.2 Monitoring of Ocular Adverse Events

At each visit, the Investigator should inquire about any ocular AEs occurring since the last study visit.

- “Have you had any health problems since your last study visit?”
- “Have there been any changes in the medicines you take since your last study visit?”

11.3 Procedures for Recording and Reporting

Any ocular AEs occurring since the Exit visit from the COMPASS trial or the COMPASS XT trial (whichever was the last study visit) will be collected from the time of informed consent. Any pre-existing medical conditions or signs/symptoms present in the subject in the COMPASS trial or COMPASS XT trial are not considered AEs in the study and should be recorded in the Medical History section of the eCRF. However, a worsening of the pre-existing ocular AEs are considered AEs.

For each recorded event, the ADEs and SAEs documentation must include: date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the Investigator must document all device deficiencies reported or observed with test and control articles on the Device Deficiency eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the Study Sponsor immediately as follows:

- All SAEs must be reported immediately (within 24 hours) of the Investigator's or site's awareness.
- ADEs that do not meet seriousness criteria and device deficiencies must be reported within 10 calendar days of the Investigator's or site's awareness.

A printed copy of the completed *Serious Adverse Event and Adverse Device Effect* and/or *Device Deficiency* eCRF must be included with product returns.

- Additional relevant information after initial reporting must be entered into the eCRF as soon as the data become available.
- Document any changes to concomitant medications on the appropriate eCRFs.
- Document all relevant information from Discharge Summary, Autopsy Report, Certificate of Death etc., if applicable, in narrative section of the *Serious Adverse Event and Adverse Device Effect* eCRF.

  Note: Should the EDC system become non-operational, the site must complete the appropriate paper *Serious Adverse Event and Adverse Device Effect* and/or *Device Deficiency* Form. The completed form is emailed to the Study Sponsor at msus.safety@alcon365.com according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

Any AEs and device deficiencies for non-study marketed devices/products will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

Study Sponsor representatives may be contacted for any protocol related question and their contact information is provided in the Manual of Procedures that accompanies this protocol.

Further, depending upon the nature of the AE or device deficiency being reported, the Study Sponsor may request copies of applicable portions of the subject's medical records. The Investigator must also report all AEs and device deficiencies that could have led to a SADE according to the requirements of regulatory authorities or IRB/IEC.

11.3.1 Intensity and Causality Assessments

Where appropriate, the Investigator must assess the intensity (severity) of the AE based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild	An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.
Moderate	An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

For every AE in the study, the Investigator must assess the causality (Related or Not Related to the medical device or study procedure). An assessment of causality will also be performed by Study Sponsor utilizing the same definitions, as shown below:

Causality

Related	An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.
Not Related	An AE classified as not related may either be definitely unrelated or simply unlikely to be related (ie, there are other more likely causes for the AE).

The Study Sponsor will assess the AEs and may upgrade the Investigator's assessment of seriousness and/or causality. The Study Sponsor will notify the Investigator of any AEs that is upgraded from non-serious to serious or from unrelated to related.

11.4 Return Product Analysis

Study Sponsor representatives and their contact information are provided in the MOP that accompanies this protocol.

Alcon products associated with device deficiencies and/or product related AEs should be returned and must include the Complaint #, which will be provided by Study Sponsor after the case is entered in the Study Sponsor's Global Product Complain Management System (GPCMS).

11.5 Unmasking of the Study Information

Not applicable; this study is an unmasked, observational, single-arm study.

11.6 Follow-up of Subjects with Adverse Events

The Investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study.

The Investigator should provide the Study Sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the device. For AEs that are unresolved/ ongoing at time of subject exit from study, any additional information received at follow-up should be documented in the eCRFs up to study completion (ie, database lock).

All complaints received after this time period will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements.

11.7 Pregnancy in the Clinical Study

Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case-by-case basis. An Alcon form will be utilized to capture all pregnancy-related information until birth of the child.

12 ANALYSIS PLAN

12.1 Subject Evaluability

Final subject evaluability must be determined prior to locking the database, based upon the Deviations and Evaluability Plan.

12.2 Analysis Sets

12.2.1 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.

