

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Intraocular Pressure Lowering Implant

Device Trade Name: CyPass[®] System (Model 241-S)

Device Procode: OGO

Applicant's Name and Address: Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150037

Date of FDA Notice of Approval: July 29, 2016

II. INDICATIONS FOR USE

The CyPass[®] System is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG).

III. CONTRAINDICATIONS

The CyPass[®] System is contraindicated under the following circumstances or conditions:

- In eyes with angle closure glaucoma.
- In eyes with traumatic, malignant, uveitic, or neovascular glaucoma or discernible congenital anomalies of the anterior chamber (AC) angle.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CyPass[®] System labeling.

V. DEVICE DESCRIPTION

The CyPass[®] System consists of the CyPass[®] Micro-Stent, which is contained in a loading device (Loader), and the CyPass[®] Applier.

The CyPass[®] Micro-Stent (**Figure 1**) is a polyimide tube with a fenestrated lumen and it is 0.25" (6.35 mm) long. The inner diameter of the stent is 0.012" (0.30mm) and the outer diameter is 0.017" (0.40 mm). At the proximal end the stent has 3 retention rings.

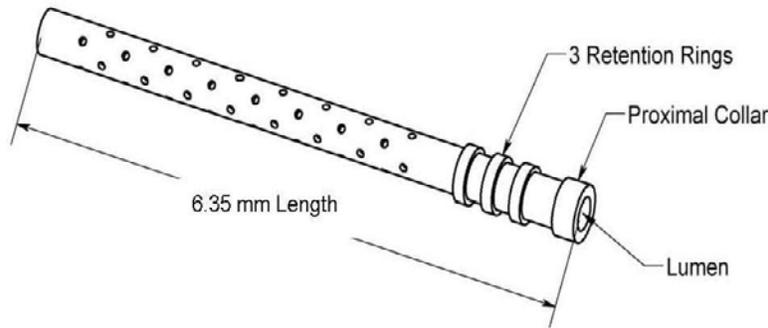


Figure 1: The CyPass[®] Micro-Stent

The CyPass[®] Micro-Stent is designed for placement in the angle of the eye, with the proximal end extending from the angle into the AC and the distal end residing in the supraciliary space. The CyPass[®] Micro-Stent is intended to allow outflow of aqueous fluid from the AC of the eye through and around the distal end of the tube (where the device proximal end resides) into the supraciliary and suprachoroidal spaces.

The CyPass[®] Micro-Stent is implanted into the eye using the CyPass[®] Applier. The CyPass[®] Applier (**Figure 2**) is the hand-held surgical instrument that consists of a medical-grade polymer hand piece with a guidewire assembly. The guidewire assembly includes the guidewire and the guidewire tube. The guidewire is manufactured of Nitinol and extends from inside of the handpiece through and beyond the distal end of the guidewire tube. The guidewire tube is manufactured of stainless steel and supports the guidewire. The guidewire is 0.11" (0.28 mm) in diameter and formed with a 0.48" (12 mm) radius of distal curvature and blunt distal tip to facilitate location and blunt dissection of the plane between the ciliary body and sclera.

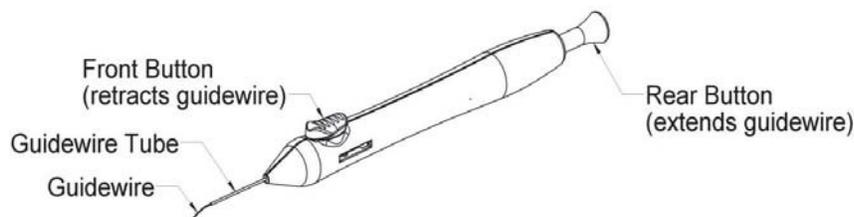


Figure 2: The CyPass[®] Applier with the guide wire extended

The CyPass[®] Micro-Stent is loaded onto the guidewire before insertion into the eye (**Figure 3**). Once the guidewire has positioned the CyPass[®] Micro-Stent at the desired location within the eye, the implant is released from the guidewire using the front button on the CyPass[®] Applier. This action withdraws the guidewire back into the guidewire tube, leaving the CyPass[®] Micro-Stent in position in the eye.

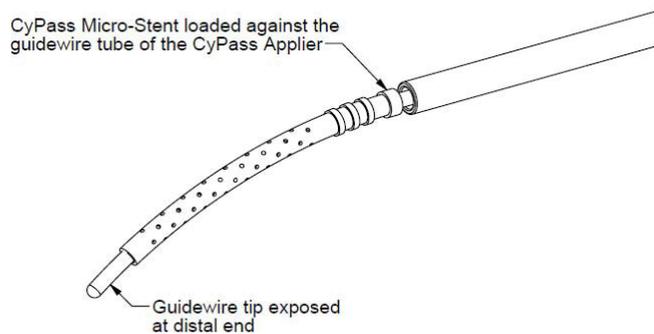


Figure 3: The CyPass[®] Micro-Stent loaded onto the CyPass[®] Applier guide wire

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of mild to moderate POAG. These alternatives include:

- Non-surgical treatment, such as IOP-lowering medications (topical eye drops or systemic IOP lowering drugs)
- Laser treatment
- Other incisional glaucoma surgery

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The CyPass[®] System is currently commercially available in the European Union countries of Germany and Spain. The CyPass[®] System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the CyPass[®] System in conjunction with cataract surgery.

Potential intraoperative adverse events (AEs) and complications accompanying CyPass[®] System in conjunction with cataract surgery may include, but are not limited to, the following:

- Posterior capsular rupture
- Vitreous in the AC
- Choroidal detachment
- Inadvertent perforation of sclera

- Hyphema obscuring the surgeon's view
- Inadvertent loss of vitreous not associated with the cataract procedure
- Choroidal hemorrhage or effusion
- Significant iris injury or trauma
- Significant corneal damage
- Zonular dialysis
- Difficulty with stent implantation, or inability to implant the stent

In addition, postoperative AEs may occur, including, but not limited to:

- Late chronic pain in the implanted eye
- Presence of a flat AC with lens/cornea touch
- Presence of a shallow chamber with peripheral iridocorneal apposition
- Loss of best-corrected visual acuity (BCVA)
- Persistent hypotony
- Maculopathy
- Hypotonic maculopathy
- CyPass[®] Micro-Stent obstruction
- CyPass[®] Micro-Stent explantation
- CyPass[®] Micro-Stent malposition, dislodgement or movement
- Wound dehiscence (persistent aqueous leak or fistula formation)
- AC cell and flare requiring either an increase in the standard protocol post-operative steroid regimen or initiation of steroid treatment following completion of the protocol postoperative steroid regimen
- Endophthalmitis
- Persistent hyphema
- Corneal opacification or corneal decompensation
- Corneal edema
- Retinal complications (dialysis, flap tears, retinal detachment, or proliferative vitreoretinopathy)
- Choroidal hemorrhage or choroidal effusion
- Elevated IOP requiring treatment with oral or intravenous medications or with surgical intervention
- Significant ptosis
- Atrophy/phthisis
- Significant foreign body sensation
- An increase in C:D ratio
- Worsening in visual field

The occurrence of some of these events may involve the necessity of secondary (additional) surgical intervention (SSI). For the specific AEs that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

1. **Biocompatibility Testing**

Biocompatibility testing was performed on the CyPass[®] Micro-Stent (or representative samples of the finished device; **Table 1A**), on the patient-contacting components of the CyPass[®] Applier (**Table 1B**) and on the Loader that holds the CyPass[®] Micro-Stent (**Table 1C**). The biocompatibility testing was performed in accordance with International Standard Organization (ISO) 10993-1: Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process, - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity, - Part 6: Tests for local effects after implantation, - Part 10: Test for irritation and skin sensitization, and – Part 11: Tests for systemic toxicity. Testing was conducted in compliance with Good Laboratory Practices.

