Alcon®

[redacted]

Clinical Trial Protocol

Post Approval Study of the CyPass System in Patients with Primary Open Angle Glaucoma Undergoing Cataract Surgery

Protocol Number:	GLD122c-C001 / NCT03273907
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
[redacted]	[redacted]
Test Article(s) / Product(s):	CyPass System (Model 241-S) consisting of the CyPass Micro-Stent contained in a loading device (loader) and the CyPass applier
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), ISO 14155-2011, the ethical principles within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Sponsor.

Principal Investigator:

Signature Date

Name and Investigator Number:

Address:

Telephone:

Release Date: Refer to e-signature date

1 PROTOCOL SYNOPSIS

[redacted]

Test Article(s) / Product(s):	CyPass System (Model 241-S) consisting of the CyPass Micro-Stent contained in a loading device (loader) and the CyPass applier	
Objective(s):	To demonstrate that the rate of clinically relevant complications associated with CyPass Micro-Stent placement and stability using the CyPass 241-S applier, as determined at 36 months in the post-market setting, is less than the pre-specified performance target, which is based on experience with the CyPass Model E applier in the COMPASS (TMI-09-01) Trial.	
Clinical Trial Design:	This is a prospective, multi-center, non-randomized, single-arm, safety and effectiveness clinical trial.	
No. of Subjects:	It is estimated that 640 subjects will be enrolled. Of these, it is estimated that 450 subjects will be successfully screened and implanted (30% screen failure rate). Of these, it is estimated that 360 subjects will complete the study and provide 36-month data for statistical analyses (20% attrition rate).	
Region(s):	US	
Clinical Trial Duration:	a) The total expected duration of the clinical study is 60 months. b) Each subject's expected participation in the study is up to 37.5 months which includes up to 42 days between the screening and surgery visits, and 36 months of post-surgery follow-up. c) A 22-month enrollment period is expected.	
Clinical Trial Population:	Adults with Primary Open Angle Glaucoma (POAG) undergoing cataract surgery	
Treatments:	***Test Article***:	CyPass Micro-Stent implanted with CyPass 241-S applier
	Administration:	The CyPass Micro-Stent is placed in the angle of the eye, with the proximal end extending from the angle into the anterior chamber (AC) and distal end residing in the supraciliary space.

	Quantity/Dosage:	Implantation of one CyPass Micro-Stent in one eye per subject
	Duration of Treatment:	The CyPass Micro-Stent is an implantable medical device and is intended for long term use.
	Control Article:	Not applicable
	Administration:	Not applicable
	Quantity/Dosage	Not applicable
	Duration of Treatment:	Not applicable
Inclusion Criteria (ocular criteria apply to the study eye only):	1. Adults, 45 years of age or older at the time of surgery 2. 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 3. Diagnosis of primary open angle glaucoma (POAG) [redacted] 4. **Medicated** IOP of ≥10 mmHg and ≤25 mmHg, or an **unmedicated** IOP of ≥21 mmHg and ≤33 mmHg (refer to Section 9.8 Ocular Hypotensive Medications at Screening, for definitions of 'medicated' and 'unmedicated') [redacted] 7. An operable age-related cataract with BCDVA of 0.3 logMAR or worse (≤85 letters read), eligible for phacoemulsification. If the	

	BCDVA is better than 0.3 logMAR (>85 letters read), testing with a Brightness Acuity Meter (BAT) on a medium setting must result in a BCDVA of 0.3 logMAR or worse (≤85 letters read).
Intraoperative Inclusion Criteria (ocular criteria apply to the study eye only):	[redacted]
Exclusion Criteria (ocular criteria apply to the study eye only, unless otherwise stated):	1. Inability to complete a reliable 24-2 SITA Standard Humphrey visual field before surgery (Visit 00) [redacted] 2. Use of more than 3 topical ocular hypotensive medications (combination medications count as 2 medications) 3. Use of oral ocular hypotensive medication treatment [redacted] 5. Diagnosis of acute angle closure, traumatic, congenital, malignant, uveitic, pseudoexfoliative, pigmentary, or neovascular glaucoma [redacted] 7. Proliferative diabetic retinopathy [redacted] 11. Previous corneal surgery (incisional correction of astigmatism

	may be performed concurrent with cataract surgery and CyPass implantation) 12. Wet age-related macular degeneration [redacted] 14. BCDVA of logMAR 1.0 or worse (≤50 letters read) in the fellow eye not due to cataract [redacted] 16. Uncontrolled systemic disease that in the opinion of the investigator would put the subject's health at risk and/or prevent the subject from completing all study visits [redacted] [redacted] 19. Women who are pregnant or nursing
Effectiveness Assessments	IOP
	Number of ocular hypotensive medications
Safety Assessments	BCDVA (logMAR with manifest refraction)
	Specular microscopy
	Visual field mean deviation
	Slit lamp examination
	Gonioscopy (with goniophotography)
	Fundus examination
	Central corneal pachymetry
	UBM or OCT (if needed)
	Adverse events
	Device deficiencies
Other Assessments	Not Applicable

Primary Endpoint	The primary endpoint is the rate of clinically relevant complications associated with CyPass Micro-Stent (CyPass) placement and stability as determined at 36 months. Specific device-related complications include: ≠ Failure to implant the CyPass, defined as inability to successfully deploy or insert the CyPass. ≠ Clinically significant CyPass malposition, defined as CyPass positioning after deployment such that: o The device is not in the supraciliary space, or o There is a clinical sequela resulting from device position including, but not limited to: ▪ Secondary surgical intervention to modify device position (eg, repositioning, proximal end trimming or explantation) ▪ Corneal endothelial touch by device ▪ Corneal edema leading to loss of BCDVA >2 lines at the last postoperative visit, in comparison with preoperative BCDVA ▪ Progressive endothelial cell loss (ECL), defined as ongoing reduction in endothelial cell count of 30% or more relative to the screening ECD value, where 'ongoing reduction in endothelial cell count' is defined as losses continuing after Visit 5 (6 Month Follow-up) ▪ Erosion of device through sclera ▪ Device obstruction requiring secondary surgical intervention.

Primary Analysis	The primary null hypothesis to be tested is that the observed rate of clinically relevant complications associated with CyPass Micro-Stent placement and stability is greater than or equal to the performance target (7.0%). The corresponding alternative hypothesis to be tested is that the observed rate of complications is less than the performance target. These hypotheses are expressed formulaically as: $H_0: p_C \geq 7\%$ $H_1: p_C < 7\%$ where p_C is the population proportion of eyes experiencing a complication event at 36 months. The primary safety hypothesis will be tested with an exact one-sided binomial test with type I error 0.05.
Sample Size Justification	The performance target for the primary endpoint is 7.0%. Based on an evaluation of COMPASS (TMI-09-01) data, the "true" event rate is assumed to be 4.0%, and the performance target is set to 7.0%. The following assumptions are used for the sample size calculation: ≠ Type I error = 0.05 ≠ One-sided alternative With a sample size of 360 subjects in the final analysis (unilateral implants only) and a performance target of 7.0%, assuming a true event rate of 4.0%, there is 80% power to reject the null hypothesis based on a one-sided 0.05-level exact test for a single proportion. To allow for attrition over this 36-month study, a cumulative rate of up to 20% of subjects lost to follow-up is assumed, corresponding to a targeted implantation of 450 eyes in 450 subjects to achieve at least 360 eyes with 36 months of follow-up.

Sample Size Justification *(cont.)*	Annex F of ANSI standard Z80.27-2014 refers to ensuring adequate sample size so that any adverse event of a given type that occurs in the population at a rate of 1% or greater is likely to be seen in the study. With 360 subjects, there is at least 97% probability that at least 1 adverse event will be detected, assuming a true rate of 1.0%. There is at least 95% probability if the true rate is 0.83%.
Interim Reports	Interim reports pertaining to the progress of the post-approval study will be submitted to the FDA for review every 6 months for the first two years, starting from the date of approval, and will continue to be submitted annually thereafter, until study completion.

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3 ABBREVIATIONS

Abbreviation	Definition
AC	Anterior chamber
ADE	Adverse device effect
AE	Adverse event
ANSI	American National Standards Institute
ASADE	Anticipated serious adverse device effect
BAT	Brightness acuity meter
BCDVA	Best corrected distance visual acuity
BID	Bis in die (two times a day)
C:D	Cup to disc (ratio)
CDE	Cumulative dissipated energy
CFR	Code of Federal Regulations
CJD	Creutzfeldt-Jacob disease
CRF	Case report form
CS	Clinically significant
CTM	Clinical trial management
CyPass	CyPass Micro-Stent
dB	Decibel
ECD	Endothelial cell density
ECL	Endothelial cell loss
EDC	Electronic data capture
EMR	Electronic medical record
EPT	Effective phacoemulsification time
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	US Food and Drug Administration
FL	Fixation losses
FP	False positive
GCP	Good Clinical Practice
GPCMS	Global Product Complaint Management System
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
I/A	Irrigation/aspiration
IB	Investigator brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFU	Instructions for use
IRB	Institutional review board
IOL	Intraocular lens
IOP	Intraocular pressure
ISO	International Organization for Standardization
ITT	Intention to treat
LCSM	Lead clinical site manager

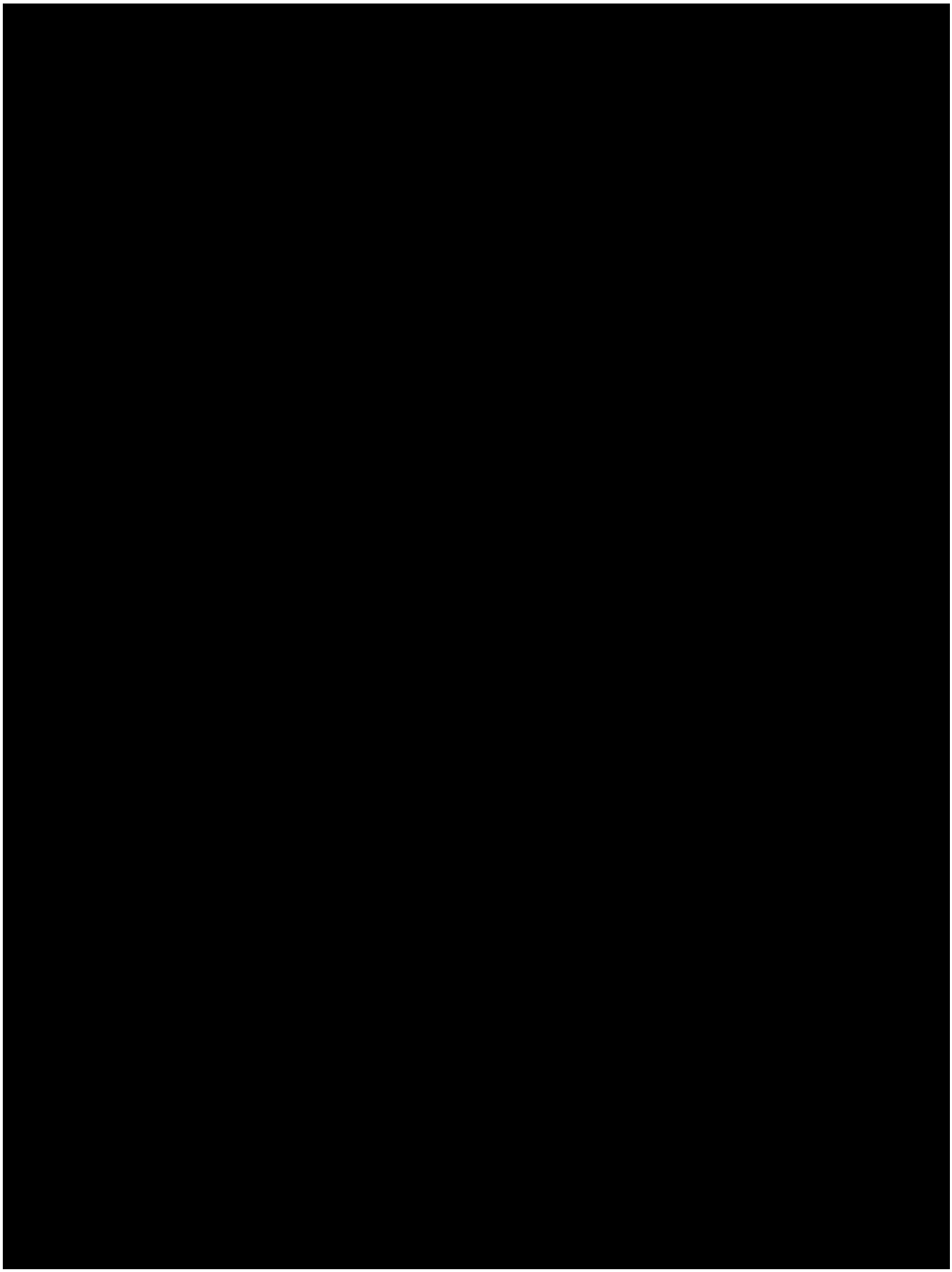
logMAR	Logarithm of the Minimum Angle of Resolution
MD	Mean deviation
MedDRA®	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of mercury
MOP	Manual of procedures
NSAID	Non-steroidal anti-inflammatory drug
NCS	Not clinically significant
OCT	Optical coherence tomography
OVD	Ophthalmic viscoelastic device
PAS	Post approval study
POAG	Primary open angle glaucoma
PP	Per protocol
QID	Quater in die (four times a day)
SAE	Serious adverse event
SAS®	Statistical analysis software, SAS Institute Inc., Cary, NC
SITA	Swedish Interactive Thresholding Algorithm
SOP	Standard operating procedure
SSI	Secondary surgical intervention
TID	Ter in die (three times a day)
UBM	Ultrasound biomicroscopy
USV	Unscheduled visit
WHO	World Health Organization