12.3 Demographic and Baseline Characteristics

Demographic characteristics will be summarized overall. Counts and percentages will be presented for categorical variables such as sex, age and race. Baseline ECD will be summarized overall. Study eye will be tabulated.

12.4 Safety Analyses

The primary 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.

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, $\leq$ 1000 cells/mm^2)
- 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

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.

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.

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

12.4.1.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.1.2 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.

12.4.2 Rate of Occurrence of Ocular AEs

12.4.2.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.2.2 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.

12.4.3 Central and Peripheral (Nasal) ECD Measurements

12.4.3.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.3.2 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 mean 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}.

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

12.4.4.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.4.2 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 endothelial cell density less than 1000 cells/mm², the proportion of subjects with central endothelial cell density less than 500 cells/mm^2, the proportion of subjects with peripheral endothelial cell density less than 500 cells/mm², 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},

95th, and 100th. 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.

12.4.5 Assessment of Stabilization of ECL

12.4.5.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.5.2 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.

12.4.6 Corneal Sequelae Associated with ECL

12.4.6.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.6.2 Analysis Methods

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

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

12.4.7.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.7.2 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.

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

12.4.8.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.8.2 Analysis Methods

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

12.4.9 Effects of SSIs on Central and Peripheral ECD

12.4.9.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.9.2 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.

12.4.10 CyPass Micro-Stent Movement and/or Malposition

12.4.10.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.10.2 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.

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

12.4.11.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.11.2 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.

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

12.4.12.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.12.2 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.

12.4.13 Change in Visual Field Mean Deviation (MD)

12.4.13.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.13.2 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.

12.4.14 Change in Central Corneal Thickness

12.4.14.1 Statistical Hypotheses

No hypothesis testing of the endpoint is planned.

12.4.14.2 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.

12.4.16 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: 0^{th}, 5^{th}, 25^{th}, 75^{th}, 95^{th}, and 100^{th}.

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: 0^{th}, 5^{th}, 25^{th}, 75^{th}, 95^{th}, and 100^{th}.

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: 0^{th}, 5^{th}, 25^{th}, 75^{th}, 95^{th}, and 100^{th}.

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

[redacted]

12.6 Interim Analyses and Reporting

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.

12.7 Handling of Missing Data

Missing data imputation will not be performed.

12.8 Sample Size Justification

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.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. At the end of the clinical study, the Study Sponsor will collect a copy of the enrollment log ***without any identifying subject information***. All documents submitted to the Study Sponsor will identify the subjects exclusively by number and demographic information. No other personally identifying information will be transmitted to the Study Sponsor.

The Study Sponsor may release anonymized study data to external researchers for purposes of future research directly related to the study objectives, or future research that is beyond the scope of the current study objectives. The Informed Consent Form explains this to study subjects. Anonymization means that all identifiable information will be removed from the dataset and all links to the subjects in the study will be removed. Anonymization of the data will maintain confidentiality of the subjects who participate in the study so that they cannot be identified by external researchers. The anonymized data set will contain records from all of the subjects in the current study, but the anonymization process might change the data set in some ways, so external researchers will be informed that they might not be able to duplicate some of the results from this study.

13.2 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor, and all discrepancies shall be appropriately documented via the query resolution process. Site monitors are appointed by the Study Sponsor and are independent of study site staff.

If electronic records are maintained, the method of verification must be determined in advance of starting the study.

At a minimum, source documents include the following information for each subject:

- Subject identification (name, sex, race/ethnicity)
- Documentation of subject eligibility
- Date of informed consent
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- IP accountability records (if applicable)
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

Only designated individuals at the site will complete the CRFs. The CRFs must be completed at regular intervals following the clinical study visit schedule. It is expected that all data reported have corresponding entries in the source documents. The Principal Investigator is responsible for reviewing and certifying that the CRFs are accurate and complete. The only subject identifiers recorded on the CRFs will be subject number, and subject demographic information.

13.3 Data Review and Clarifications

A review of CRF data to the subject's source data will be completed by the site monitor to ensure completeness and accuracy. After the CRFs have been completed, additional data clarifications and/or additions may be needed as a result of the data cleaning process. Data clarifications are documented and are part of each subject's CRF.