Table 1A: Biocompatibility testing on the CyPass[®] Micro-Stent

Test	Test method	Results
Cytotoxicity	Minimum Essential Media (MEM) elution	Non-cytotoxic
Sensitization	Murine Local Lymph Node Assay (LLNA)	Non-sensitizer
Irritation	Intra-ocular irritation study in rabbits	Non-irritant
Acute Systemic Toxicity	Systemic injection in mice	Non-toxic
Sub-acute Systemic Toxicity	Intraperitoneal injection in mice	Non-toxic
Sub-chronic Systemic Toxicity	Intravenous injection in mice	Non-toxic
Pyrogenicity	Rabbit pyrogen test	Non-pyrogenic

Test	Test method	Results
Genotoxicity	Bacterial reverse mutation assay (Ames)	Non-mutagenic
Genotoxicity	In vitro mouse lymphoma assay	Non-mutagenic and non-clastogenic
Genotoxicity	In vivo mouse micronucleus assay	Non-clastogenic and non-aneugenic
Implantation	Intramuscular (3 months) implantation in rabbits	No significant biological local response
Implantation	Intraocular (1 month, 3 months and 6 months) implantation in rabbits	No significant biological local response

Table 1B: Biocompatibility testing on the CyPass[®] Applier

Test	Test method	Results
Cytotoxicity	MEM Elution	Non-cytotoxic
Sensitization	Guinea pig maximization study	Non-sensitizer
Irritation	Intra-ocular irritation study in rabbits	Non-irritant
Acute Systemic Toxicity	Systemic injection in mice	Non-toxic

Table 1C: Biocompatibility testing on the Loader

Test	Test method	Results
Cytotoxicity	MEM elution	Non-cytotoxic
Sensitization	LLNA	Non-sensitizer
Irritation	Intra-ocular irritation study in rabbits	Non-irritant
Acute Systemic Toxicity	Systemic injection in mice	Non-toxic

2. Physico-chemical Testing

Physico-chemical testing was conducted to physically characterize and verify the stability of the device throughout the potential implant life span. Physico-chemical testing (**Table 2**) of the CyPass[®] Micro-Stent was performed on test articles representative of the finished device in accordance with ISO 11979-5: Ophthalmic implants- Intraocular lenses- part 5: Biocompatibility and American National Standard for Ophthalmic - Implantable Glaucoma devices (ANSI Z80.27).

Table 2: Physico-chemical testing on the CyPass[®] Micro-Stent

Test	Purpose	Results
Infrared Scanning	Test for acceptance and identity of raw material	Pass
Exhaustive extraction	Identification and quantification of extractable compounds	No liquid and volatile extractable detected. The non-volatile and metal levels identified did not raise toxicology concerns
Leachable	Identification and quantification of leachable compounds	No liquid and volatile leachables detected. The metal levels identified did not raise toxicology concerns
Hydrolytic stability	Demonstrate the hydrolytic stability of the device	The device is stable for a time period equivalent to 5 years of real time hydrolytic exposure

3. Physical and Mechanical Testing

The CyPass[®] Micro-Stent, CyPass[®] Applier and the CyPass[®] Loader were subjected to the physical and mechanical testing in accordance with ANSI Z80.27. These tests are summarized in the tables below:

Table 3: Physical and mechanical testing of the CyPass[®] Micro-Stent

Test	Purpose	Acceptance Criteria	Results
Surface quality	Ensure device components are free from pits, scratches, cracking and crazing	Surface defects not observed at $\geq 10x$ magnification or visible to a trained observer without magnification	Pass

Test	Purpose	Acceptance Criteria	Results
Edge quality	The edges of the CyPass [®] Micro-Stent appear smooth and free of burrs and flash magnification.	Edge defects are not visible at 10x magnification	Pass
Dimensions	Device overall dimensions are within tolerances.	Nominal length, outer diameter (OD) and inner diameter (ID) meet pre-specified tolerances	Pass
Physical stability	The physical properties of the device are maintained stability under physiological conditions	Functional testing and dimensional stability are maintained following immersion in Solution (BSS) for 14 days at 37°C ± 2°C.	Pass
Pressure/Flow Characteristics	Characterize the flow dynamics of the device	Device resistance and pressure/flow characteristics are tested under physiological conditions with no observable unintended leaks	Pass
Structural integrity (Pull force)	Determine if the stent could withstand an appropriate axial-pull force load.	The CyPass [®] Micro-Stent can withstand an axial-pull force of 0.5N without breaking	Pass
Structural integrity (Lateral load)	The CyPass [®] Micro-Stent maintained structural integrity in the presence of lateral forces associated with implantation and <i>in situ</i> placement.	The CyPass [®] Micro-Stent has sufficient strength to maintain structural integrity in the presence of lateral forces that are expected to be experienced clinically.	Pass

4. Sterilization, Package Integrity, Shelf Life, and Transport Stability

CyPass[®] Micro-Stent System is sterilized by electron (E) beam irradiation. The sterilization validation and dose audit verifications were performed in accordance with ISO 11137-1, “Sterilization of health care products- Radiation - Part 1: Requirements for development, validation, and routine control of sterilization process for medical devices” and ISO 11137-2, “Sterilization of health care products -Radiation – Part 2:

Establishing the sterilization dose.” The validation and dose audit verifications confirmed that the E beam sterilization process achieves a Sterility Assurance Level (SAL) of 10^{-6} . Bacterial endotoxin testing was performed to demonstrate that the CyPass[®] System is non-pyrogenic using the Limulus Amebocyte Lysate (LAL) Kinetic Chromogenic method.

The CyPass[®] Micro-Stent is supplied inside a polycarbonate “Loader” that is packaged together with the CyPass[®] Applier in a thermoform tray. The tray is heat sealed with a Tyvek lid. The tray is enclosed in a chipboard box.

Packaging, shipping, and shelf life studies were conducted to verify that the packaging for the CyPass[®] System maintains a sterile barrier and that the device performance meets product specification through a shelf life of 18 months. Following distribution simulation and real time aging, the applicant performed dye penetration testing, peel strength testing, bubble leak testing, and visual inspection. The results of the sterilization, packaging, shelf life and transport stability studies are summarized in **Table 4**.

Table 4: Sterility, Shelf Life, and Transport Stability Testing

Test	Purpose	Acceptance Criteria	Results
E Beam Validation	Evaluate sterility	No positive sterility results after exposure to the verification dose	Pass
Bioburden Determination	Evaluate sterility	<1000 cfu/unit	Pass
Bacterial endotoxin	Evaluate sterility	≤0.2 EU/device	Pass
Package Evaluation – Peel Strength Testing	Evaluate seal integrity	Peel strength ≥ 1.0 lbf.	Pass
Package Evaluation –Dye Penetration Testing	Evaluate seal Integrity	Dye does not penetrate to the opposite side of the seal or to the interior of the seal via a defined channel	Pass

Test	Purpose	Acceptance Criteria	Results
Package Evaluation – Bubble Leak Testing	Evaluate whole package integrity	No constant stream of bubble indicating a specific area of failure	Pass
Transport Stability	Evaluate package integrity and device stability	Manufacturing specification met after exposing samples to simulated transport conditions and aging.	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDY

The safety and effectiveness of the CyPass[®] System was assessed through a clinical trial, known as the COMPASS Study (Protocol TMI-09-01) under Investigational Device Exemption (IDE) G080209. The applier that was utilized in the COMPASS Trial differs in design from the applier that will be marketed as part of the CyPass[®] System. See Section XI below for supportive data for the modified applier. The aim of the COMPASS study was to establish a reasonable assurance of safety and effectiveness of cataract surgery with the CyPass[®] Micro-Stent for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma (POAG) in the US. Data from this clinical study were the primary basis for the PMA approval decision. Key safety and effectiveness information derived from the pivotal study are summarized below.

A. Study Design

The COMPASS Trial (Protocol TMI-09-01) was a prospective, randomized, comparative, multicenter investigation conducted in the United States, in which a total of 505 subjects from 24 sites were randomized in a 3:1 fashion to undergo either implantation of the CyPass[®] Micro-Stent after uncomplicated cataract surgery (CyPass[®] group) or to undergo cataract surgery without implantation of the CyPass[®] Micro-Stent (Control group). A total of 374 subjects were randomized to the CyPass[®] group and 131 subjects were randomized to the Control group. In each subject, only one eye was considered to be the study eye. Enrollment in the study began in September of 2009 and the last study subject was randomized in March of 2013. Randomized subjects were followed for 2 years postoperatively. The database for this PMA reflected data collected through April 3, 2015.

The subjects and Medical Monitor were masked to treatment assignments. The observer turning the dial for Goldmann applanation was masked.

In the initial phase of the study, 75 subjects (49 in the CyPass[®] group and 26 in the Control group) were randomized and followed for a minimum of 3 months

postoperatively. Safety data, which included 3 to 6 month follow-up for these 75 subjects were submitted to the FDA and approval for expansion to include the full study population was granted on June 14, 2011. During the expansion phase, 430 additional subjects (325 in the CyPass[®] group and 105 in the Control group) were randomized.