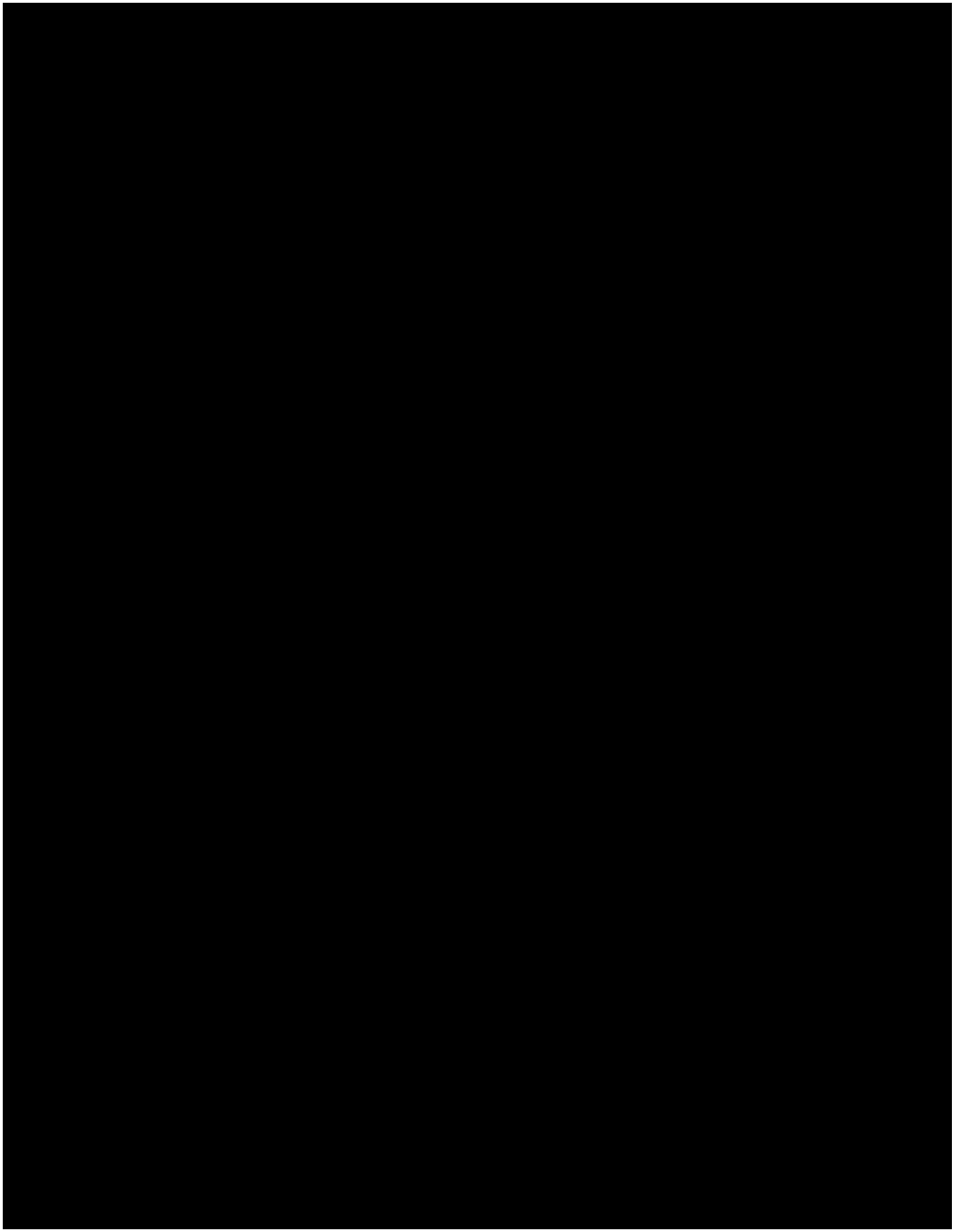
4 GLOSSARY OF TERMS

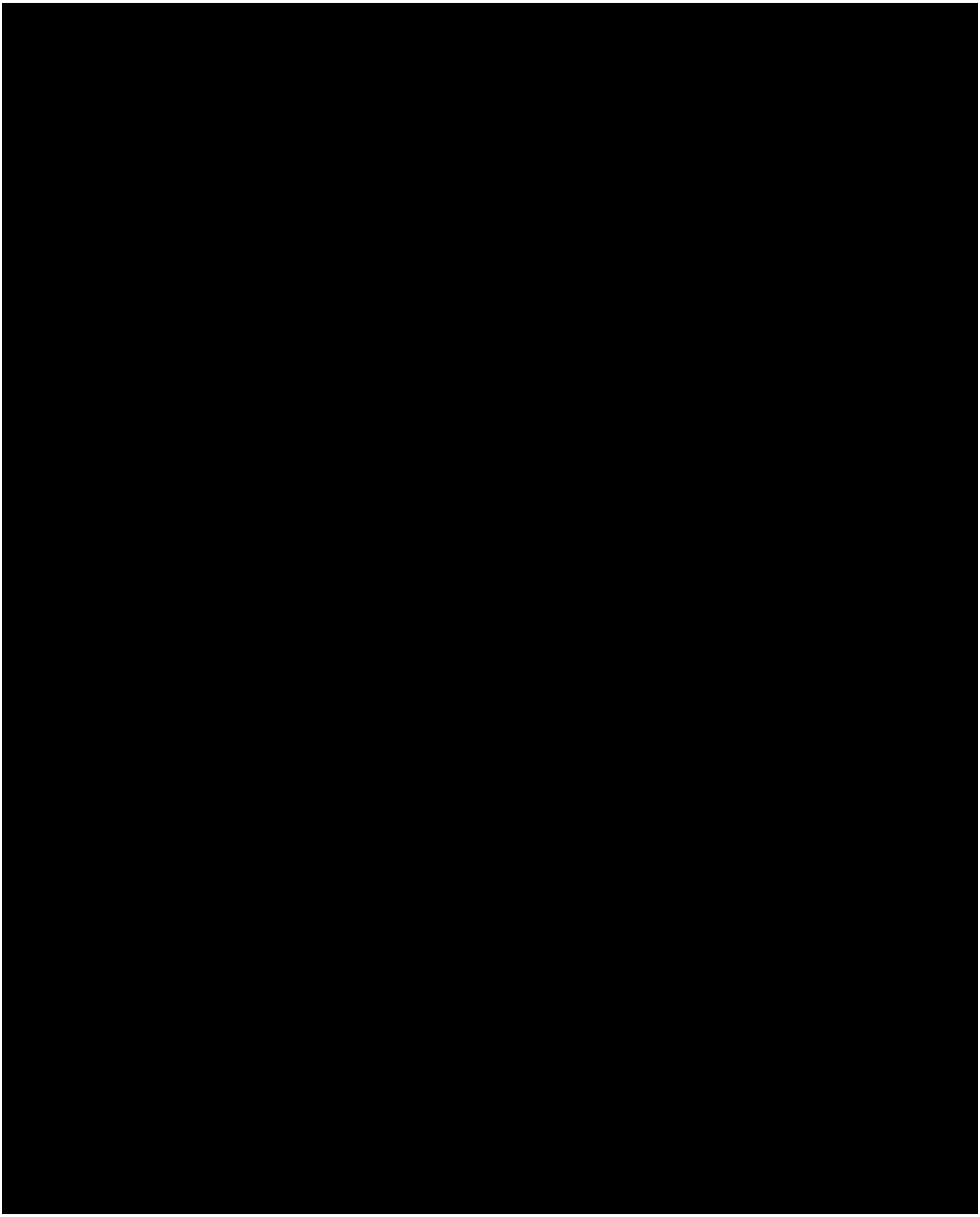
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (test article) or control article. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the investigational medical device or comparator, if applicable.*
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 article). *Note: For subjects, this definition includes events related to the test article, the control article, or the procedures involved. For users or other persons, this definition is restricted to events related to the test article.*
Anticipated Serious Adverse Device Effect (ASADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the risk management file.
Assessment	A procedure used to generate data required by the study.
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.*
Malfunction	Failure of a medical device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of the device refers to the intended use for which the device is labeled or marketed.
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Product Complaint	Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling or packaging to meet specifications, whether or not the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.

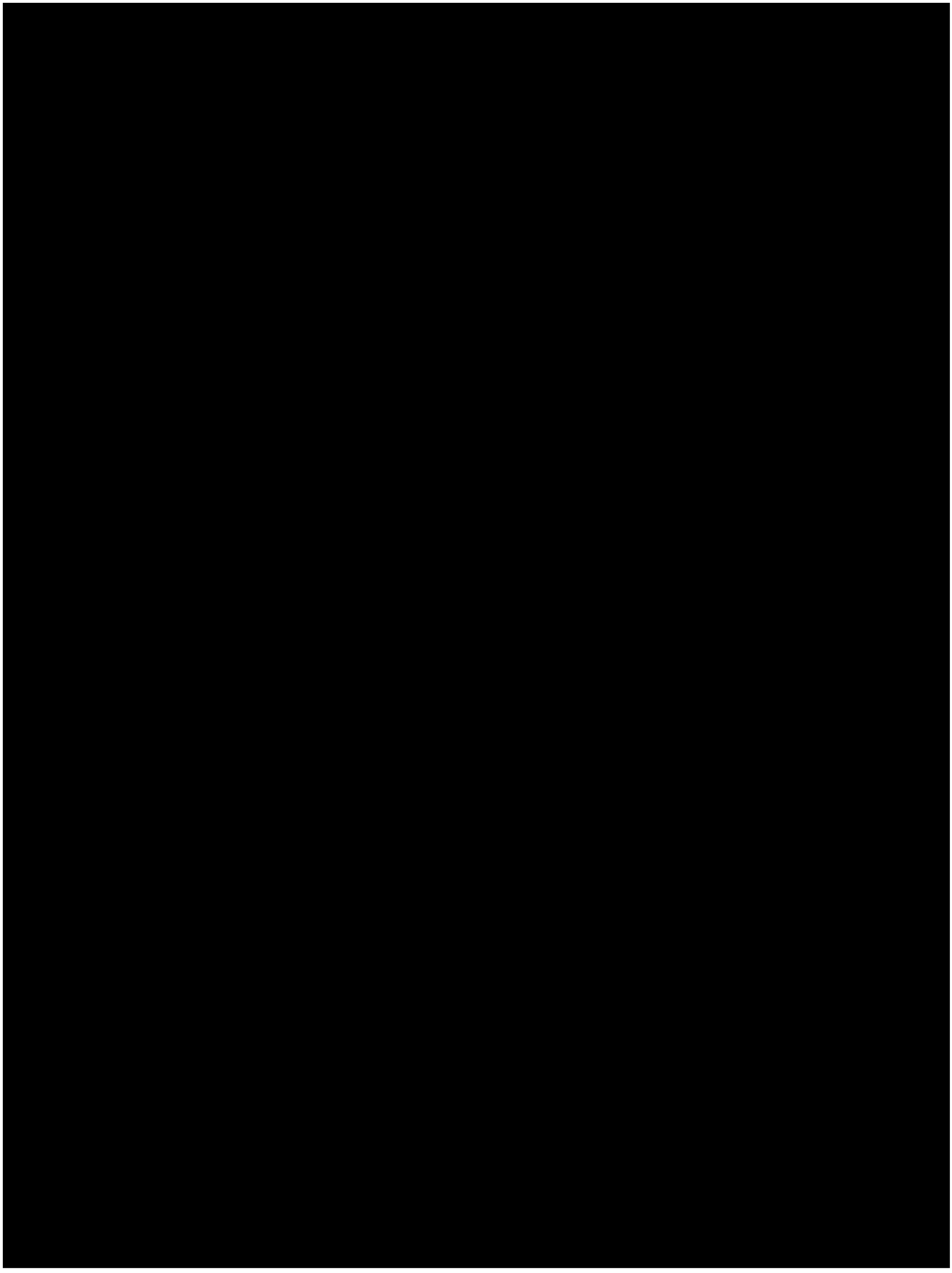
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: ≠ Death. ≠ A serious deterioration in the health of the subject that either resulted 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, or a procedure required by the clinical investigation plan, 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 AEs. 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 list of pre-defined AEs in Section 13.
Serious Public Health Threat	Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: Events that are of significant and unexpected nature such that they become alarming as a potential

	public health hazard, eg, human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD).
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis.
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.*









6 SCHEDULE OF VISITS

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

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

[2] In women of child bearing potential only.

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

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

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

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

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

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

7 INTRODUCTION

7.1 Background

Note: A summary of known and potential risks and benefits to humans, as identified in the literature or through preclinical testing and/or prior clinical evaluations, for the investigational product can be found in the Instructions for Use for the CyPass System.