13.4 Sponsor and Monitoring Responsibilities

The Study Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals according to the study monitoring plan. The clinical investigation will be monitored to ensure that the rights and well-being of the subjects are protected, the reported data are accurate, complete, and verifiable from the source documents, and the study is conducted in compliance with the current approved protocol (and amendments[s], if applicable), with current GCP, and with applicable regulatory requirements.

The site may not screen subjects or perform the informed consent process on any subject until it receives a notification from an appropriate Study Sponsor representative that the site may commence conducting study activities. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and fax correspondence. Close-out visits will take place after the last visit of the last subject at the site.

A Coordinating Investigator may be identified by the Study Sponsor to review and endorse the final study report. In cases where a Coordinating Investigator is engaged, the Study Sponsor will select the Coordinating Investigator based upon their experience, qualifications, active study participation, and their willingness and availability to take on this role.

13.5 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Study Sponsor and the Investigator’s files will be reviewed as part of the ongoing study monitoring. Financial information is to be kept separately.

Additionally, the Investigator must keep study records and source documents consistent with the terms of the clinical study agreement with the Study Sponsor. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, then the Study Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations.

13.6 Quality Assurance and Quality Control

The Study Sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Study Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all

data are reliable and have been processed correctly. Agreements made by the Study Sponsor with the Investigator/Institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

This clinical study must be conducted in accordance with the ethical principles contained within:

- The Declaration of Helsinki, and in compliance with the ICH E6 GCP Consolidated Guideline, ISO 14155:2011, and the applicable US FDA 21 CFR Regulations.
- SOPs of the Study Sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations.
- Notifications and timelines for reporting protocol deviations should be based upon applicable Ethics Committee requirements

The Investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The Investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. Deviations from this protocol, regulatory requirements and/or GCP must be recorded and reported to the Sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol, the informed consent form, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an IRB/IEC. The Investigator must provide documentation of the IRB/IEC approval to the Study Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IRB/IEC must be provided with a copy of the Package Insert, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the study, the Investigator must notify the IRB/IEC about the study's completion. The IRB/IEC also must be notified if the study is terminated prematurely. Finally, the Investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

Voluntary informed consent must be obtained in writing from every subject and the process shall be documented before any procedure specific to the clinical investigation is applied to

the subject. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or their delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the IP and the study, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and must be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also must be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent (file in subject's medical records) and must provide a duplicate copy to each subject according to local regulations.

The Study Sponsor assures that the key design elements of this protocol will be registered on www.clinicaltrials.gov as required by current regulations and, if applicable, other public databases as required by local country regulations. In addition, results of this study will be made publicly available on www.clinicaltrials.gov regardless of outcome as required by current regulations and, if applicable, in other public databases as required by local country regulations.

15 REFERENCES

15.1 References Applicable for All Clinical Studies

- ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice

15.1.1 US References Applicable for Clinical Studies

- 21 CFR Part 11 - Electronic Records; Electronic Signatures
- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 812 - Investigational Device Exemptions
- 21 CFR Part 54 - Financial Disclosure by Clinical Investigators

- The California Bill of Rights

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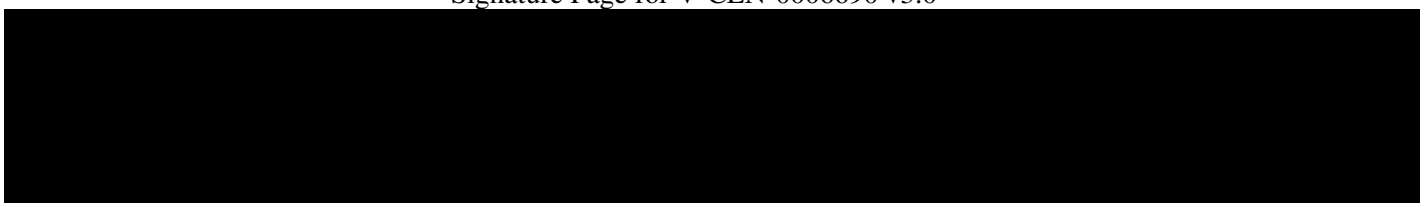

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