There were two (2) hypotheses for the primary effectiveness endpoint. The first hypothesis was that a larger proportion of subject eyes who received the CyPass[®] device would meet the primary effectiveness endpoint than those who received cataract surgery alone. In order to demonstrate the effectiveness of the CyPass[®] Micro-Stent, the 24-month IOP response rate of the CyPass[®] group was better than that of the Control group and the 24-month IOP response rate of the CyPass[®] group was better than 0.5 (conditioned on the observed Cataract-only rate greater than 35%).

The sample size calculation was based on the hypothesis testing for effectiveness, and that for the evaluation of safety. At 24 months, because the CyPass[®] subject sample size (300) required for observing at least 1 safety event was larger than the CyPass[®] subject sample size (266) required to detect a difference in 24-month IOP response rate, at least 505 subjects (372 subjects for the CyPass[®] group and 133 subjects for the Control group) needed to be randomized in this study.

The study included a clinical events committee (CEC), data safety monitoring board (DSMB), medical monitor, and specular microscopy reading center.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the COMPASS study was limited to subjects who met the following preoperative inclusion criteria:

- Male or female, 45 years of age or older.
- Diagnosis of POAG in the designated study eye.
- At the Screening Visit, a mean (or median) medicated IOP ≤ 25.0 mmHg or an unmedicated IOP ≥ 21.0 mmHg and ≤ 33.0 mmHg in the designated study eye.
- At the Baseline Visit, an unmedicated mean diurnal IOP ≥ 21.0 mmHg and ≤ 33.0 mmHg, which also had to be ≥ 3.0 mmHg higher than the medicated IOP measured at the Screening Visit, in the study eye.
- Diagnosis of glaucoma in the designated study eye within 90 days prior to the Screening Visit, which was substantiated with ophthalmoscopy and visual field testing with the Humphrey automated perimeter using the SITA Standard 24-2 testing algorithm. Mean deviation score had to be ≥ -12.0 dB and < 0 dB.

For subjects without a previously documented history of glaucoma, Humphrey 24-2 SITA Standard visual field testing confirming diagnosis of glaucoma had to be performed at least twice by the time of the Baseline Visit.

- Gonioscopy confirming normal angle anatomy in the designated study eye at the anticipated site of CyPass[®] Micro-Stent implantation.
- Shaffer grade of \geq III in all four quadrants of the designated study eye.
- Operable age-related cataract with BCVA of 20/40 or worse in the designated study eye, and eligible for phacoemulsification cataract surgery. If BCVA was better than 20/40, testing with a Brightness Acuity Meter (BAT) on a medium setting had to result in BCVA of 20/40 or worse.

Enrollment in the COMPASS study was limited to subjects who met the following operative inclusion criteria:

- Capsulorhexis was intact and centered.
- Posterior capsular bag was intact.
- The intraocular lens (IOL) was well-centered in the capsular bag.
- There was no evidence of zonular dehiscence/rupture.
- The AC angle was able to be clearly visualized using direct gonioscopy.

Subjects were not permitted to enroll in the COMPASS study if they met any of the following exclusion criteria:

- Inability to complete a reliable 24-2 SITA Standard Humphrey visual field on the designated study eye at screening (fixation losses, false positive errors and false negative errors should not be greater than 30%).
- Use of more than 3 ocular hypotensive medications (combination medications counted as 2 medications) in the designated study eye.
- Use of oral hypotensive medication treatment for glaucoma in the fellow eye.
- The subject would be at significant risk by washout of ocular hypotensive medication in the designated study eye. Note, this subjects at significant risk where those with advanced glaucoma evidenced by an afferent pupillary defect, a C:D ratio \geq 0.9 or encroachment of field loss within the central 5° as indicated by \geq 2 depressed points of 0.5% probability on the 24-2 SITA Standard Humphrey visual field.
- Previous glaucoma procedure with or without an implantable glaucoma device in the designated study eye. *Note that laser treatments to the trabecular meshwork performed >3 months prior to study enrollment were not exclusionary.*
- History of elevated IOP due to steroid response in the designated study eye.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at defined intervals through 24 months. **Table 5** shows the schedule of events and procedures at each protocol-required visit.

Table 5: Schedule of events and procedures

PROCEDURE	PREOPERATIVE VISITS		POSTOPERATIVE VISITS										
	SCREEN	BASE-LINE	OP	1 DAY	1 WK	1 M	3 M	6 M	12 M	12 M WASHOUT ²	18 M	24 M	24 M WASHOUT ³
Informed Consent	X												
Demographics	X												
Medical History	X	X											
Ocular Medications	X	X	X	X	X	X	X	X	X		X	X	
Randomization			X										
BCVA (Snellen)	X												
BCVA (ETDRS)		X			X	X	X	X	X		X	X	
Pinhole VA				X									
IOP	X	X ¹		X	X	X	X	X	X ¹	X ¹	X	X ¹	X ¹
Manifest Refraction	X	X			X	X	X	X	X		X	X	
Pachymetry	X								X			X	
Gonioscopy	X		X		X	X	X	X	X		X	X	
Slit Lamp Exam	X	X		X	X	X	X	X	X		X	X	
Visual Field	X						X	X	X			X	
C:D Ratio	X						X	X	X			X	
Specular Microscopy		X					X	X	X			X	
AE Assessment			X	X	X	X	X	X	X		X	X	
Subject Questionnaire	X						X		X			X	

¹ Diurnal IOP measurements were performed at the Baseline, 12 M and 24 M Postoperative Visits. At the 12 M and 24 M Postoperative Visits, only subjects who were ocular hypotensive medication-free had diurnal IOP measurements performed. Subjects using ocular hypotensive medications at these visits underwent medication washout and returned for the 12 M or 24 M Postoperative Washout Visit for diurnal IOP measurements. All diurnal IOP measurements were performed at 8:00 AM (± 1 hr), 4 hours (± 0.5 hr) later, and again 4 hours (± 0.5 hr) later.
² The 12 M Washout Visit was required only for subjects using ocular hypotensive medications at the 12 M Postoperative visit.
³ The 24 M Washout Visit was required only for subjects using ocular hypotensive medications at the 24 M Postoperative visit.

3. Clinical Endpoints

The primary effectiveness endpoint was the proportion of eyes with $\geq 20\%$ decrease in the 24- month unmedicated mean diurnal intraocular pressure (DIOP) from baseline.

Subjects were defined as non-responders if they did not achieve the primary effectiveness endpoint, they were missing 24-month IOP assessment outcomes, if ocular hypotensive medications were not washed out at the 24-month visit, if they underwent an IOP-affecting secondary surgical procedure (i.e., iridotomy, iridectomy, trabeculectomy, glaucoma shunt implantation, argon laser trabeculoplasty, selective laser trabeculoplasty), or other surgery that would affect IOP, or if they underwent CyPass[®] Micro-Stent explant or repositioning.

The first secondary effectiveness endpoint was the mean change in 24-month DIOP from baseline, and the second secondary effectiveness endpoint was defined as the proportion of eyes with 24-month unmedicated mean DIOP ≥ 6 mmHg and ≤ 18 mmHg.

Each endpoint required a comparison between the CyPass[®] and Control groups. The primary effectiveness analysis was performed using the Intent to Treat (ITT)

population, comprised of all randomized subjects grouped according to their randomization assignment.

With regard to safety, anticipated and unanticipated AEs were reported for all subjects randomized in the study. Best Corrected Visual Acuity (BCVA), central corneal pachymetry, slit lamp and fundus exams, gonioscopy and central corneal endothelial cell density (ECD) were also used to assess safety.

B. Accountability of PMA Cohort

At the time of database lock, of 897 subjects enrolled in the PMA study, 53.5% (480/897) subjects are available for analysis at the completion of the study, the 24 month post-operative visit.

Of the 897 subjects enrolled, 43.0% (n = 386) were discontinued prior to surgery, primarily due to failure to meet eligibility criteria or withdrawal of consent prior to the operative day. An additional 6 subjects (0.7%) were discontinued due to cataract surgery-related complications rendering them ineligible for study randomization. The remaining 56.3% (n = 505) subjects were randomized. Upon completion of uncomplicated cataract surgery, 374 subjects were randomized to the CyPass[®] group in which the CyPass[®] Micro-stent was to be implanted, and 131 subjects were randomized to the Control group, in which no additional surgery was planned. At 24 months postoperatively, 355 subjects in the CyPass[®] group and 125 Control group subjects completed the study, which included the 24-month washout postoperative visit if it was required.