As described in the American Academy of Ophthalmology Preferred Practice Pattern, POAG represents a significant public health problem. In the United States, the overall prevalence of open-angle glaucoma for adults 40 years old and older is estimated to be 1.86% (Friedman 2004). Open-angle glaucoma (not including the major forms of secondary open-angle glaucoma, pseudoexfoliation glaucoma and pigmentary glaucoma) affects an estimated 2.22 million people in the United States, and that number will increase to 3.3 million in 2020 as the population ages (Friedman 2004). Based on data extrapolated from the Baltimore Eye Survey, about half of those with glaucoma may be unaware that they have the disease (Tielsch 1991, Quigley 1997). In the United States, more than 7 million office visits occur per year for the primary purpose of monitoring patients with glaucoma and patients at risk for developing glaucoma (Javitt 1993, Schappert 1995). Glaucoma of all types is one of the leading causes of legal blindness in the United States (Congdon 2004, Sommer 1991, POAG Preferred Practice Patterns 2008). The findings of epidemiological investigations and risk factor analyses provide a framework for considering the cause and management of POAG. There are five important risk factors associated with glaucomatous optic neuropathy:

1. Elevated IOP
2. Older age
3. Family history of glaucoma
4. African or Hispanic/Latino descent
5. Thinner central corneal thickness

While the relationship between IOP and loss of vision is fundamental to all current therapy for open-angle glaucoma, there are several other factors (eg, blood supply to the optic nerve, substances toxic to the optic nerve or retina, axonal or ganglion cell metabolism, and the lamina cribosa extracellular matrix) that may play a role in the progressive loss of vision due to glaucoma. Because elevated IOP is a treatable cause of glaucomatous optic nerve damage, one can expect to inhibit progression of glaucomatous optic neuropathy in many patients by lowering the IOP by means of medication, laser, filtering, implantation of aqueous drainage device, or cyclodestructive surgery. Results from randomized controlled trials and other studies reinforce this expectation and provide evidence that the more the IOP is lowered, the

more likely it is that progressive loss of vision will be halted (Jay 1989, Migdal 1994, GLT 2 1990, GLT and GLT Follow-up Study 1995, Kass 2002, Gordon 1999, Collaborative Normal-Tension Glaucoma Study Group 1998, Heijl 2002, Leske 2003, Lichter 2001, AGIS 13 2004, EGPS 2005, EGPS 2002).

Medical and surgical therapies to treat elevated IOP are directed towards either reducing the rate of aqueous production, increasing the rate of aqueous outflow through the normal outflow channels, or a combination of both. For example, laser treatment of the trabecular meshwork works by increasing outflow. Surgical interventions are directed almost exclusively at increasing outflow, by creating an alternate or improved pathway to Schlemm's canal or by directing aqueous outflow to alternative drainage sites outside of the interior of the eye.

While filtering surgery such as trabeculectomy and implantation of an aqueous shunt to external reservoir directs aqueous outflow via drainage sites outside of the interior of the eye, there are significant risks of complication associated with this approach, including hypotony, infection, bleb fibrosis and erosion. Nevertheless, filtering surgery does provide an alternative path for the escape of aqueous humor and often reduces IOP and the need for medical treatment. The best estimate of the failure rate of filtering surgery alone or combined with medical therapy in a previously unoperated eye comes from the Advanced Glaucoma Intervention Study (AGIS 13 2004). The 10-year results indicate about 30% failure in African American patients and 20% failure in Caucasian American patients. While long-term control is often achieved, many patients will require further therapy or a re-operation, which carries a higher failure rate (Lichter 2001). Furthermore, filtering surgery increases the likelihood that phakic eyes will undergo cataract surgery. These limitations of filtering surgery have led to interest in devices which employ alternative approaches to increasing aqueous outflow, such as the CyPass Implant.

The CyPass Implant is a surgically implantable micro-device composed of the same polyimide material currently used for conventional intraocular lens haptics. This implant is inserted into the eye in the same general location as the tubes of conventional aqueous shunts. However, instead of shunting aqueous fluid to an external polymer plate, the CyPass Implant redirects aqueous fluid into the supraciliary space and the suprachoroidal space.

The supraciliary space, which is continuous with the suprachoroidal space, has a negative hydrostatic fluid pressure relative to the anterior chamber (Jordan 2007, Ozdamar 2003). When the normal anatomical barrier is crossed via the CyPass Implant, aqueous fluid drains away from the anterior chamber, thus reducing the IOP. In this fashion, the CyPass Implant

allows aqueous fluid to bypass a major site of resistance that has been associated with elevated IOP and the development of glaucoma. By guiding fluid directly into the supraciliary space rather than to the surface of the eye, complications such as hypotony, flat chamber and bleb fibrosis or erosion commonly encountered with conventional glaucoma surgery may be avoided. Shunting aqueous fluid flow directly into the supraciliary space and avoiding conjunctival and scleral incisions should minimize scarring since the angle region is populated with a single line of non-proliferating trabecular cells. Finally, shunting aqueous flow directly into the supraciliary space should also reduce long term complications such as endophthalmitis and external leaks since an external filtering bleb is not a characteristic of this surgery.

7.2 Clinical Trial Design

This study is a prospective, non-randomized, multicenter, single arm, post approval study of the CyPass System. Approximately 640 subjects with POAG will be enrolled. Assuming a 30% screen-fail rate, a total of up to 450 subjects will be implanted and followed for 36 months. All subjects will receive the same treatment consisting of CyPass Micro-Stent implantation following uncomplicated cataract surgery in one eye. An attrition rate of approximately 20% is expected, leaving 360 subjects evaluable for statistical analyses with 36-month data.

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

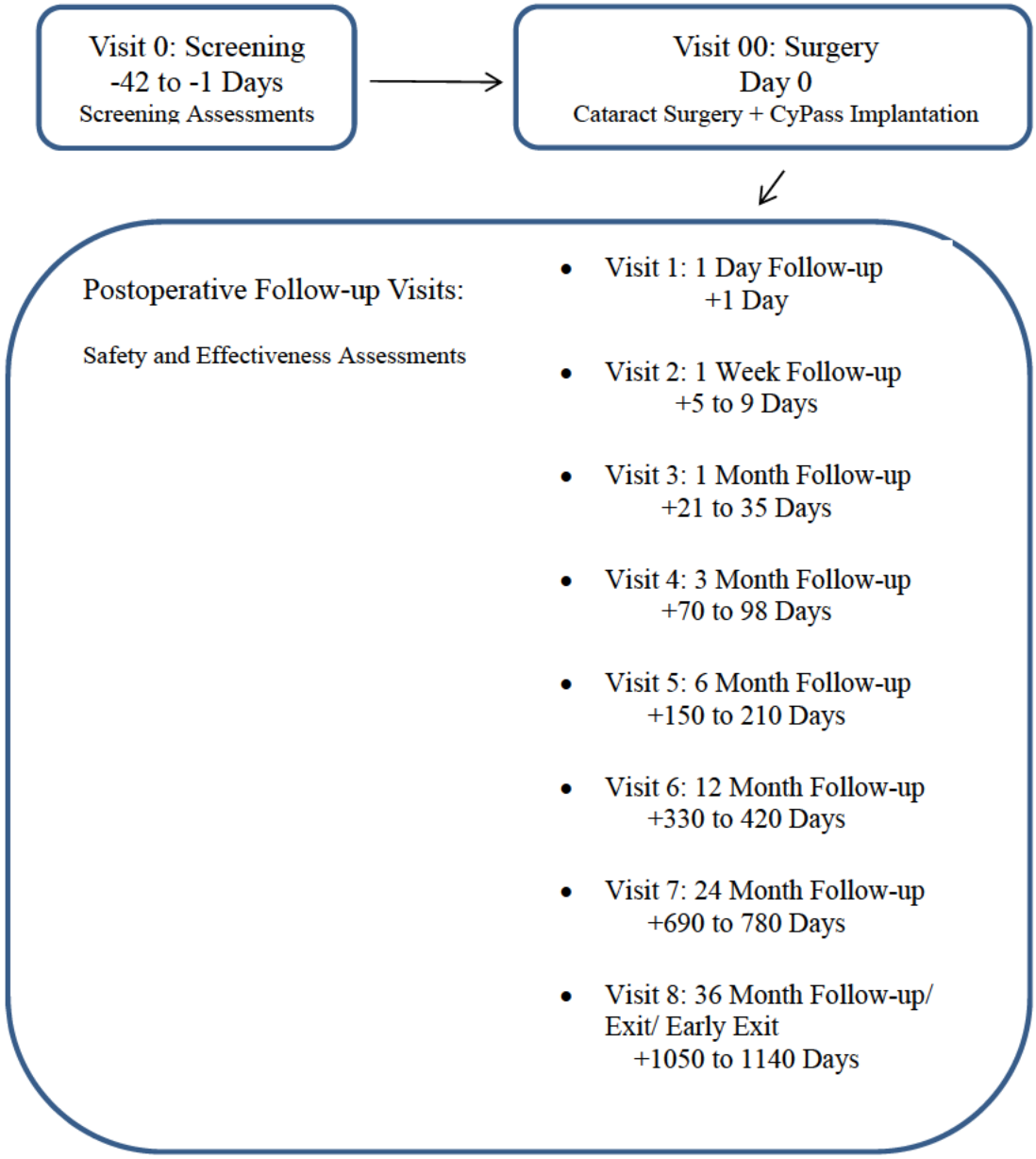
7.3 Study Milestones Timeline

The study milestone timeline presented below is based on the expectation that, following the initiation of the first site, the remaining study sites will be activated at a rate of approximately 3 per month, and the enrollment rate at activated sites will be approximately 2 subjects per month.

Table 7-1 Study Milestones

Key Milestone	Target Date
First Site Initiated	August 20, 2017
First Patient First Visit	September 20, 2017
Last Patient First Visit	February 20, 2020
Last Patient Last Visit	April 20, 2023
Database Lock	May 20, 2023
Submit PAS Final Report	July 20, 2023

Figure 7–1 Study Design



8 CLINICAL TRIAL OBJECTIVES

8.1 Primary Objective

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

8.2 Study Endpoints

8.2.1 Effectiveness Endpoints

8.2.1.1 Primary Effectiveness Endpoint

There is no primary effectiveness endpoint for this study.

8.2.1.2 Secondary Effectiveness Endpoints

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

- ≠ Mean change in IOP
- ≠ Proportion of subjects with IOP reduction ≥ 20% while using the same or fewer topical ocular hypotensive medications
- ≠ Proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg

8.2.2 Safety Endpoints

8.2.2.1 Primary Safety Endpoint

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

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

8.2.2.2 Secondary Safety Endpoints

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

- ≠ Rate of occurrence of sight-threatening adverse events including
    - Persistent (at time of study exit) BCDVA loss of 3 or more lines compared to best BCDVA achieved during the course of study
    - Endophthalmitis
    - Corneal decompensation
    - Retinal detachment
    - Severe choroidal hemorrhage or detachment
    - Aqueous misdirection
- ≠ The rate of ocular secondary surgical interventions (SSI)
- ≠ The rate of ocular SSIs associated with CyPass placement and stability

8.2.2.3 Other Safety Endpoints

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

- ≠ Increase from baseline IOP of 10 mmHg or greater at any time at/after 30 days postoperative
- ≠ BCDVA loss of 2 or more lines compared to screening (Visit 0)
- ≠ BCDVA loss of 2 or more lines in comparison with best recorded BCDVA at any postoperative visit
- ≠ Device movement, defined as a change by at least 1 in the number of CyPass rings visible (eg, from 1 ring to 2 rings or from 3 rings to 2 rings) that does not result in clinical sequelae (eg, secondary surgical intervention to modify device position, corneal endothelial touch by device, corneal edema leading to loss of BCDVA > 2 lines at the last postoperative visit in comparison with preoperative BCDVA, progressive endothelial cell loss, erosion of device through sclera, or device obstruction requiring secondary surgical intervention), and that is not attributable to any one or more of the following:
    - variations in gonioscopic viewing angle or illumination
    - changes in angle anatomy due to concomitant findings such as resolution of hyphema
    - changes in anterior chamber depth
    - development of focal peripheral anterior synechiae

9 INVESTIGATIONAL PLAN

9.1 Outline of Clinical Trial

This study is a prospective, non-randomized, multicenter, single arm, post approval study of the CyPass System. A total of 450 eyes from 450 subjects with POAG will be implanted to ensure 360 eyes of 360 subjects are available for analysis at 36 months. All subjects will receive the same treatment consisting of CyPass Micro-Stent implantation with cataract surgery in one eye.

9.2 Study Design

Subject participation in this study is expected to last up to 37.5 months and include 10 study visits. Approximately 640 subjects will be enrolled at the screening visit, to identify up to 450 qualified subjects. Within 42 days of screening, qualified subjects will receive cataract surgery followed by implantation of the CyPass Micro-Stent in one eye (the study eye) at the surgery visit. Eight postoperative follow-up visits are planned to occur at 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, 24 months, and 36 months after surgery. Upon completion of the 36-month follow-up visit, subjects will be exited from the study.

9.3 Rationale for Study Design

This post-approval study is designed to provide continued reasonable assurance of the safety and effectiveness of the device. The safety and effectiveness endpoint was identified based on the findings from the pivotal clinical trial (COMPASS, TMI-09-01) for the CyPass Micro-Stent. Since the safety and effectiveness in comparison with cataract surgery has been rigorously evaluated in the pivotal clinical trial, and another study (COMPASS-XT, GLD122b-C001) is ongoing to provide further long term follow up of the pivotal trial study population, there is no additional information that is necessary to be collected from a control arm of cataract surgery population; therefore, this study is a single arm study.

9.4 Risk Benefit Assessment

CyPass Micro-Stent is indicated for use in conjunction with cataract surgery for the reduction of IOP in adult patients with mild to moderate POAG.

During the development of the CyPass Micro-Stent, the safety and performance aspects of the CyPass Micro-Stent have been evaluated using risk analysis techniques, and clinical hazards are addressed by the clinical study data.

In the pivotal clinical trial for the CyPass Micro-Stent, the COMPASS trial, the safety and effectiveness of CyPass implantation in conjunction with cataract surgery in subjects with mild to moderate POAG have been demonstrated. The study has shown that the additional reduction of IOP provided by the CyPass does not impact cataract surgery outcomes. The expected improvement in visual acuity has been shown to be nearly identical in each treatment group, while the reduction in IOP has been shown superior in subjects receiving the CyPass. Adverse events specifically related to the CyPass device were mostly transient in nature. There have been no reports of choroidal detachment, choroidal hemorrhage or flat anterior chamber. The COMPASS study has demonstrated that the benefit of CyPass implantation at the time of cataract surgery in patients with mild to moderate POAG outweighs its risks. Hence, FDA's PMA approval was obtained for commercial distribution.

Following FDA's approval, in order to provide continued reasonable assurance of the safety and effectiveness of the device, a post-approval study (PAS) will be conducted.

In the post-approval clinical study, a careful evaluation will be performed according to the inclusion/exclusion criteria to ensure that vulnerable or inappropriate subjects are not allowed to participate in the clinical study. Subject safety will be monitored closely via the collection of adverse events, safety parameter assessments, and postoperative visits (either planned or unplanned) throughout the course of the study. In addition, per IFU, the investigators will receive training by certified Alcon personnel prior to clinical study surgery.

Overall, the information that will be gained in the post-approval study will provide continued evidence with regard to safety and effectiveness of the device. With the mitigations that have been implemented to reduce the risk to subjects participating in the clinical study, the Sponsor concludes that the benefit/risk assessment for this clinical study is acceptable.

9.5 Study Entry

Participants will be recruited from the Investigators' patient population, referrals, or IRB approved materials. Patients that appear to be eligible subjects will be approached for study participation and sign an Informed Consent Form (ICF) prior to the commencement of study related procedures.

The investigator or designee will explain the study purpose, procedures, and subject responsibilities to the potential participant. The subject must be given the opportunity to ask questions and allowed time to consider the information provided. The subject's willingness and ability to meet the follow-up requirements will be determined. When it has been established that the subject is eligible for possible participation in the study, written informed

consent will be obtained. Upon signing the ICF, the subject will be enrolled into the study. The original signed copy of the informed consent form will be retained with the subject's medical records, and a copy will be provided to the subject.

9.6 Procedures Per Study Visit

Procedures required by the protocol to be conducted at each study visit are listed in the table in Section 6 SCHEDULE OF VISITS and detailed in Section 12 CLINICAL TRIAL PROCEDURES and in the GLD122c-C001 Manual of Procedures (MOP) that accompanies this protocol. A brief summary of the procedures performed by visit is provided here.

- ≠ At screening (Visit 0) the subject will complete the informed consent process and sign an informed consent document. Standard procedures will be performed to determine subject eligibility. If needed, a second visual field exam may be conducted before surgery to confirm study eligibility.
- ≠ At surgery (Visit 00), standard cataract surgery will be performed in the study eye and the CyPass Micro-Stent will be implanted.
- ≠ At postoperative follow-up (Visits 1 through 8), safety and effectiveness assessments will be performed.

9.7 Selection of the Study Eye

Only one qualified eye per subject may be treated under the study protocol. If both eyes qualify for the study during screening, the eye with the worse BCDVA will be designated as the study eye. If the qualifying visual acuity is obtained using the BAT meter to assess BCDVA in both eyes, the eye with the worse BCDVA using the BAT meter will be designated as the study eye. If the visual acuity of both eyes is the same, then the investigator will determine the study eye. The fellow eye will be followed according to the standard of care. Subjects who screen fail during cataract surgery may not be rescreened for inclusion of the fellow eye.

9.8 Ocular Hypotensive Medications at Screening

At Visit 0, the subject's current ocular hypotensive medication usage will be recorded. Based on current ocular hypotensive medication use, the subject will be assessed as either 'medicated' or 'unmedicated'.

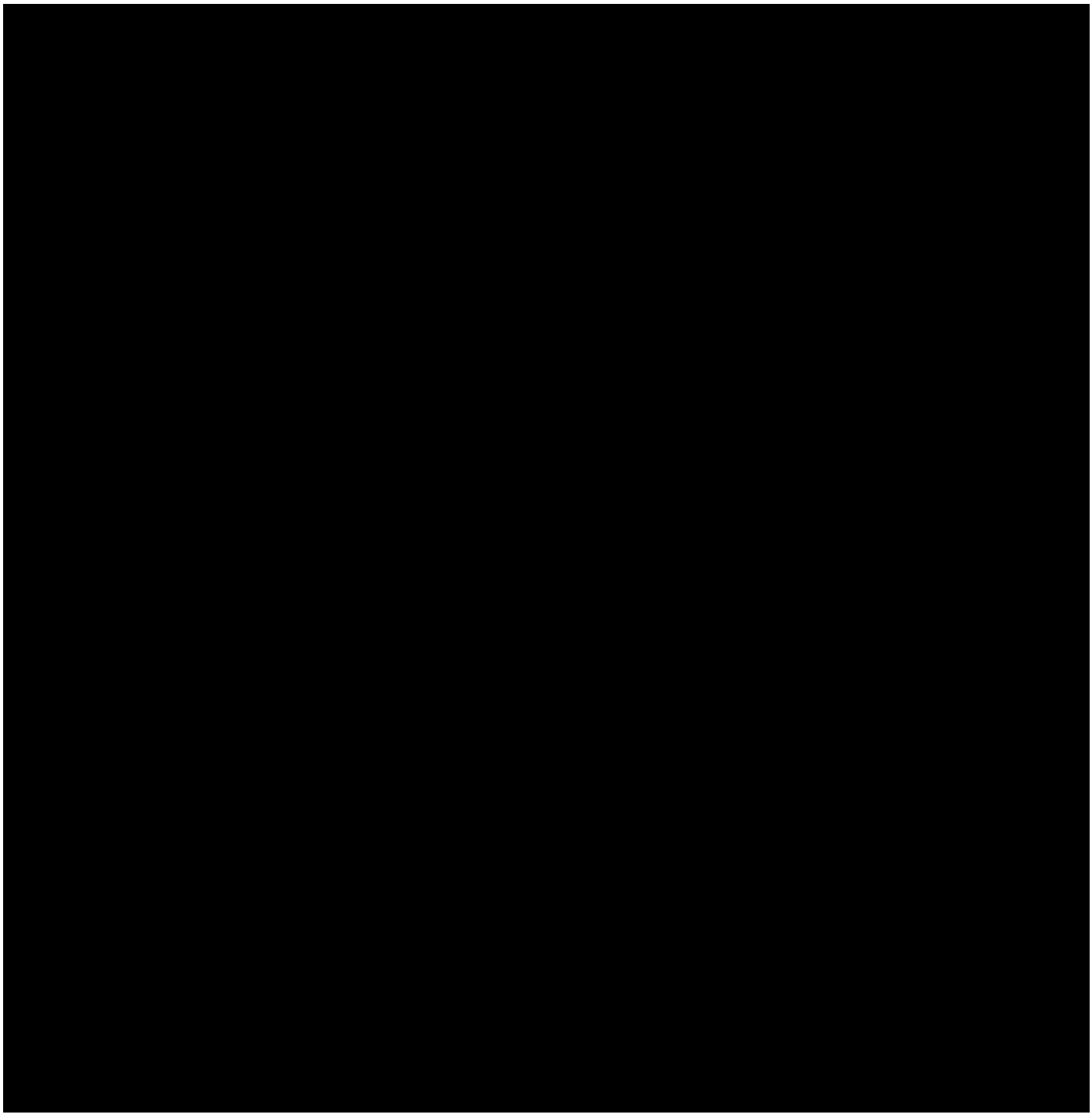
- ≠ 'Medicated' subjects must have used an ocular hypotensive medication(s) per a single prescribed regimen over the previous 28 days.
- ≠ 'Unmedicated' subjects must have not used any ocular hypotensive medications over the previous 28 days.

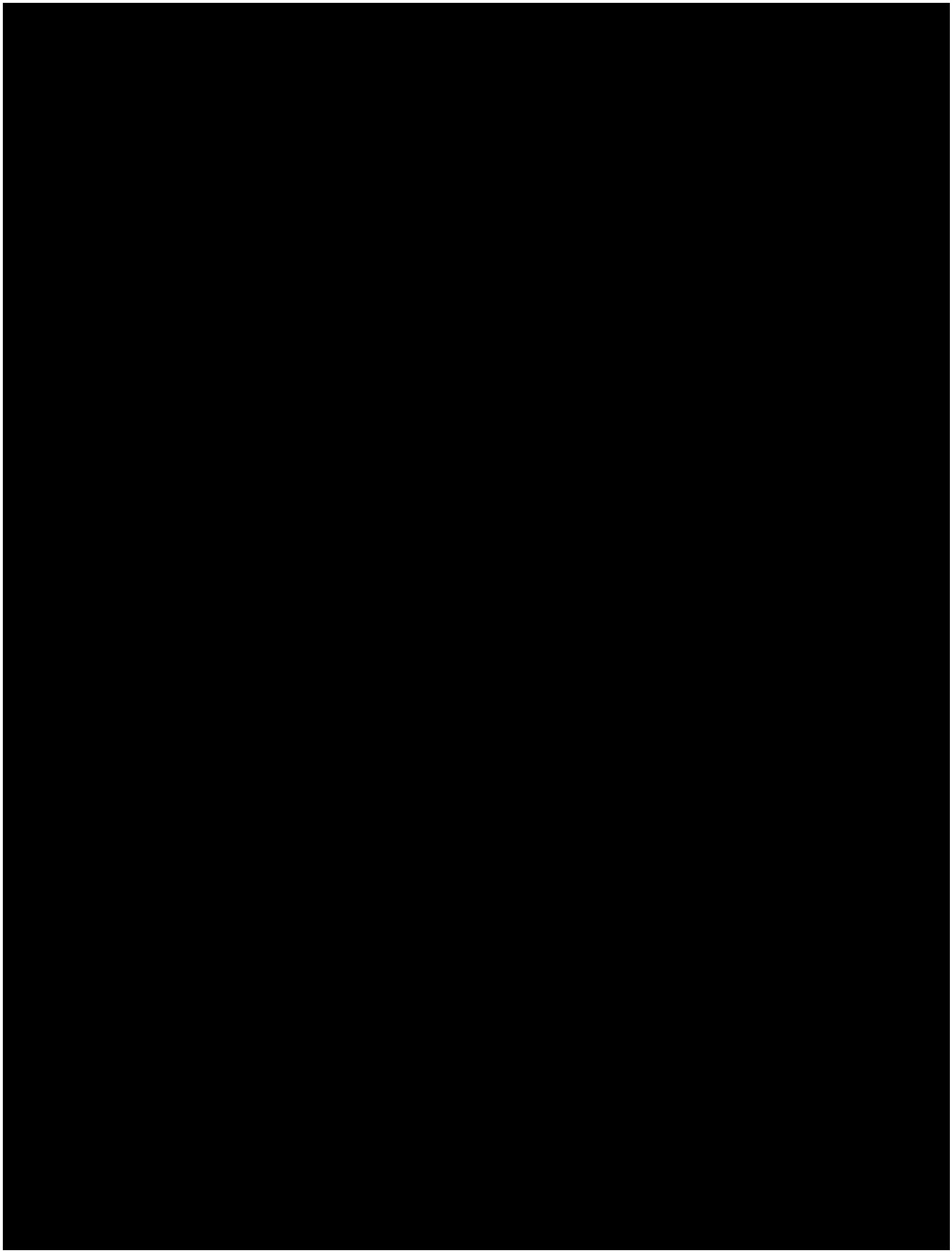
Ocular hypotensive medication usage must be established at the beginning of the screening visit. If a potential subject has been using ocular hypotensive medications inconsistently over the past 28 days, or the prescribed regimen has changed during the past 28 days, the screening visit must be halted and rescheduled for a time when the subject's status is either clearly 'medicated' or 'unmedicated'.