Subjects were analyzed according to 4 separate population cohorts:

- The Intent to Treat (ITT) population was used for the primary effectiveness analysis. The ITT analysis population included all subjects randomized. Subjects were grouped according to their randomization assignment (as randomized).
- The safety analysis population included all subjects who were randomized and treated. Subjects were grouped according to whether CyPass[®] Micro-Stent implantation was initiated and not according to their randomization assignment. CyPass[®] Micro-Stent implantation initiation included successful implantation as well as implantation that was attempted but discontinued. Note that subjects who exited during the Screening or Baseline visits and subjects who underwent cataract surgery but were not randomized are not included in the safety analysis population.
- A modified ITT population was also analyzed. This population consisted of all but 6 subjects in the ITT population who no longer met study eligibility after amendment of the study protocol.
- The Per Protocol (PP) analysis population included all randomized subjects who met all of the following criteria:
 - All inclusion criteria listed in Sections 6.1 and 6.2 of the protocol.

- No exclusion criterion listed in Section 6.3 in the protocol.
- Treatment was consistent with randomization schedule.
- Completion of the 12 month follow-up exam for the 12-month data analyses.
- Completion of the 24- month follow-up exam for the 24-month data analyses.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population were as follows:

Table 6: Demographic information

Characteristic	Parameter	Randomization Group		Total N = 505
		Cataract Surgery with CyPass [®] N = 374	Cataract Surgery Only N = 131	
Age (Years)	n	374	131	5
	Mean	70.3	70.2	70
	Std. Dev.	8.45	8.17	8.
	Median	70	70	7
	Minimum	45	48	4
	Maximum	89	93	9
	p-value		0.8567	
Age Category n (%)	< 60 years	40 (10.7)	12 (9.2)	52 (10.3)
	60 to < 70 years	132 (35.3)	50 (38.2)	182
	70 to < 80 years	148 (39.6)	54 (41.2)	202
	>= 80 years	54 (14.4)	15 (11.5)	69
	p-value		0.7857	
Gender n (%)	Male	177 (47.3)	59 (45.0)	236 (46.7)
	Female	197 (52.7)	72 (55.0)	269

Table 6 (Continued)

Characteristics	Parameter	Randomization Group		Total N=505
		Cataract Surgery with CyPass [®] N = 374	Cataract Surgery Only N = 131	
Race n (%)	p-value		0.6847	
	White	314 (84.0)	108 (82.4)	422 (83.6)
	Black or African	36 (9.6)	11 (8.4)	47 (9.3)
	Hispanic or Latino	15 (4.0)	7 (5.3)	22 (4.4)
	Asian	5 (1.3)	1 (0.8)	6 (1.2)
	American Indian or Alaska Native	4 (1.1)	2 (1.5)	6 (1.2)
	Caribbean	0 (0.0)	1 (0.8)	1 (0.2)
	Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.8)	1 (0.2)
Study eye n (%)	p-value		0.3732	
	OD	196	64 (48.9)	260
	OS	178	67 (51.2)	245
	p-value		0.5424	

The p-value tests for differences between the CyPass and Control groups.

Table 7: Screening and baseline parameters for randomized subjects

Parameter		Randomization Group		Total N = 505 n (%)
		Cataract Surgery with CyPass [®] N = 374 n (%)	Cataract Surgery Only N = 131 n (%)	
Number of Ocular Hypotensive Medications Used at Screening Visit ¹	0	62 (16.6)	25 (19.1)	87 (17.2)
	1	153 (40.9)	60 (45.8)	213 (42.2)
	2	101 (27.0)	26 (19.8)	127 (25.1)
	3	58 (15.5)	20 (15.3)	78 (15.4)
	p-value		0.4020	
Screening BCVA ² (Snellen)	20/30	1 (0.3)		1 (0.2)
	20/40 or Worse	373 (99.7)	131 (100.0)	504 (99.8)
	p-value		1.0000	

Smaller sample sizes (n) for some clinical parameters are due to missing values. The p-value test for difference between the CyPass[®] and Control groups.

¹Combination ocular hypotensive medications were counted as 2 medications. No subjects randomized to the study were using oral glaucoma medications at the Screening or Baseline Visit.

²Screening BCVA is the worse of either the Snellen BCVA or Median BAT assessments performed at the Screening Visit.

Table 7 (Continued)

Parameter		Randomization group		Total N = 505 n (%)
		Cataract Surgery with CyPass [®] N = 374 n (%)	Cataract Surgery Only N = 131 n (%)	
Baseline BCVA (ETDRS)	20/20 or Better	21 (5.6)	3 (2.3)	24 (4.8)
	20/25	54 (14.4)	22 (16.7)	76 (15.0)
	20/32	95 (25.4)	36 (27.4)	131 (25.9)
	20/40 or Worse	204 (54.5)	70 (53.4)	274 (54.2)
	p-value		0.4283	
Visual Field Mean Deviation (MD)	n	374	131	505
	Mean (SD)	-3.4 (2.86)	-3.7 (2.87)	-3.5 (2.86)
	Median	-2.7	-3.4	-2.8
	Min, Max	-16, 1.7	-13, 0.8	-16, 1.7
	p-value		0.2580	
Central Pachymetry (µm)	n	374	131	505
	Mean (SD)	550.0 (36.18)	549.9 (35.25)	550.0
	Median	550.0	548.0	550.0
	Min, Max	452, 654	467, 619	452, 654
	p-value		0.9770	
Screening IOP (mmHg) for Subjects Not Using Ocular Hypotensive Medication	n	62	25	87
	Mean (SD)	24.2 (2.93)	25.2 (3.85)	24.5 (3.23)
	Median	23.8	24.5	24.0
	Min, Max	21.0, 33.0	18.5, 32.0	18.5, 33.0
	p-value		0.1763	
Screening IOP (mmHg) for Subjects Using Ocular Hypotensive Medication	N	312	106	418
	Mean (SD)	17.4 (2.91)	17.6 (2.98)	17.5 (2.93)
	Median	17.0	17.0	17.0
	Min, Max	11.0, 25.0	11.5, 25.0	11.0, 25.0
	p-value		0.1763	
Baseline Unmedicated DIOP (mmHg)	N	374	131	505
	Mean (SD)	24.4 (2.77)	24.5 (2.95)	24.4 (2.82)
	Median	23.7	23.7	23.7
	Min, Max	21.0, 33.0	21.0, 32.3	21.0, 33.0
	p-value		0.8763	

Table 7 (Continued)

Parameter		Randomization group		Total N = 505 n (%)
		Cataract Surgery with CyPass® N = 374 n (%)	Cataract Surgery Only N = 131 n (%)	
Axial Length (mm)	n	360	127	487
	Mean (SD)	24.1 (1.20)	24.3 (1.26)	24.2 (1.22)
	Median	23.9	24.1	24.0
	Min, Max	20.8, 28.7	21.6, 30.0	20.8, 30.0
	p-value		0.1933	
Keratometry, Flattest (Diopters)	N	360	127	487
	Mean (SD)	43.6 (1.54)	43.5 (1.51)	43.6 (1.53)
	Median	43.6	43.6	43.6
	Min, Max	39.0, 47.5	40.1, 48.5	39.0, 48.5
	p-value		0.4528	
Keratometry, Steepest (Diopters)	N	360	127	487
	Mean (SD)	44.6 (1.58)	44.5 (1.64)	44.5 (1.59)
	Median	44.5	44.4	44.5
	Min, Max	39.9, 49.6	40.4, 49.6	39.9, 49.6
	p-value		0.6254	

The p-value tests for differences between the CyPass® and Control groups.

D. Safety and Effectiveness Results

1. **Safety Results**

The analysis of safety was based on the safety cohort of 505 randomized subjects and 480 subjects available for analysis at the 24 month evaluation. The key safety outcomes for this study are presented below in **Tables 8 to 10**.

Adverse effects that occurred in the PMA clinical study

Intraoperative AEs

Because final study eligibility and randomization to treatment was determined post-cataract surgery, no subjects experiencing a cataract-surgery related AE were randomized to the study. Accordingly, intraoperative AEs occurred only in the CyPass® group. A summary of intraoperative AEs is shown in **Table 8**.

A total of 25 intraoperative AEs were reported in 20 out of 374 CyPass[®] subjects (5.3%). Implantation of the CyPass[®] Micro-Stent was successful in almost all cases, with non-implantation reported in only 2 subjects (0.5% (2/374)).

**Table 8: Intraoperative AEs
Available data for safety population**

AE	Cataract Surgery with CyPass[®] (N = 374) n (%)
Subjects with Any AE	20 (5.3%)
Secondary ocular surgical intervention – AC lavage	1 (0.3%)
Choroidal detachment	0 (0.0%)
Choroidal hemorrhage or effusion	0 (0.0%)
Corneal abrasion	1 (0.3%)
Corneal damage, significant	0 (0.0%)
Cyclodialysis cleft, oversized	7 (1.9%)
CyPass [®] non-implantation	2 (0.5%)
Descemet’s membrane break	1 (0.3%)
Hyphema obscuring surgeon’s view	10 (2.7%)
Iris injury or trauma, significant – iridodialysis	1 (0.3%)
Scleral perforation	0 (0.0%)
Subconjunctival hemorrhage	2 (0.5%)
Vitreous loss (not associated with cataract surgery)	0 (0.0%)
Zonular dialysis	0 (0.0%)

Postoperative AEs

Postoperative ocular AEs are reported in **Table 9**. There were no reports of flat AC with lens cornea touch, shallow AC with iridocorneal apposition, shallow AC with peripheral iridocorneal apposition, wound dehiscence, endophthalmitis, corneal opacification or decompensation, choroidal hemorrhage or effusion, ptosis, atrophy/phthisis or cup-to-disc (C:D) increase of ≥ 0.3 . Moreover, no cases of retinal detachment, pupillary block, endophthalmitis, or hypopyon were reported during the study.

A similar number of subjects in each group experienced postoperative ocular AEs (39.3% of subjects [n = 147] in the CyPass[®] group and 35.9% of subjects [n = 47] in the Control group). A similar proportion of randomized subjects in both groups underwent secondary ocular surgical intervention during the study. In the CyPass[®] group, 5.3% of subjects (n = 20) underwent secondary ocular surgeries,

while in the Control group, 5.3% of subjects (n = 7) had secondary ocular surgeries.

Corneal edema associated with the surgical procedure resolved within the first postoperative month in 98% of CyPass[®] group subjects. A single case of persistent corneal edema occurred, an incidence of 0.27% in the CyPass[®] group. Anterior segment inflammation, which was generally mild, resolved in 95% of CyPass[®] subjects by 3 months. Based on available data at the 24-month visit, BCVA was 20/40 or better for 98.6% of subjects (n = 350) in the CyPass[®] group and 98.4% of subjects (n = 126) in the Control group.

Two (2) serious AEs (SAE) were reported during the course of the study. One of these SAEs, peripheral anterior choroidal effusion, was considered to be related to the CyPass[®] Micro-Stent. This event was not reported as “choroidal hemorrhage or effusion” because it did not meet the pre-specified criteria for that AE (i.e., there was no hemorrhagic component obstructing vision or causing pain). In addition, the effusion was restricted to the anterior supraciliary space and was only detectable with ultrasound imaging. This SAE was associated with IOL subluxation, which was successfully addressed with IOL repositioning and other complications, all of which resolved without sequelae by the 24-month visit. The other SAE was pseudophakic bullous keratopathy (PBK). Descemet stripping endothelial keratoplasty (DSEK) was performed approximately 1 year postoperatively.

Table 9: Postoperative AEs*

AE	Cataract Surgery with CyPass[®] (N = 374) n (%)	Cataract Surgery Only (N = 131) n (%)
Subjects with Any AE	147 (39.3%)	47 (35.9%)
Corneal edema at/after 30 days postoperative, or severe in nature	13 (3.5%)	2 (1.5%)
Subconjunctival hemorrhage	6 (1.6%)	1 (0.8%)
CyPass [®] malposition ¹	7 (1.9%)	Not applicable
CyPass [®] movement/dislodgement without sequelae ²	10 (2.7%)	Not applicable
CyPass [®] obstruction by iris, vitreous, lens, fibrous overgrowth, fibrin or blood	8 (2.1%)	Not applicable
Hypotony (IOP < 6 mmHg) at/after 30 days postoperative	11 (2.9%)	0 (0.0%)
IOP => 10 mmHg over baseline at/after 30 days	16 (4.3%)	3 (2.3%)
Maculopathy, cystoid edema	5 (1.3%)	1 (0.8%)
Maculopathy, hypotonic	3 (0.8%)	0 (0.0%)

AE	Cataract Surgery with CyPass[®] (N = 374) n (%)	Cataract Surgery Only (N = 131) n (%)
Worsening in visual field MD by => 2.5 dB as compared with preoperative	25 (6.7%)	13 (9.9%)
AC cell and flare requiring steroid treatment at/after 30 days postoperative ³	32 (8.6%)	5 (3.8%)
Conjunctivitis	4 (1.1%)	3 (2.3%)
Keratitis	1 (0.3%)	1 (0.8%)
BCVA loss => 10 letters read at/after 3 month postoperative visit	33 (8.8%)	20 (15.3%)
Worsening in any ocular symptom by ≥ 2 points to severe/very severe at/after 3 months postoperative:	21 (5.6%)	4 (3.1%)
- Blurred vision	7 (1.9%)	2 (1.5%)
- Dry eye	2 (0.5%)	1 (0.8%)
- Foreign body sensation	4 (1.1%)	1 (0.8%)
- Glare	10 (2.7%)	3 (2.3%)
- Halos	10 (2.7%)**	2 (1.5%)
- Inability to read without glasses	1 (0.3%)	0 (0.0%)
- Ocular pain	5 (1.3%)	1 (0.8%)
- Pulsing lines of light	1 (0.3%)	0 (0.0%)
- Redness	1 (0.3%)	0 (0.0%)
- Scratchiness & itchiness	0 (0.0%)	1 (0.8%)
- Starbursts	1 (0.3%)	0 (0.0%)

*Occurring at 2% or greater in either group, or other adverse events known to be associated with glaucoma procedures or potential risks with stent implantations

**Two subjects in the CyPass[®] group who reported worsening of symptoms of halos had received multifocal IOLs.

¹CyPass[®] malposition is defined as CyPass[®] Micro-Stent positioning after deployment with resulting clinical sequelae, including secondary surgical intervention to modify device position (e.g., repositioning, proximal end trimming or explantation), corneal endothelial touch by device, or progressive endothelial cell loss > 30%. All cases of CyPass[®] Micro-Stent malposition were reported within the first postoperative week. Secondary surgical intervention to modify device position was performed in 5 cases: surgeries were performed within the first postoperative week in 3 cases (CyPass[®] Micro-Stent explant and repositioning) and at postoperative months 32 and 48 months (CyPass[®] Micro-Stent proximal end trimming) for the remaining 2 cases. Endothelial cell loss > 30% at 24 months postoperatively was reported in 3 cases; 2 cases were those in which device trimming surgery was performed at postoperative 32 and 48 months respectively.

²One case of CyPass[®] Micro-Stent movement without sequelae was reported within the first postoperative week, while the remaining 9 cases were reported between 3 and 24 months

postoperatively. No secondary surgeries to modify device positioning were performed in these cases and none of the cases had endothelial cell loss > 30% at 24 months postoperatively.

³One case of chronic anterior uveitis was reported in a subject in whom CyPass[®] Micro-Stent implantation was complicated by an oversized cyclodialysis cleft.

[^]While not reported as an AE, IOP \geq 10 mmHg over baseline *within* the initial 30 days postoperatively occurred in 6.4% (n = 24) of CyPass[®] subjects and 20.6% (n = 27) of Control subjects. Short-term use of oral ocular hypotensive medication for pressure control was employed for 3 subjects in the CyPass[®] group and 3 subjects in the Control group; paracentesis on postoperative day 1 was performed in 1 additional subject in the Control group.

In addition to the AEs reported in Table 9, AEs that occurred at <2% in both groups included ocular medication allergy, corneal abrasion, non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, diabetic macular edema, eyelid dermatitis and significant foreign body sensation at or after 3 months postoperative. AEs that occurred at <2% in the CyPass[®] group included environmental allergy, map-dot fingerprint dystrophy, dry eye syndrome, hordeolum, trichiasis, foreign body with mucus filament, peripheral anterior choroidal effusion, ciliary body edema, hyphema >2mm after 1 day postoperative, IOL complication (Crystalens Z syndrome, anterior malposition, and subluxation), worsening in slit lamp findings at or after 3 months postoperative (corneal staining and pigment deposition), choroidal folds without hypotony, wet age-related maculopathy, posterior vitreous detachment, vitreal-macular traction, blepharitis, episcleritis, ocular migraine, and vertical binocular diplopia. AEs that occurred at < 2% in the control group included chalazion, metallic foreign body, ectropion, and chronic ocular pain after 3 months postoperative.