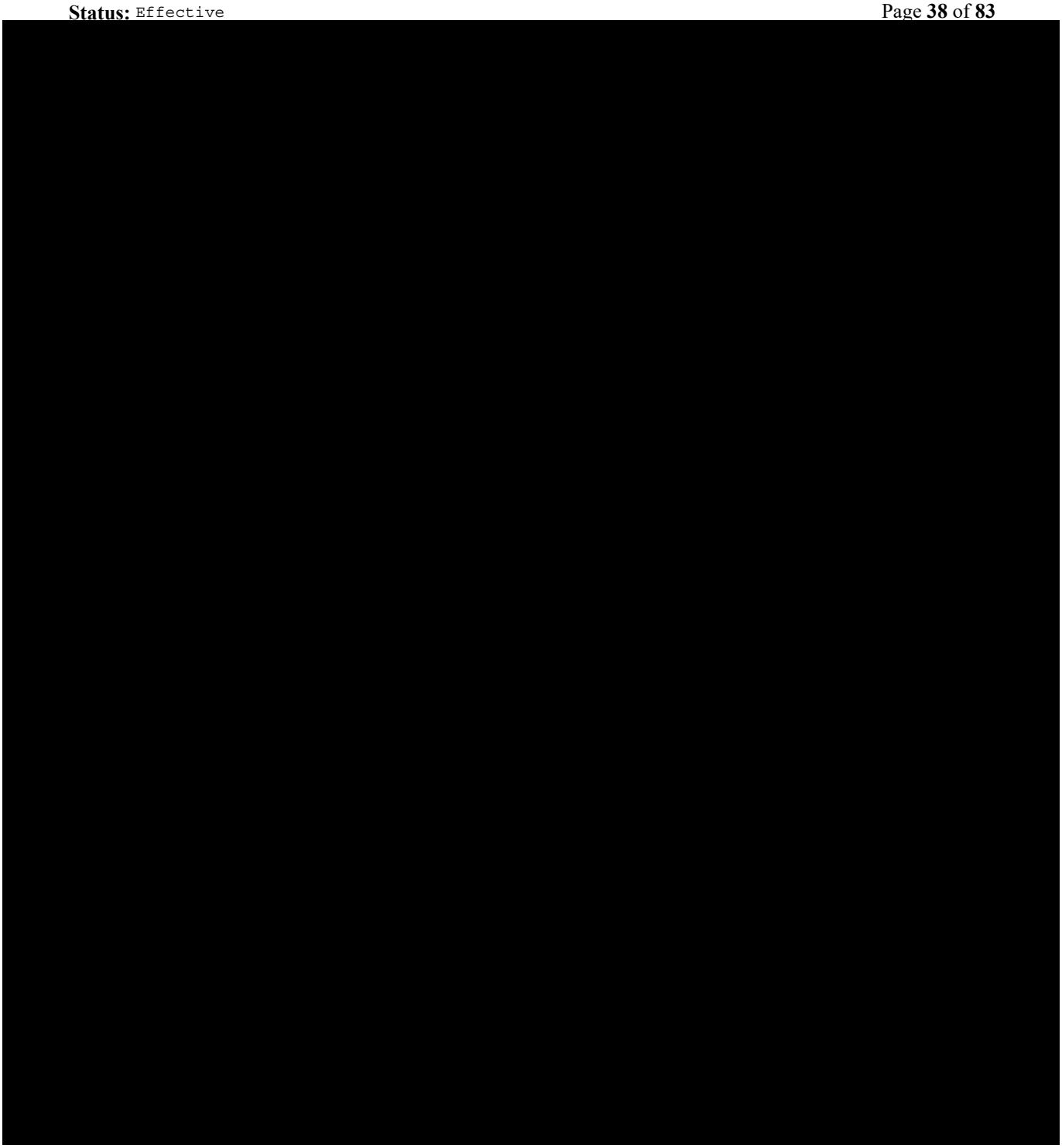
The inclusion requirements for baseline IOP at screening are different for medicated and unmedicated subjects (refer to inclusion criterion #4 in Section 10.1).

10 SUBJECT POPULATION

The study population includes approximately 450 qualified subjects to be enrolled and implanted at approximately 20 sites (approximately 22 subjects implanted per site). To participate in the clinical trial, subjects must have primary open angle glaucoma in the study eye and also be undergoing cataract surgery in that eye. The study enrollment period is expected to last approximately 22 months. No single site is permitted to implant more than 25% of the total subjects.







11 TREATMENT

In this single arm study, all subjects will receive the same treatment: implantation of one CyPass Micro-Stent in one eye per subject.

11.1 Investigational Products

11.1.1 Test Article

The test article in this clinical study is the CyPass System (Model 241-S) which consists of the CyPass Micro-Stent contained in a loading device (loader) and the CyPass applier. The CyPass System is manufactured by Alcon Laboratories.

Figure 11–1 CyPass Micro-Stent

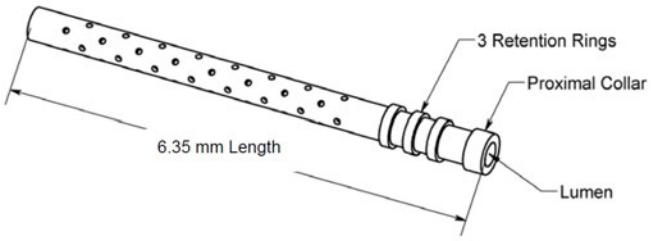
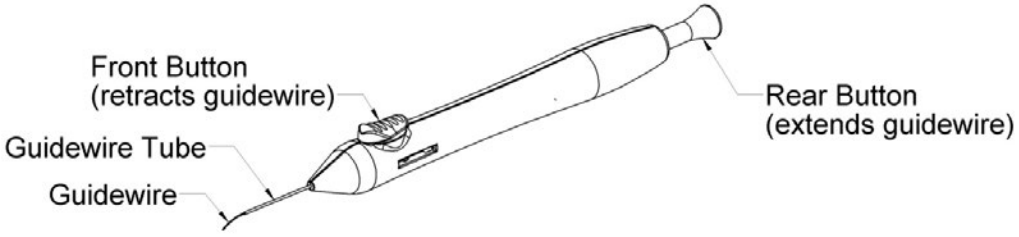


Figure 11–2 CyPass Applier with Guidewire Extended



11.1.2 Control Article

There is no control article in this clinical study.

11.2 Package Contents

The CyPass System (Model 241-S) consists of the CyPass Micro-Stent, which is contained in a loading device (loader), and the CyPass applier. The device is supplied sterile and non-pyrogenic in a sealed tray. The sealed tray is placed in a unit box containing product labeling and product information. The CyPass System has been sterilized using radiation.

11.3 Usage

The CyPass Micro-Stent is placed in the angle of the eye, with the proximal end extending from the angle into the anterior chamber and the distal end residing in the supraciliary space. It is implanted through the primary corneal incision made for cataract extraction / IOL implantation, following routine cataract surgery. One CyPass Micro-Stent will be implanted into one study eye of each qualified subject. CyPass implantation will be performed by a licensed physician who is a study Investigator.

11.4 Accountability Procedures

Details related to the procurement, labeling, handling, dispensing, and final disposition are outlined below. Throughout the clinical study, the Investigator is responsible for accounting for all investigational product and must ensure that the clinical study investigational product is not used in any unauthorized manner.

11.4.1 Procurement

The CyPass System is the sole study investigational product and will be procured by each investigative site through their usual commercial channels. A device accountability log will be maintained for all CyPass devices used in the study eyes of enrolled subjects.

11.4.2 Labeling

The CyPass System is commercially available and will be supplied with commercial labeling.

11.4.3 Handling

Investigational product provided for use in this clinical study must be stored in a safe, secure location with limited access, separated from general stock. Daily temperature of test article storage conditions will be monitored and recorded. Transportation or transfer of product from one location to another must be documented, utilizing a Transportation Log (or similar documentation) for appropriate accountability.

11.4.4 Dispensing

The Investigator must keep a current record of the dispensing of all investigational products. This record must be made available to the Sponsor’s monitor to account for all investigational product. Any discrepancy and/or deficiency must be recorded, with an explanation.

11.4.5 Returns of Damaged Products

Refer to the MOP for the procedures for returning damaged investigational product.

11.4.6 Final Disposition

It is the Investigator's responsibility to return any and all unused investigational product to the Sponsor, as directed.

11.5 CyPass Post-implant Adjustment or Removal

Refer to the MOP for the procedures for CyPass repositioning, CyPass trimming, CyPass lumen occlusion, and CyPass explant.

12 CLINICAL TRIAL PROCEDURES

12.1 Clinical Trial Assessments

The following section outlines the assessments to be performed in this clinical study. Assessments are described in detail in the GLD122c-C001 MOP, and are outlined in tabular format in Section 6 of this protocol.

12.2 Study Visits

All subjects will participate in defined follow-up visits through 36 months. A follow-up electronic Case Report Form (eCRF) shall be completed for each scheduled exam. Unscheduled visits must also be recorded using the appropriate eCRF.

Informed consent MUST be properly completed and documented prior to performing any study-specific testing. Upon signing informed consent, subjects are considered enrolled in the study. All subjects will be assigned a single subject identifier at the screening visit. The subject identifier consists of a combination of a 4-digit investigator number and a 5-digit subject number. The number is automatically generated sequentially by the electronic data capture (EDC) system. As an example: “1234.00001” (the investigator number and the subject number are separated by a “.” character). This number will be used throughout the clinical study.

It is recommended that ocular assessments be performed in the order presented below. All assessments must be recorded in source documentation, and also in the eCRF, if applicable.

Adverse events are collected and reported for both the study eye and the fellow eye (refer to Section 13 DEVICE DEFICIENCIES AND ADVERSE EVENTS).

12.2.1 Screening (Visit 0)

Below is a list of study procedures to be undertaken at screening (Visit 0) which must take place from 42 days to 1 day before surgery. Data collected at screening (Visit 0) are considered baseline data. Conduct ocular assessments in both eyes.

1. Upon identification of a possible study participant, carry out the informed consent

process. Refer to Section 16.2 Informed Consent Procedures.

NOTE: Subjects must formally consent to participate in the study prior to undergoing any study specific testing.

2. Document demographics, child bearing potential, ocular and non-ocular medical history, and ocular and non-ocular concomitant medications, including the number of ocular hypotensive medications being used.

3. Perform a urine pregnancy test if the subject is a female of child bearing potential.

4. Perform manifest refraction and record monocular best corrected distance visual acuity (BCDVA) using an ETDRS chart at 4 meters.

5. Perform specular microscopy.

6. If a reliable visual field has not been obtained in the past 6 months with a Humphrey automated perimeter using the 24-2 SITA standard threshold strategy, then conduct a visual field assessment in accordance with these requirements and confirm its reliability. If needed, this test may be repeated up until 1 day before surgery in order to obtain a reliable result.

7. Measure IOP with Goldmann tonometer between 8:00 am and 10:00 am (refer to MOP, Measuring IOP).

   NOTE: At this and all subsequent visits, if the first two measurements are within ±2 mmHg of one another, use the mean of these two readings. If the first two measurements differ by more than 2 mmHg, perform a third measurement and use the median of the three measurements.

8. Conduct slit lamp examination (refer to MOP for grading scales).

9. Perform Gonioscopy (including Shaffer grading for all 4 quadrants).

10. Conduct dilated fundus examination (including C:D assessment).

11. Conduct central corneal pachymetry.

    NOTE: Collect three measurements and use the median value.

Following confirmation of eligibility per study inclusion and exclusion criteria, subjects will be scheduled for surgery (Visit 00) within 42 days of screening (Visit 0). Ineligible subjects must be exited from the study. The reason for exit must be documented for each enrolled subject. Refer to Section 12.4 for further detail.

12.2.2 Surgery (Visit 00)

Study investigators will be trained on CyPass Micro-Stent implantation prior to site activation. However, as a newly approved device, Alcon may have an expert observer present during implantation (Visit 00) to offer guidance to the Investigator on implantation of the device. The presence and activities of the Alcon observer will be described in the Informed Consent. The Alcon observer will be under the supervision of the Investigator and will not intervene with the standard of care provided to study subjects or make safety-related decisions or assessments.

Surgery will take place after the subject successfully completes all screening assessments and is confirmed eligible to participate in the study per inclusion / exclusion requirements, but not more than 42 days after the date of screening (Visit 0). Prior to surgery, the subject must be instructed to use the following topical medications perioperatively: a 4th generation fluoroquinolone, eg, moxifloxacin 0.5% QID; a steroid, eg, difluprednate 0.05% QID; and a non-steroidal anti-inflammatory, eg, nepafenac 0.1% TID.

All eligible subjects will undergo cataract surgery and receive implantation of the CyPass Micro-Stent. The following information will be captured at this visit:

- ≠ Type of anesthesia (for cataract surgery and CyPass implantation)
- ≠ Type, size, and location of incision
- ≠ Effective Phacoemulsification Time (EPT)
- ≠ Cumulative Dissipated Energy (CDE)
- ≠ Clock hour location of inserted CyPass Implant
- ≠ Duration of CyPass implantation portion of the surgery
- ≠ Viscoelastic used prior to CyPass implantation and/or during cataract surgery
- ≠ Type of IOL implanted (monofocal, multifocal, toric, etc.)
- ≠ Surgical complications, including any blockage of the lumen or malposition
- ≠ Number of CyPass implantation attempts, defined as penetration of the tissue plane between the ciliary body and the scleral spur
- ≠ Intraoperative AEs (for cataract surgery and CyPass implantation)
- ≠ Perioperative medications (topical hypotensive medications administered)

12.2.2.1 Surgical Procedure

The surgical procedure will be performed per the following instructions.

Record and maintain a video copy of the entire surgical procedure for each subject with the site's study documentation.

1. Anesthetize the eye using a retro-bulbar, peri-bulbar, sub-Tenon and/or topical agent supplemented with intracameral anesthesia, per the investigator's standard operating procedures.

2. Perform cataract surgery using standard microsurgical techniques and the Investigator's routine instrumentation.

3. Confirm that all intraoperative inclusion criteria have been met:

    - ≠ an intact and centered capsulorhexis or capsulotomy
    - ≠ an intact posterior capsular bag,
    - ≠ no evidence of zonular dehiscence/rupture (uncomplicated cataract extraction)
    - ≠ a well-centered IOL implant placed in the capsular bag
    - ≠ a clear view using direct gonioscopy of an open anterior chamber angle

NOTE: Subjects who do NOT meet intraoperative inclusion criteria must be exited from the study.

Subjects meeting these criteria will have the CyPass device implanted per the following instructions:

4. Instill a miotic agent to constrict the pupil.

5. Tilt the microscope approximately 35-45º towards the surgeon and rotate the subject's head approximately 10º away from the surgeon to facilitate direct visualization of the anterior chamber (AC) angle.

6. Confirm the AC angle is open.

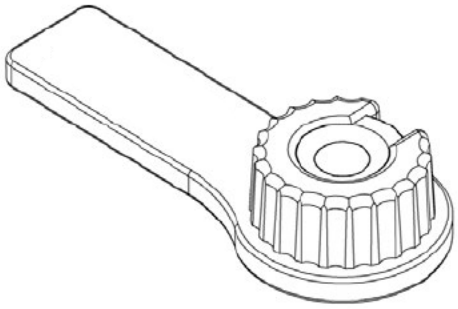
7. Open the tray containing the CyPass system onto a sterile field. Do not use either the CyPass Micro-Stent or the CyPass applier if the packaging has been opened or damaged.