Secondary Ocular Surgical Interventions

Secondary ocular surgeries during the course of the study occurred in 5.3% of CyPass[®] group subjects (n = 20) and 5.3% (n = 7) of subjects in the control group. Secondary surgeries reported in both groups are shown in **Table 10**. Three (3) additional subjects had CyPass[®]-related surgical procedures after completion of study participation.

Table 10: Secondary ocular surgical intervention AEs
Available data from safety population

AE	Cataract Surgery with CyPass [®] (N = 374) n (%)	Cataract Surgery Only (N = 131) n (%)
Subjects with any event in category	20 (5.3%)	7 (5.3%)
AC reformation for choroidal folds treatment ¹	1 (0.3%)	0 (0.0%)
CyPass [®] explantation	1 (0.3%)	Not applicable
CyPass [®] obstruction lysis ²	1 (0.3%)	Not applicable

AE	Cataract Surgery with CyPass [®] (N = 374) n (%)	Cataract Surgery Only (N = 131) n (%)
CyPass [®] reposition	3 (0.8%)	Not applicable
DSEK	1 (0.3%)	0 (0.0%)
IOL reposition	3 (0.8%)	0 (0.0%)
Combined procedure – CyPass [®] lumen occlusion/trabeculectomy/vitreotomy	1 (0.3%)	Not applicable
Laser trabeculectomy	0 (0.0%)	3 (2.3%)
Paracentesis at/after 1 week postoperative	5 (1.3%)	0 (0.0%)
Pigment lysis ³	1 (0.3%)	0 (0.0%)
Trabeculectomy	0 (0.0%)	2 (1.5%)
Tube-shunt implant	2 (0.5%)	0 (0.0%)
Secondary surgeries related to trabeculectomy or tube-shunt implant	2 (0.5%)	1 (0.8%)
Secondary Surgeries unrelated to CyPass[®]		
Aspiration of lens material	2 (0.5%)	0 (0.0%)
Combined procedure - blepharoplasty/browpexy	0 (0.0%)	1 (0.8%)
Combined procedure – pars plana vitrectomy/membrane	1 (0.3%)	0 (0.0%)
Lid cyst excision	1 (0.3%)	0 (0.0%)
Limbal relaxing incisions	1 (0.3%)	2 (1.5%)
Macular photocoagulation	0 (0.0%)	1 (0.8%)
Panretinal photocoagulation	2 (0.5%)	1 (0.8%)

¹Sodium hyaluronate AC reformation was performed 5 times for treatment of low IOP and persistent choroidal folds.

²Nd:YAG laser photolysis was performed a single time for removal of iris tissue obstructing CyPass[®] Micro-Stent.

³Laser photolysis was performed 4 times for removal of pigment deposition on the anterior IOL optic secondary to iris trauma caused by a failed CyPass[®] Micro-Stent implant attempt.

Other Postoperative Observations

Reporting of other ocular observations was at the study investigator's discretion. Similar data may not be reported for every subject, or consistently within the course of a given subject's study participation. Consequently, no conclusions regarding the overall frequency of these findings can be drawn from the incidence rates noted. The other ocular observations that were reported postoperatively and which could impact safety in CyPass[®] subjects included, but were not limited to: microhyphema (16%; 59/374); focal peripheral anterior synechiae (13%; 48/374); early hypotony, defined as IOP < 6 mmHg with the first 30 days postoperatively (9%; 35/374); partial obstruction of the CyPass[®] Micro-Stent lumen (5%;

31/374); pigment dispersion (5%; 16/374); and AC shallowing (6% ; (21/374). Other ocular observations reported at a rate < 2% include: chemosis (2.4% 9/374), CyPass[®] Micro-Stent intraluminal blood (1.9%; 7/374), Schlemm's intracanalicular blood (1.6%; 6/374), pseudophacodonesis (0.5%; 2/374), posterior synechiae (0.5%; 2/374), pupillary miosis (0.3%; 1/374), and transient forward IOL movement related to AC shallowing (0.3%; 1/374).

Additional Safety Data Gathered after Study Exit

Post-study exit, the following CyPass[®]-related secondary ocular surgeries have been reported, which are not included in Table 10:

- One subject underwent planned surgical occlusion of the CyPass[®] Micro-Stent lumen with Prolene suture for IOP control approximately 28 months post-CyPass[®] Micro-Stent implantation.
- Another subject underwent secondary surgery for CyPass[®] Micro-Stent proximal end trimming due to anterior device positioning associated with significant endothelial cell loss approximately 32 months post-CyPass[®] Micro-Stent implantation. Anterior device positioning was reported within the first postoperative week.
- One subject underwent secondary surgery for CyPass[®] Micro-Stent proximal end trimming due to anterior device positioning associated with significant endothelial cell loss approximately 48 months post-CyPass[®] Micro-Stent implantation. Anterior device positioning was reported within the first postoperative week.

Corneal Endothelial Cell Density

There was little difference in endothelial cell loss (ECL) between the CyPass[®] and Control groups and results were consistent with the peer-review literature benchmarks of cataract-related ECL.^{1,2} In the 24-month consistent cohort of subjects in the safety population (n = 322 CyPass[®] subjects and 114 Control subjects), mean endothelial cell density (ECD) was 2107 cells/mm² (± 482) at 24 months in comparison with 2422 cells/mm² (± 409) at baseline in the CyPass[®] group. Mean ECD was 2181 cells/mm² (± 441) at 24 months in comparison with 2427 cells/mm² (± 359) at baseline in the Control group. Mean ECD change at 24 months in the CyPass[®] group was -13% (± 14). Mean ECD change at 24 months in the Control group was -10% (± 14). A similar proportion of subjects in each group (11% [95% Confidence Interval (CI): 7.2, 13.9] in the CyPass[®] group and 9% [95% CI: 3.6, 14.0]) experienced significant ECL (e.g., ECL > 30%) at 24 months postoperatively.

Endothelial cell loss > 30% occurred in 9.6% (16/166) of subjects for whom 1 CyPass[®] Micro-Stent retention ring was reported visible at 2 or more postoperative examinations and there were no reports of 2 or more rings visible at any examination for these subjects. In the group of subjects for whom 2 CyPass[®]

Micro-Stent rings were visible at two (2) or more postoperative examinations, ECL > 30% occurred in 9.8% (4/41) of subjects. The denominators are not representative of the full study cohort because data collection methodology was a confounding factor in the determination of a relationship between CyPass[®] Micro-Stent positioning and ECL. The primary landmark used for determination of CyPass[®] positioning was the number of CyPass[®] Micro-Stent retention rings visible. However, these data were not reported for every subject, nor were they reported consistently within the course of a given subject's study participation.

Effectiveness Results

Results from the primary and secondary endpoints are shown in **Table 11**. The primary effectiveness endpoint was met, with 72.5% (271/374) in the CyPass[®] group and 58.0% (76/131) in the Control group achieving a clinically significant ($\geq 20\%$) decrease in unmedicated mean DIOP from baseline to the hypotensive medication-free 24-month postoperative examination. This difference between groups was statistically significant ($p=0.0030$).

The first secondary endpoint, a clinically significant mean change in IOP between baseline and hypotensive medication-free 24-month postoperative examination, was met. The mean reduction in unmedicated mean DIOP from baseline to 24 months was 7.0 mmHg (SD 4.5) in the CyPass[®] group compared to 5.3 mmHg (SD 4.0) in the Control group ($p < 0.0001$).

The second secondary effectiveness endpoint was also met, with 61.2% (229/374) in the CyPass[®] group and 43.5% (57/131) in the Control group achieving unmedicated mean DIOP ≥ 6 mmHg and ≤ 18 mmHg at the hypotensive medication-free 24-month postoperative examination. The difference between groups was statistically significant ($p=0.0005$).

Table 11: Primary and secondary effectiveness results

Effectiveness Endpoint (Evaluated at 24 Months Postoperatively)	CyPass® N=374	Control N=131	Difference (CyPass® - Control)	p-value
Primary Effectiveness Endpoint				
Proportion of subject eyes with unmedicated mean DIOP reduction \geq 20% from baseline	72.5%	58.0%	14.4%	0.003
1st Secondary Effectiveness Endpoint				
Difference in unmedicated mean DIOP (mmHg) reduction from baseline	-7.0	-5.3	-1.7	<0.0001
2nd Secondary Effectiveness Endpoint				
Proportion of subject eyes with unmedicated mean DIOP \geq 6 mmHg and \leq 18 mmHg	61.2%	43.5%	17.7%	0.0005

Additional detail regarding the reasons patients did not achieve the primary endpoint (IOP non-responders) is shown in **Table 12**.

Table 12: Summary of IOP non-responder categories

	Cataract Surgery with CyPass® N = 374 n (%)	Cataract Surgery Only N = 131 n (%)
Total Non-Responders	103 (27.5%)	55 (42.0%)
Non-Responders: 24-month unmedicated mean DIOP reduction < 20% vs. baseline	74 (19.8%)	44 (33.6%)
Non-Responders for reasons other than IOP reduction ¹	29 (7.8%)	11 (8.4%)
- Did not undergo glaucoma medication washout	0 (0.0%)	1 (0.8%)
- Secondary glaucoma surgery ²	3 (0.8%)	4 (3.1%)
- Other IOP-affecting secondary surgery ³	6 (1.6%)	0 (0.0%)
- CyPass implantation discontinued	2 (0.5%)	NAP
- Missed 24-month visit	19 (5.1%)	6 (4.6%)

n = number of eyes meeting corresponding criteria.

¹One subject is included in more than 1 category of “Non-Responders for reasons other than IOP reduction”

²Secondary glaucoma surgeries include iridotomy, iridectomy, trabeculectomy, glaucoma shunt implantation and laser trabeculoplasty.

³Other IOP-affecting secondary surgeries include CyPass[®] Micro-Stent reposition, CyPass[®] Micro-Stent explant, vitrectomy, and laser lysis of presumed CyPass[®] Micro-Stent obstruction.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 29 investigators of which none were full-time or part-time employees of the sponsor and 1 investigator had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 investigators
- Significant payment of other sorts: 1 investigator
- Proprietary interest in the product tested held by the investigator: 0 investigators
- Significant equity interest held by investigator in sponsor of covered study: 0 investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The applicant indicated that one investigator had financial arrangements with the applicant. However, due to the study design this financial arrangement did not affect the interpretation of the results. Specifically, the COMPASS trial was a multicenter pivotal study in which 24 sites randomized 505 subjects to one of two (2) treatment groups. The study's effectiveness endpoints were objective consisting of IOP measurements taken at least six (6) times at the study baseline and the endpoints visits. In addition, statistical analyses indicated that there is no significant interaction effect of treatment by sites. Therefore, these characteristics of the study design mitigated the potential for bias to be introduced in the study results and the information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

- A. During the COMPASS Trial, the CyPass[®] Micro-Stent was implanted using a CyPass[®] applier slightly different from the commercially available applier. The applier used in the COMPASS Trial used a different mechanism to hold the CyPass[®] on the delivery guidewire prior to implantation, and guidewire retraction was performed by sliding the retraction button toward the back of the applier hand piece. The commercially available CyPass[®] applier was clinically tested in the RePass Study, a multi-surgeon case series of 91 subjects evaluating the intraoperative safety

and performance in a similar patient population to that of the COMPASS Trial. In this study, the CyPass[®] Micro-Stent was successfully implanted in all cases. Device implantation was successful on the initial placement attempt in 87 cases (95.6%); 1 case required two (2) implantation attempts, while the number of attempts was undocumented for the remaining three (3) cases. Postoperative gonioscopy revealed the CyPass[®] Micro-Stent to be visible, adequately positioned and without obstruction in the vast majority of cases reviewed. AEs related to device placement and stability were similar in nature to AEs observed in the CyPass[®] arm of the COMPASS Trial.

From the CyCLE and DUETTE Studies, number of implant attempts, intraoperative complications, long-term postoperative safety findings/events, and gonioscopy examinations were provided for eight (8) subjects. From the European Union, 13 (0.6%) complaints were collected related to the loading of the CyPass[®] Micro-Stent onto the implant delivery guidewire since the device was introduced in 2012. Clinical concern was not raised with the information provided.

Study	Purpose	Control arm	Primary Endpoint
RePass Study (Protocol TMI-14-03)	Safety and Performance of the Transcend CyPass [®] System Applier Model 241 (91 cases of Model 241)	None	None. Retrospective, consecutive case series.
CyCLE Clinical Studies (Protocol TMI-09-02)	A Multi-Center Registry Study to Capture Data with Respect to CyPass [®] System Clinical Experience (4 cases of Model 241)	Cypass [®] -cataract surgery and Cypass [®] -standalone	Incidence of intraoperative and postoperative AEs to 3 years
DUETTE Clinical Studies (Protocol TMI-10-03)	Study of CyPass [®] Micro-Stent Implantation in Patients with Open angle Glaucoma Refractory to Single or Multi-Agent Topical Therapy (4 cases of Model 241)	None	IOP reduction at 12 months

B. For the COMPASS Trial, presented in **Table 13** are incidence rates of ocular symptoms reported by patients in the CyPass[®] and Control groups to be “severe” or “very severe” at various time points during the study. The questionnaire used to collect these data has not been validated, and therefore the true rates of these symptoms may differ from those presented in Table 13.

**Table 13: Ocular symptoms considered by patients to be severe or very severe
Available data from safety population**

Symptom	Severity	Screening n (%)	Month 3 n	Month 12 n	Month 24 n
Cataract Surgery with CyPass[®] (N = 374)					
Blurred Vision	Severe	44 (11.8)	5 (1.4)	4 (1.1)	3 (0.8)
	Very Severe	7 (1.9)	1 (0.3)	2 (0.6)	
Glare	Severe	62 (16.6)	11 (3.1)	9 (2.6)	9 (2.5)
	Very Severe	13 (3.5)	1 (0.3)	1 (0.3)	1 (0.3)
Foreign Body Sensation	Severe	11 (2.9)	1 (0.3)	2 (0.6)	3 (0.8)
	Very Severe	5 (1.3)	1 (0.3)	2 (0.6)	
Pain in Eye	Severe	4 (1.1)	2 (0.6)	2 (0.6)	2 (0.6)
	Very Severe			1 (0.3)	
Halos	Severe	22 (5.9)	7 (1.9)	3 (0.9)	3 (0.8)
	Very Severe	6 (1.6)	1 (0.3)	1 (0.3)	
Cataract Surgery Only (N = 131)					
Blurred Vision	Severe	12 (9.2)	3 (2.4)	2 (1.6)	1 (0.8)
	Very Severe	4 (3.1)			1 (0.8)
Glare	Severe	21 (16.0)	4 (3.3)	3 (2.5)	5 (3.9)
	Very Severe	7 (5.3)		1 (0.8)	2 (1.6)
Foreign Body Sensation	Severe	2 (1.5)	2 (1.6)	2 (1.6)	1 (0.8)
	Very Severe				
Pain in Eye	Severe	1 (0.8)		2 (1.6)	1 (0.8)
	Very Severe	1 (0.8)			
Halos	Severe	12 (9.2)			1 (0.8)
	Very Severe	5 (3.8)		1 (0.8)	1 (0.8)

C. For the COMPASS Trial, of subjects who were responders (e.g., 24-month unmedicated mean DIOP was reduced by $\geq 20\%$ as compared with baseline in the absence of IOP-affecting surgery during the study), 96.5% of subjects in the CyPass[®] group (251/271) and 72.4% of subjects in the Control group (55/74) were not using ocular hypotensive medication at 24 months.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The COMPASS pivotal trial met its primary and secondary effectiveness endpoints.

B. Safety Conclusions

The risks of the CyPass[®] Micro-Stent are based on data collected in the pivotal COMPASS clinical study conducted to support PMA approval as described above.