8. Remove the CyPass applier from the sterile tray and examine its condition. First press the rear button on the handle to verify the guidewire extends from the guidewire tube. Then, press the front button on the handle to confirm the guidewire fully retracts into the

guidewire tube.

9. Remove the loader containing the CyPass Micro-Stent (Figure 12-1) from the sterile tray.

Figure 12–1 CyPass Micro-Stent Packaged in the Loader



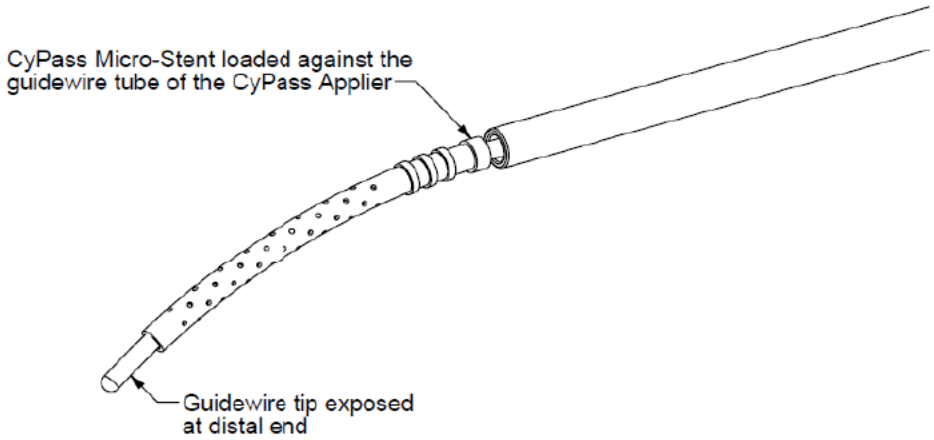
10. Rotate the cap of the loader clockwise until the opening is aligned with the CyPass Micro-Stent.

11. Confirm the CyPass applier guidewire is fully retracted into the guidewire tube.

12. Push the distal tip of the guidewire tube into the loader until it contacts the CyPass Micro-Stent and stops. Push the rear button of the applier to extend the guidewire into the Micro-Stent. Remove the CyPass applier with loaded CyPass Micro-Stent.

13. Examine the assembly. Confirm the condition of the CyPass Micro-Stent and that the guidewire is fully exposed at the distal end (Figure 12-2). If either the CyPass Micro-Stent or the CyPass applier guidewire is damaged, do not use. Set aside for return to Alcon (refer to Section 13.1.2). Use a back-up CyPass System for implantation.

Figure 12–2 CyPass Micro-Stent Loaded onto CyPass Applier Guidewire



14. Examine the AC angle with the gonio lens under the microscope. Take note of angle anatomy to identify the best implantation site. Avoiding the area of the anterior ciliary arteries at 3, 6, 9 and 12 o'clock may help reduce the possibility of significant bleeding.

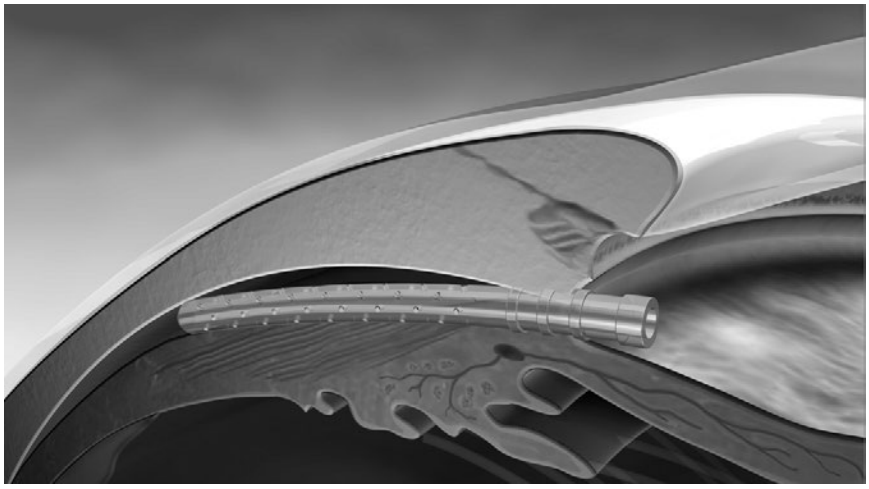
15. Fill the AC with ophthalmic viscoelastic (OVD) and use additional OVD as necessary to maintain a deep, stable AC during the CyPass Micro-Stent implantation process.

16. Introduce the loaded CyPass applier guidewire tube through the cataract incision and advance towards the intended site of implantation until the guidewire tube and sleeve have cleared the incision. When crossing the AC, rotate the CyPass applier guidewire such that its curvature is parallel to the iris plane.

17. Position the CyPass applier guidewire radially toward the scleral spur/ciliary body interface. Care should be taken to align the curvature of the CyPass on the guidewire with the curvature of the sclera bordering the supraciliary space to reduce the possibility of encountering resistance during insertion. To gain access, place the distal end of the guidewire at the scleral spur/ciliary body interface and smoothly advance the guidewire through the tissue plane between the ciliary body and adjacent sclera to separate the ciliary body from the scleral spur at the point of implantation.

18. Continue to advance the guidewire until only the most proximal retention ring and the collar of the CyPass Micro-Stent are located in the AC (Figure 12-3). An additional confirmatory placement landmark is when the top of the CyPass Micro-Stent collar is even with Schwalbe's line. In this position, the distal tip of the CyPass Micro-Stent should be resting against the sclera in the supraciliary space anterior to both retinal and choroidal tissues.

Figure 12–3 CyPass Micro-Stent at Implant Site



19. Hold the CyPass applier stationary and carefully press the front button on the CyPass applier to retract the guidewire into the guidewire tube, leaving the Micro-Stent anchored between the sclera and ciliary body.

20. Remove the CyPass applier from the eye.

21. If resistance is encountered or adequate implantation is not achieved at the initial implant site, implantation at a location at least 2 clock hours away from any area of ciliary body disinsertion can be considered if there is no significant iris trauma, the CyPass Micro-Stent remains properly positioned on the guidewire, and adequate hemostasis and visualization can be maintained. Make sure that the position of the patient's head and the tilt of the microscope allow adequate gonioscopic visualization of the angle structures. Increase magnification and fine focus the microscope as needed. Additional viscoelastic tamponade may be needed to assure hemostasis and maintain visibility during CyPass Micro-Stent implantation. Align the curvature of the CyPass on the guidewire with the curvature of the sclera bordering the supraciliary space to reduce the possibility of encountering resistance during insertion.

22. Termination of the procedure should be considered after 2 failed attempts at device placement or if adequate visibility cannot be maintained during implantation.

23. Use gonioscopy to confirm CyPass Micro-Stent position. Optimal position of the CyPass Micro-Stent is when only the collar and the first retention ring are visible in the AC. Anterior positioning with more than 2 retention rings visible in the AC can be associated with corneal endothelial cell loss. Posterior positioning such that the collar is not visible can be associated with reduced device effectiveness.

    a. If the CyPass Micro-Stent appears to be too anterior, use the guidewire tube of the CyPass applier to gently push the device deeper into the supraciliary space until it is optimally positioned. If the proximal end of the CyPass Micro-Stent appears to be too posterior, use a micro-forceps to grasp the CyPass Micro-Stent collar and gently pull it into the AC until the implant is optimally positioned. Do not use the irrigation/aspiration (I/A) tip for CyPass Micro-Stent positioning.

    b. If proper placement cannot be achieved, implant removal should be considered. Use direct gonioscopy visualization and supplementary viscoelastic for safe removal.

24. Since retained viscoelastic can lead to elevated IOP in the early postoperative period, irrigate and aspirate viscoelastic from the AC, taking care to avoid I/A tip proximity to the CyPass Micro-Stent.

    NOTE: The flow of irrigation fluid near the Micro-Stent may cause implant movement.

25. After completion of I/A, use gonioscopy to verify CyPass Micro-Stent location and confirm the absence of CyPass Micro-Stent lumen obstruction.

26. Confirm that the surgical incision is sealed by either pressure challenge testing or Seidel testing. Use a suture or ocular sealant for closure, if needed.

Apraclonidine, brimonidine, or other topical hypotensive agents may be administered at the conclusion of the procedure. Oral or intravenous ocular hypotensive agents (eg, acetazolamide) should be avoided due to the potential for postoperative hypotony. All medication use must be documented.

During the immediate preoperative and early postoperative period, the following regimen of topical anti-inflammatory ocular medication is recommended to reduce anticipated inflammation (see Table 12.1). A topical antibiotic is prescribed to reduce the risk of postoperative infection.

Table 12–1 Medication Regimen

Time Period	Antibiotic	Steroid	NSAID
1-3 Days Preoperatively	4th generation fluoroquinolone (eg, moxifloxacin) QID	eg, difluprednate 0.05% QID	eg, nepafenac 0.1% TID
Surgery Day – Week 1	4th generation fluoroquinolone (eg, moxifloxacin) QID	eg, difluprednate 0.05% QID	eg, nepafenac 0.1% TID
Week 2	N/A	eg, difluprednate 0.05% QID	eg, nepafenac 0.1% TID
Week 3	N/A	eg, difluprednate 0.05% TID	eg, nepafenac 0.1% TID
Week 4	N/A	eg, difluprednate 0.05% BID	eg, nepafenac 0.1% TID

Adjustment of the postoperative ocular medication regimen may be made as necessary for subject safety. Any change in postoperative ocular medications must be documented.

12.2.3 1 Day Follow-up (Visit 1)

Visit 1 must occur on the first day postoperatively. The following information will be captured at this visit. Ocular assessments will be conducted for the study eye only.

1. Document changes in concomitant medications.
2. Perform pinhole visual acuity measurement using an ETDRS chart at 4 meters.
3. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
4. Conduct slit lamp examination.
5. Perform Gonioscopy to determine CyPass positioning (goniophotography optional at Visit 1)
6. Record any adverse events and/or device deficiencies.

   NOTE: Serious adverse events (SAEs) must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

12.2.4 1 Week Follow-up (Visit 2)

Visit 2 must occur 5-9 days postoperatively. Below is a list of study procedures to be undertaken at this visit. Ocular assessments will be conducted for the study eye only.

1. Document changes in concomitant medications.
2. Perform manifest refraction and record monocular BCDVA using an ETDRS chart at 4 meters.
3. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
4. Conduct slit lamp examination.
5. Perform Gonioscopy (including Shaffer grading for all 4 quadrants) with goniophotography of CyPass location.

6. Record any adverse events and/or device deficiencies.

   NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

12.2.5 1 Month Follow-up (Visit 3)

Visit 3 must occur 21-35 days postoperatively. Below is a list of study procedures to be undertaken at this visit. Ocular assessments will be conducted for the study eye only.

1. Document changes in concomitant medications.
2. Perform manifest refraction and record monocular BCDVA using an ETDRS chart at 4 meters.
3. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
4. Conduct slit lamp examination.
5. Perform Gonioscopy (including Shaffer grading for all 4 quadrants) with goniophotography of CyPass location.
6. Record any adverse events and/or device deficiencies.

   NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

12.2.6 3 Month Follow-up (Visit 4)

Visit 4 must occur 70-98 days postoperatively. Below is a list of study procedures to be undertaken at this visit. Ocular assessments will be conducted for the study eye only.

1. Document changes in concomitant medications.
2. Perform manifest refraction and record monocular BCDVA using an ETDRS chart at 4 meters.
3. Perform specular microscopy.

4. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
5. Conduct slit lamp examination.
6. Perform Gonioscopy (including Shaffer grading for all 4 quadrants) with goniophotography of CyPass location.
7. Conduct dilated fundus examination (including C:D assessment).
8. Record any adverse events and/or device deficiencies.

   NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

12.2.7 6 Month Follow-up (Visit 5)

Visit 5 must occur 150-210 days postoperatively. Below is a list of study procedures to be undertaken at this visit. Ocular assessments will be conducted for the study eye, unless otherwise noted.

1. Document changes in concomitant medications.
2. Perform manifest refraction and record monocular BCDVA using an ETDRS chart at 4 meters.
3. Perform specular microscopy. If requested by the sponsor, may also be performed in the fellow eye.
4. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
5. Conduct slit lamp examination.
6. Perform Gonioscopy (including Shaffer grading for all 4 quadrants) with goniophotography of CyPass location.
7. Conduct dilated fundus examination (including C:D assessment).
8. Record any adverse events and/or device deficiencies.

   NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge.

Refer to Section 13 for further detail.

12.2.8 12 Month Follow-up (Visit 6)

Visit 6 must occur 330 - 420 days postoperatively. Below is a list of study procedures to be undertaken at this visit. Ocular assessments will be conducted for the study eye, unless otherwise noted.

1. Document changes in concomitant medications.
2. Perform manifest refraction and record monocular BCDVA using an ETDRS chart at 4 meters.
3. Perform a Humphrey 24-2 SITA standard visual field.
4. Perform specular microscopy. If requested by the sponsor, may also be performed in the fellow eye.
5. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
6. Conduct slit lamp examination.
7. Perform Gonioscopy (including Shaffer grading for all 4 quadrants) with goniophotography of CyPass location.
8. Conduct dilated fundus examination (including C:D assessment).
9. Conduct central corneal pachymetry.
10. Record any adverse events and/or device deficiencies.

    NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

12.2.9 24 Month Follow-up (Visit 7)

Visit 7 must occur 690-780 days postoperatively. Below is a list of study procedures to be undertaken at this visit. Ocular assessments will be conducted for the study eye, unless otherwise noted.

1. Document changes in concomitant medications.
2. Perform manifest refraction and record monocular BCDVA using an ETDRS chart at 4 meters.
3. Perform a Humphrey 24-2 SITA standard visual field.
4. Perform specular microscopy. If requested by the sponsor, may also be performed in the fellow eye.
5. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
6. Conduct slit lamp examination.
7. Perform Gonioscopy (including Shaffer grading for all 4 quadrants) with goniophotography of CyPass location.
8. Conduct dilated fundus examination (including C:D assessment).
9. Conduct central corneal pachymetry.
10. Record any adverse events and/or device deficiencies.

    NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

12.2.10 36 Month Follow-up / Exit / Early Exit (Visit 8)

Visit 8 must occur 1050-1140 days postoperatively. Below is a list of study procedures to be undertaken at this visit. Ocular assessments will be conducted for the study eye, unless otherwise noted.

1. Document changes in concomitant medications.
2. Perform manifest refraction and record monocular BCDVA using an ETDRS chart at 4 meters.
3. Perform a Humphrey 24-2 SITA standard visual field.
4. Perform specular microscopy. If requested by the sponsor, may also be performed in the fellow eye.
5. Measure IOP with Goldmann tonometer between 8:00 and 10:00 am.
6. Conduct slit lamp examination.
7. Perform Gonioscopy (including Shaffer grading for all 4 quadrants) with goniophotography of CyPass location.
8. Conduct dilated fundus examination (including C:D assessment).
9. Conduct central corneal pachymetry.
10. Record any adverse events and/or device deficiencies.

    NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge. Refer to Section 13 for further detail.

11. Exit the subject from the study after completion of this visit.

12.3 Unscheduled Visits

An unscheduled visit (USV) is defined as one that meets all of the following:

- ≠ Examination that is not required by the protocol
- ≠ Examination conducted by the study staff
- ≠ New finding, continuation of an existing finding, or a change to a previous finding is noted in the study eye

An USV may or may not result in the capture of an adverse event. Likewise, an AE may be captured without the report of an USV (eg, AE identified subsequent to study eye examination by non-study personnel).

The assessments captured at the USV are dictated by the Investigator per his/her medical judgment. The following assessments/documentation are recommended:

- ≠ Concomitant medications
- ≠ Manifest refraction and BCDVA
- ≠ Specular microscopy (study eye or fellow eye)
- ≠ IOP
- ≠ Slit lamp examination
- ≠ Gonioscopy
- ≠ Fundus examination
- ≠ Adverse events
- ≠ Device deficiencies

NOTE: Assessments/documentation not limited to the above list.

For safety purposes, if an USV is required after the final study visit, document the visit. Refer to Section 13.6 for further detail.

12.4 Discontinued Subjects

Subjects may be discontinued (exited) from the study early due to:

- ≠ Failure to meet protocol eligibility criteria prior to or during surgery
- ≠ Adverse event(s)
- ≠ Administrative reasons (eg, voluntary withdrawal, lost to follow-up)

Subjects who fail to meet protocol eligibility criteria prior to implantation will not be followed beyond the date of determination of ineligibility unless the reason for ineligibility is the occurrence of an adverse event. Subjects who are discontinued due to an adverse event occurring prior to implantation will be followed until resolution or stabilization of the event. Implanted subjects and subjects with failed implantation (inability to successfully deploy or insert the CyPass) will be followed until the planned end of study period.

Discontinued subjects who have been implanted or in whom implantation failed will not be replaced. Notification of a subject's early discontinuation should be made immediately to the sponsor and documented on the appropriate eCRF.

If a subject exits the study before completion of the final, planned study visit (Visit 8), the Investigator should make reasonable attempts to have the subject return to the site to perform early exit procedures. Early exit procedures are all study procedures to be conducted at Visit 8 (see Section 12.2.10).

12.5 Clinical Trial Termination

The Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause. The Investigator also may terminate the study at his/her site for reasonable cause. Reasons for the closure of an investigational site or termination of the study may include:

- ≠ The Investigator fails to comply with the protocol or GCP guidelines
- ≠ Safety concerns
- ≠ Inadequate recruitment of subjects by the Investigator

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities (where applicable) of the termination/suspension and the reason for the termination/suspension. The Investigator should promptly notify the IRB/IEC of the termination or suspension and the reasons.

If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s), and provide written instructions for study termination and applicable subject follow-up.

13 DEVICE DEFICIENCIES AND ADVERSE EVENTS

13.1 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 13–1 Categorization of All Adverse Events

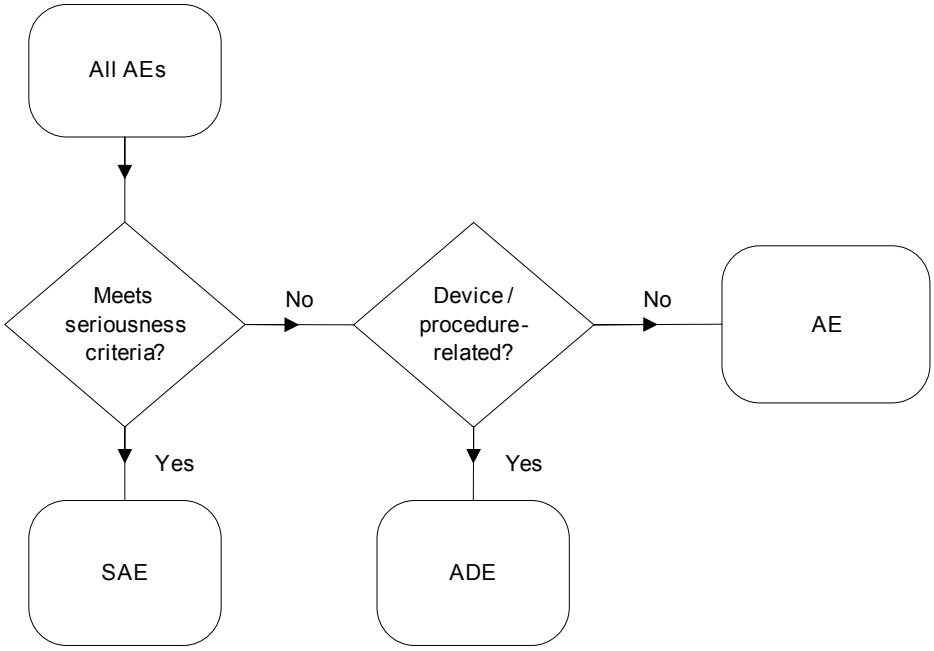
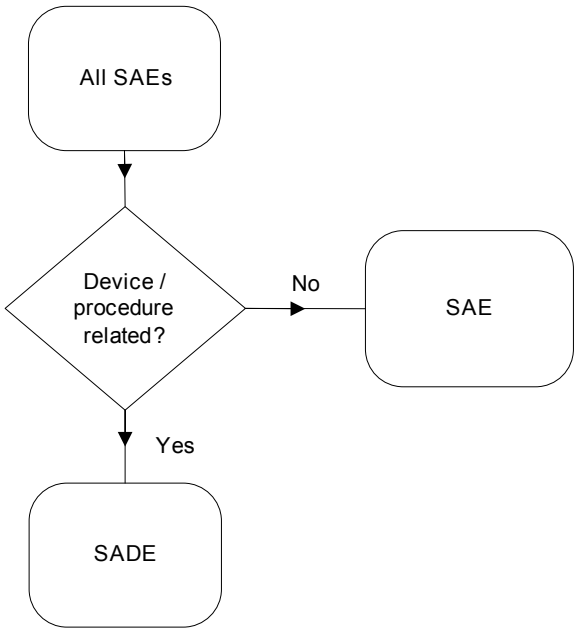


Figure 13–2 Categorization of All Serious Adverse Events



13.1.1 Intraoperative Adverse Events

Anticipated intraoperative adverse events include, but are not limited to, the following cataract surgery and other intraoperative complications.

a) Anterior capsule tear
b) Choroidal detachment
c) Posterior capsular rupture
d) Vitreous in the anterior chamber
e) Choroidal hemorrhage or effusion
f) Cyclodialysis cleft – oversized
g) CyPass non-implantation after penetration of the tissue plane between the ciliary body and the scleral spur
h) Descemet's membrane break
i) Hyphema obscuring the surgeon's view
j) Inadvertent loss of vitreous not associated with the cataract procedure
k) Inadvertent perforation of sclera
l) Secondary ocular surgical intervention – AC lavage
m) Significant corneal damage
n) Significant iris injury or trauma
o) Subconjunctival hemorrhage
p) Zonular dialysis

13.1.2 Postoperative Adverse Events

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

a) BCDVA loss of 2 lines (10 letters) or more on the ETDRS chart measured at or after 3 months postoperative compared to BCDVA at Visit 3 (1 Month Follow-up)
b) Persistent (at time of study exit) BCDVA loss of 3 or more lines compared to best BCDVA achieved during the course of study
c) 2-point worsening to severe on the slit lamp examination findings (other than cells and flare) at or after 3 months postoperative not associated with a pre-existing condition compared to Visit 0 (Screening)
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) Anterior chamber cell and flare requiring either an increase in the standard protocol postoperative steroid regimen or initiation of steroid treatment following completion of the protocol postoperative steroid regimen
j) Conjunctivitis
k) Keratitis
l) Corneal edema (mild to moderate corneal edema prior to 1 month postoperative is not considered an adverse event)
m) Corneal opacification
n) Corneal decompensation
o) Persistent hyphema of >2 mm present greater than 1 day postoperative
p) Retinal detachment
q) Other retinal complications (eg, dialysis, flap tears, or proliferative vitreoretinopathy)
r) Increase in C/D ratio of ≥0.3 units on slit lamp biomicroscopic examination
s) Confirmed worsening in the visual field mean deviation (MD) of ≥2.5 dB compared to the MD used to determine subject eligibility
t) 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
u) Peripheral anterior choroidal effusion
v) Maculopathy associated with hypotony
w) Maculopathy associated with cystoid edema
x) Hypotony (defined as IOP <6 mmHg) at or after 1 month postoperative

y) 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

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

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

bb) CyPass device malposition – positioning after deployment such that the device is not in the supraciliary space

cc) CyPass device malposition – positioning after deployment such that there is a clinical sequela 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 at the last postoperative visit, 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 Visit 5 (6 Month Follow-up)
   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 anterior chamber 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 paracentesis to relieve pressure prior to 1 week postoperative or Nd:YAG 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 present greater than 3 months postoperative
nn) Significant foreign body sensation at or after 3 months postoperative
oo) IOL subluxation

13.1.3 Sight Threatening Adverse Events

Of the postoperative adverse events listed in Section 13.1.2, the following are pre-defined as sight threatening and must therefore be reported as Serious Adverse Events (SAEs) per the guidelines for reporting in Section 133:

- ≠ 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 adverse events may also be considered potentially sight threatening, or may meet other seriousness criteria. Any adverse event meeting any SAE seriousness criterion, as defined in the Glossary of Terms, must be reported as an SAE per Section 13.3.

13.1.4 Other Postoperative Events/Findings

The following events are anticipated postoperative events. In the absence of an untoward effect to the subject, these should not be reported as AEs. These findings will be captured on the eCRF under Gonioscopy, Slit Lamp Examination, or IOP findings, etc.

a) AC shallowing
b) Chemosis
c) CyPass intraluminal blood
d) Early hypotony
e) Focal peripheral anterior synechiae
f) Microhyphema
g) Partial obstruction of CyPass lumen
h) Pigment dispersion

i) Posterior synechiae
j) Pseudophacodenesis
k) Pupillary miosis
l) Schlemm's intracanalicular blood
m) Transient forward IOL movement related to AC shallowing

13.1.5 Device Deficiencies

A device deficiency 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 patient harm separately. Examples of device deficiencies include, but are not limited to the following:

- ≠ Failure to meet product specifications
- ≠ CyPass applier issues
  - o Guidewire bent
  - o Inability to retract the guidewire
  - o Deployment button resistance
  - o Inability to deploy CyPass Micro-Stent due to applier performance or design
- ≠ CyPass Micro-Stent issues
  - o CyPass Micro-Stent damage
  - o Defective CyPass Micro-Stent surface or interior lumen
- ≠ Other device issues
- ≠ Packaging issue
  - o Pouch not sealed

13.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions:

- ≠ "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?"

13.3 Procedures for Recording and Reporting

AEs are collected from the time of informed consent. Any preexisting medical conditions or signs/symptoms present in a subject prior to the start of the study (ie, before informed consent is signed) 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 medical condition or signs/symptoms are considered AEs.

In addition, aqueous cells and flare, corneal edema, raised IOP and superficial punctate keratitis are examples of early postoperative findings that are typically observed following ocular surgery. These are not considered AEs if they are not severe in nature or can reasonably be expected to resolve within a month and not result in any untoward long term visual outcome impact. The Investigator must assess and determine whether an AE has occurred.

All ocular AEs for the study eye and the contralateral non-study eye, as well as non-ocular AEs, must be reported as part of this study.

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 faxed or emailed to the Study Sponsor at 1-817-302-1927 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 post-market 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.

13.3.1 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.

13.4 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 Complaint Management System (GPCMS).

13.5 Unmasking of the Study Information

Not applicable; this study is open-label.

13.6 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 post-market vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements.

The Investigator should also report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

13.7 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.

14 DATA REVIEW AND HANDLING

14.1 Completion of Source Documents and Case Report Forms

The nature and location of all source documents must be identified to ensure that original data required to complete the eCRFs exist and are accessible for verification by the monitor. If electronic source records are maintained, the EMR system will be reviewed for 21 CFR Part 11 compliance and the method of verification will be determined in advance of starting the study. Data reported on the eCRFs must be derived from source documentation and be consistent with source documentation, and any discrepancies must be explained in writing. At a minimum, source documentation must include the following information for each subject:

- ≠ Subject identification (name, sex)
- ≠ Documentation of subject eligibility
- ≠ Date of informed consent, and a copy of signed informed consent form
- ≠ Dates of visits
- ≠ Documentation that protocol-specific procedures were performed
- ≠ Results of study assessments, as required by the protocol
- ≠ Documentation of AEs and other safety parameters (as 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 each entry in the source documents be identifiable (eg, initials or signature and date). Any change or correction to data reported in the source, or on a eCRF, must be dated, initialed, and explained if necessary. Changes must not obscure the original entry (ie, an audit trail must be maintained). Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

EDC is designated for data collection and should be completed by designated individuals only. Required examinations must be recorded on the eCRFs. All data reported must have corresponding entries in the source documents. The Investigator will review the reported data and certify that the eCRFs are accurate and complete as indicated by signature. Subject identifiers must not be recorded on the eCRFs beyond subject number, demographics information, and/or other study identifiers.

Deviations from this protocol, regulatory requirements, and Good Clinical Practice (GCP) must be recorded in the study records. An explanation of the deviation should be included, as applicable. In addition, corrective and preventive action should be identified, implemented, and documented within the study records.

14.2 Data Review and Clarifications

Upon completion of the eCRFs, the data will be reviewed by Alcon study personnel for accuracy and completeness. If corrections and/or any additions to the data are deemed necessary, queries will be generated by Alcon data management or the site management (study monitor) team and forwarded to the investigative site. Staff at each site are expected to respond to data queries in a timely manner and ensure that the corrections and changes made to the data in the EDC system are reflected in the subjects' source documentation. In addition, prior to study start (first subject first visit) a plan for data validation will be completed by Alcon Clinical Data Management and agreed upon by members of the Clinical Trial Management (CTM) team.

Concomitant medications entered into the database will be coded using the current version of the WHO (World Health Organization) Drug Reference List. Medical history and adverse events will be coded using the medical dictionary for regulatory activities (MedDRA) terminology.

Upon completion of the study and once the database is declared complete and accurate, the database will be locked and data will be available for the final data analysis. Any changes to the database after lock will be implemented upon agreement between Alcon's clinical trial management and biostatistics department, and will be completed following Alcon's procedures for changes to a database after database lock.

15 ANALYSIS PLAN

This information may also be contained within a separate biostatistical analysis plan which will be prepared and finalized prior to database lock.

15.1 Subject Evaluability

All patients will be considered enrolled once they have signed the informed consent form. The assignment of each study eye to the study analysis sets will be made prior to database lock.

15.2 Analysis Data Sets

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

15.2.1 Intention to Treat

The intention to treat (ITT) analysis set will be defined as the set of study eyes for which a CyPass Micro-Stent implant is attempted; the ITT analysis set will be the primary analysis set for all study analyses.

[redacted]

15.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized with appropriate summary statistics. Eye level summaries will be based on all study eyes in the ITT analysis set; subject level summaries (eg, age) will be based on all subjects with an eye in the ITT analysis set.

15.4 Effectiveness Analyses

15.4.1 Primary Effectiveness

There is no primary effectiveness endpoint for this study.

15.4.2 Secondary Effectiveness

The secondary effectiveness endpoints are listed in Section 8.2.1.2.

15.4.2.1 Statistical Hypotheses

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

15.4.2.2 Analysis Methods

Continuous endpoints will be summarized by number of observations (n), mean, median, standard deviation, minimum and maximum; binary endpoints will be summarized by numerator (number of eyes meeting the endpoint), denominator , and the proportion of ITT eyes meeting the endpoint. Denominators for adverse events, slit lamp findings, and other events will be the number of eyes in the ITT set. Denominators for data such as visual acuity and other subject data that is collected at protocol-required visits will reflect the number of eyes with non-missing data in the ITT set. Summary statistics will be presented at all postoperative visits for which the endpoint data are collected. Supportive analysis will be conducted using the DI analysis set for all secondary effectiveness outcomes.

15.5 Safety Analyses

15.5.1 Primary Safety

The primary safety endpoint is detailed in Section 8.2.2.1.

15.5.1.1 Statistical Hypothesis

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

$$H_0: p_C \geq 7\%$$

$$H_1: p_C < 7\%$$

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

15.5.1.2 Analysis Methods

The primary safety hypothesis will be tested with an exact one-sided binomial test with type I error 0.05. The ITT analysis set will be used for the primary safety analysis.

15.5.2 Secondary Safety

The secondary safety endpoints are listed in Section 8.2.2.2.

15.5.2.1 Statistical Hypotheses

There are no statistical hypotheses for the secondary safety endpoints.

15.5.2.2 Analysis Methods

Continuous endpoints will be summarized by number of observations (n), mean, median, standard deviation, minimum and maximum; binary endpoints will be summarized by numerator (number of eyes meeting the endpoint), denominator (number of eyes in the ITT set), and the proportion of eyes meeting the endpoint. Summary statistics will be presented at all follow-up visits for which the endpoint data are collected. Supportive analysis will be conducted using the DI analysis set for all secondary safety outcomes.

15.5.3 Other Safety

The other safety endpoints are listed in Section 8.2.2.3.

15.5.3.1 Statistical Hypotheses

There are no statistical hypotheses for the other safety endpoints.

15.5.3.2 Analysis Methods

Continuous endpoints will be summarized by number of observations (n), mean, median, standard deviation, minimum and maximum; binary endpoints will be summarized by numerator (number of eyes meeting the endpoint), denominator (number of eyes in the ITT set), and the proportion of eyes meeting the endpoint. Summary statistics will be presented at all follow-up visits for which the endpoint data are collected. Supportive analysis will be conducted using the DI analysis set for all other safety outcomes.

15.5.4 Ocular Adverse Events

The number of events, number of eyes experiencing the event, and the rate of the event will be reported for all postoperative ocular adverse events occurring in study eyes. Any ocular events occurring pre-operatively in study eyes will be listed separately. Any ocular events occurring in non-study eyes will also be listed separately.

15.5.5 Non-Ocular Adverse Events

The number of events, number of subjects experiencing the event, and the rate of the event will be reported for all non-ocular adverse events.

15.5.6 Device Deficiencies

The number of device deficiencies by type will be calculated, and a listing of all device deficiencies will be provided.

15.5.7 Endothelial Cell Count

Specular microscopy data at baseline and at each follow-up visit at which the exam is conducted will be summarized with number of observation (n), mean, median, standard deviation, minimum, and maximum. Change and percentage change from baseline as well as change between two consecutive visits will also be summarized with number of observations (n), mean, median, standard deviation, minimum, and maximum.

15.5.8 Slit Lamp and Fundus Examinations

Slit lamp and fundus examination results at baseline and at each follow-up visit at which the exams are conducted will be summarized by the number of subjects in each category (numerator), the number of subjects with data (denominator), and the percentage of subjects in each category (numerator / denominator).

15.5.9 Corneal Pachymetry

Corneal pachymetry data recorded at screening and at each follow-up visit at which the exam is conducted will be summarized descriptively with number of observations (n), mean, median, standard deviation, minimum, and maximum.

15.5.10 Visual Field Loss Mean Deviation Testing

The visual field mean deviation testing data collected at baseline and at each follow-up visit at which the exam is conducted will be summarized with number of observations (n), mean, standard deviation, minimum, and maximum.

15.5.11 Manifest Refraction

The number of observations (n), mean, median, standard deviation, minimum, and maximum for sphere, cylinder, and manifest refraction spherical equivalent will be reported at baseline and at each follow-up visit for which manifest refraction is scheduled.

15.6 Handling of Missing Data

A tipping point analysis will be performed for the primary safety endpoint.

In addition, a comparison of baseline characteristics including age, gender, race, site, and baseline unmedicated IOP will be performed between those subjects who complete Visit 8 (36 Month Follow-up) and those who do not.

15.7 Interim Analyses

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

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

15.8 Sample Size Justification

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

An evaluation of COMPASS (TMI-09-01) data showed that through 24 months of follow-up, there were two eyes with failures to implant and eight eyes with CyPass malposition events, respectively, corresponding to the above definitions. In addition, there were four eyes with documentation of three rings visible within the first postoperative week that likely would have undergone early secondary surgical intervention due to anterior CyPass positioning under the approach documented in the Instructions for Use (IFU). Inclusion of these cases would increase the number of observed events from 10 to 14 (3.74%, 95% confidence interval: 2.1% – 6.2%). Of note, not all investigators documented the number of rings visible in the early postoperative period because this was not a study requirement (data regarding the number of rings is recorded for only 96 subjects at 1 Day and 139 subjects at 1 Week), so this number likely underestimates the number of subjects who would have been candidates for early surgical re-intervention under the new criteria described in the IFU.

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

- ≠ Type I error = 0.05
- ≠ one-sided alternative

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

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

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

16 ADMINISTRATIVE PROCEDURES

16.1 Regulatory and Ethical Compliance

This clinical trial will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with ISO 14155:2011 Clinical investigation of medical devices for human subjects, Good Clinical Practice (GCP), and the Code of Federal Regulations (CFR). The study will also be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs), and the SOPs of Contract Research Organizations participating in the conduct of the clinical trial, and all other applicable regulations. The Investigator and all clinical trial staff will conduct the clinical trial in compliance with this protocol. The Investigator will ensure that all personnel involved in the conduct of the clinical trial are qualified to perform their assigned duties through relevant education, training, and experience.

16.2 Informed Consent Procedures

Voluntary informed consent will be obtained from every subject prior to the initiation of any screening or other clinical trial-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical trial to each potential subject and the subject must indicate voluntary consent by signing and dating the IRB/IEC 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 will provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the clinical trial, along with any known risks and potential benefits associated with the investigational product, 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 clinical trial and will be provided with contact information for the appropriate individuals should questions or concerns arise during the clinical trial. The subject also will 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 and must provide a duplicate copy to each subject.

16.3 Responsibilities of the Investigator and IRB/IEC

Before clinical trial initiation, this protocol, the informed consent form (and assent form, if applicable), any other written information provided to subject, and any advertisements

planned for subject recruitment must be approved by an Institutional Review Board / Independent Ethics Committee (IRB/IEC). Documentation of IRBs/IECs for this clinical trial can be found in the Trial Master File. The Investigator must provide documentation of IRB/IEC approval to the 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 subjects, and subject compensation programs. The IRB/IEC must be provided with a copy of the Investigator's Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the clinical trial or in the case of early termination, the Investigator will notify the IRB/IEC of the clinical trial's final status. Finally, the Investigator will report to the IRB/IEC on the progress of the clinical trial at intervals stipulated by the IRB/IEC.

16.4 Sponsor and Monitoring Responsibilities

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; the equipment used to assess variables in the clinical investigation is maintained and calibrated per manufacturer instructions and Sponsor requirements; and the study is conducted in compliance with the current approved protocol (and amendment[s], if applicable), with current GCP, and with applicable regulatory requirements.

All investigative sites will have a site initiation. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written, and fax correspondence. The assigned CSM will contact each site at appropriate intervals. The Lead Clinical Site Manager (LCSM) will determine the frequency of site visits. Close-out visits will take place after the last visit of the last subject.

Enrollment will be tracked and reported at regular intervals. Details regarding enrollment (eg, number of subjects pre-screened, screened, reasons for screen failures, etc.) may be requested of the investigative site and must be provided within a reasonable time period.

The Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements. The 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 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 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.

16.5 Regulatory Documentation and Records Retention

The Investigator is accountable for the integrity, retention, and security of all study related data. The Investigator must maintain accurate, complete, and current records relating to the clinical study. The Investigator must maintain the required records during the investigation and for a period of time specified by local law or per the Clinical Study Agreement, whichever is longer. If the Investigator retires, relocates, of for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations.

16.6 Clinical Trial Results

Any information other than that which is disclosed upon registration should not be discussed with persons outside the study. The protocol, study data, and information related to the study or to Alcon's products or research programs that is provided by Alcon (Confidential Information) is to be kept confidential, and not disclosed directly or indirectly to any third party other than those involved in the study who have a need to know.

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of Alcon, Inc. Alcon reserves the right of prior review of any publication or presentation of information related to the study. Alcon may use these data now and in the future for presentation or publication at Alcon's discretion or for submission to government regulatory agencies.

The existence of this clinical study is confidential and should not be discussed with persons outside of the study. You shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Alcon's products or a research program that is provided by Alcon to you (the "Confidential Information"). All such persons must be instructed not to further disseminate this information to others. You shall not use the Confidential Information for any purpose other than the study.

The foregoing obligations of confidence and non-use assumed by you shall not apply to : (a) information which at the time of disclosure is in the public domain; (b) information which

thereafter lawfully becomes part of the public domain other than through disclosure by or through you; (c) information which, as evidenced by your written records, was known by you prior to Alcon's disclosure; (d) information which is lawfully disclosed to you by a third party not under any obligation of confidence to Alcon; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to Alcon.

In signing this protocol, you agree to the release of the data from this study and acknowledge the above confidentiality and publication policy. The provisions of this Statement shall survive the completion of the study.

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18 APPENDICES