Device-related serious AEs include:

- Hypotony maculopathy was reported in 0.8% of CyPass[®] subjects (3/374). In one difficult case, peripheral anterior choroidal effusion in 1 subject led to IOL subluxation and hypotony maculopathy requiring secondary surgical procedures
- Maculopathy un-associated with hypotony occurred in 0.5% (2/374) of CyPass[®] subjects leading to secondary surgical procedure in 1 case.
- Persistent corneal edema requiring corneal transplant was reported in 0.3% (1/374) of CyPass[®] subjects with baseline compromised cornea.
- Malposition was reported in 1.9% of CyPass[®] subjects (7/374) and resulted in device explant, device reposition, device trimming, and significant endothelial cell loss.
- SSIs were needed in 5.3% of CyPass[®] subjects (20/374) during the study, not including 2 cases of device trim and 1 case of surgical occlusion needed afterwards.
- Chronic anterior uveitis was reported in 1/374 subjects (0.3%) in whom CyPass[®] Micro-Stent implantation was complicated by an oversized cyclodialysis cleft.

Device-related non-serious AEs include:

- The most common AEs in the CyPass[®] arm included:
 - Iritis (8.6% or 32/374)
 - Loss of BCVA at least 10 letters (0.8% or 33/374)
 - Visual field loss progression (6.7% or 25/374)
 - Corneal edema (3.5% or 13/374)

- Later hypotony (2.9% or 11/374)
- Later IOP \geq 10 mmHg over baseline (4.3% or 16/374)
- The most common clinical safety findings in the CyPass[®] arm included:
 - Microhyphema (16% or 59/374)
 - Focal peripheral anterior synechiae (13% or 48/374)
 - Early hypotony (9% or 35/374)
 - AC shallowing (6% or 21/374)
 - Partial obstruction of the CyPass[®] Micro-Stent device lumen (5% or 31/374)
 - Pigment dispersion (5% or 16/374)

Intraoperative AEs of note include:

- Hyphema obscuring surgeon's view (2.7% or 10/374)
- Larger than expected cyclodialysis cleft (1.9% or 7/374)
- Inability to implant stent (0.5% or 2/374)
- Iridodialysis (0.3% or 1/374)
- Secondary ocular surgical intervention –AC lavage (0.3% or 1/374).

C. **Benefit-Risk Determination**

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. As such, the COMPASS pivotal trial achieved its primary and secondary effectiveness endpoints.

There were no cases of loss of light perception, endophthalmitis, suprachoroidal hemorrhage, diplopia, wound leak, flat AC, or bleb complications - AEs anticipated with conventional incisional glaucoma surgery (i.e., tube or trabeculectomy).

The most serious AEs were related to rare instances of hypotony maculopathy, peripheral anterior choroidal effusion, IOL subluxation and corneal compromise.

The most common safety issues were related to bleeding, inflammation, and damage to angle tissue (i.e., iridodialysis, larger than expected cyclodialysis cleft, ciliary body edema, and chronic anterior uveitis).

Due to the relatively small size of the CyPass[®] Micro-Stent, device malposition, device movement and tube obstruction was a challenge. SSIs and close supervision (i.e., specular microscopy) were needed to address these concerns.

Additional factors to be considered in determining probable risks and benefits for the CyPass[®] System device included:

- Although the CyPass[®] System is a second-of-a-kind minimally invasive glaucoma surgical (MIGS) device, it is the first glaucoma device approved or cleared to be implanted in the suprachoroidal space.

- The COMPASS Trial was a prospective, randomized, controlled, multicenter study in which 505 subjects were randomized and followed for 24 months postoperatively. The study incorporates glaucoma medication washout, safety and effectiveness determination with 2-year follow-up, specular microscopy, and sample size which exceeded the sufficient number of subjects to have 95% probability of detecting AEs occurring at a rate of 1%.
- Of note, there was a very low percentage of major protocol deviations (0.02%) and high degree of subject accountability. Ninety-five percent (95%) of subjects randomized (n = 480) completed the 24 month study follow-up period, which is significant given the age and co-morbidity associated with the study.
- Though it is the first non-refractory glaucoma study to incorporate specular microscopy, not all items in the recognized ANSI Z80.27-2014 standard were implemented (e.g., baseline minimum for endothelial cell count, standardized AE definitions) which led to complicated AEs adjudication and need for a post-approval study.
- The safety of the Model 241 applier was supported by studies conducted outside the United States and European Union complaint information from the CE marked device.
- The effectiveness of the Control arm was underestimated and led to a difference between the CyPass[®] and cataract only arm that was not very large in the COMPASS trial.
- The sponsor proposes a surgeon training program and has revised its product labeling.
- Mild to moderate primary open angle glaucoma can also be managed with medicine, lasers, and other incisional glaucoma surgeries. Conventional incisional glaucoma surgeries (i.e., tube or trabeculectomy) are typically reserved for more severe disease because it is marked with a turbulent postoperative course.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information summarized above, the data support that for the modest reduction of intraocular pressure in adult patients with mild to moderate primary open-angle glaucoma the probable benefits outweigh the probable risks when used in conjunction with cataract surgery.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The CyPass[®] System in conjunction with cataract surgery is a novel addition to an ophthalmologist's toolkit to address mild to moderate primary open angle glaucoma which is not anticipated to preclude other options.

Since it is implanted in conjunction with cataract surgery, the CyPass[®] System offers a safer surgical option with the aim of a modest reduction in intraocular pressure.

XIV. CDRH DECISION

CDRH issued an approval order on July 29, 2016. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – An Observational Multicenter Clinical Study to Assess the Long-Term Safety and Long-Term Effectiveness of the Transcend CyPass[®] System Glaucoma Implant in Patients with Primary Open-Angle Glaucoma Who Have Completed Participation in the COMPASS Trial. The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The COMPASS trial extension (COMPASS-XT) received on May 4, 2016, is a multicenter, observational study with no planned interventions to evaluate the long-term safety of the CyPass[®] Micro-Stent in subjects who have completed Study Protocol TMI-09-01 in IDE G080209 to support the PMA. Enrolled subjects from G080209 will be recruited. Subjects will be followed until 5 years post-randomization in study protocol TMI-09-01.

The safety endpoints include the rate of occurrence of sight-threatening AEs; change in best corrected visual acuity (BCVA); rate of occurrence of ocular adverse events (AE); slit lamp, gonioscopy and fundus findings; change in visual field mean deviation (MD) change in central corneal thickness, change in central corneal endothelial cell density (ECD). The effectiveness endpoints include mean change in IOP, proportion of subjects who are not using ocular hypotensive medication with $\geq 20\%$ decrease in IOP from baseline, and proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg.

2. OSB Lead PMA Post-Approval Study – CyPass[®] System New Enrollment Post-Approval Study. The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. On July 19, 2016 (email) you agreed to conduct a study as follows:

The CyPass[®] System New Enrollment Post-Approval Study is designed to evaluate the rate of clinically relevant complications associated with CyPass[®] Micro-Stent placement

and stability using the CyPass[®] 241-S applier as determined through 36 months of follow-up in the post-market setting.

The study will be a prospective, multicenter, single arm, new enrollment study of patients implanted with the CyPass[®] System after cataract surgery for the reduction of IOP in adult patients with mild to moderate POAG.

The primary endpoint for the study is the rate of clinically relevant complications associated with CyPass[®] Micro-Stent implantation, specified as follows:

1. Failure to implant the CyPass[®] Micro-Stent, defined as inability to successfully deploy or insert the CyPass[®] Micro-Stent.
2. Clinically significant CyPass[®] Micro-Stent malposition is defined as CyPass[®] Micro-Stent positioning after deployment such that:
 - a. The device is not in the supraciliary space, or
 - b. There is a clinical sequela resulting from device position including, but not limited to:
 - Secondary surgical intervention to modify device position (e.g., repositioning, proximal end trimming or explantation),
 - Corneal endothelial touch by device,
 - Corneal edema leading to loss of BCVA greater than two lines at the last postoperative visit, in comparison with preoperative BCVA,
 - Progressive endothelial cell loss (ECL), defined as reduction in endothelial cell count of 30% or more,
 - Erosion of device through sclera,
 - Device obstruction requiring secondary surgical intervention

The corresponding primary null hypothesis to be tested is that the observed rate of complications is greater than or equal to the performance target of 7.0%. The corresponding alternative hypothesis to be tested is that the observed rate of complications is less than the performance target.

Based on the study hypothesis, 450 eyes from 450 patients will need to be enrolled in order to ensure that 360 eyes of 360 patients are available for analysis at 36 months (allowing for 20% overall attrition). This sample size will provide 80% power to determine that the rate of clinically relevant complications associated with CyPass[®] Micro-Stent implantation is less than 7.0%.

Secondary safety endpoints to be assessed through 36 months postoperatively in this study are:

1. Rate of occurrence of sight-threatening adverse events including:
 - a. Persistent Best Spectacle Corrected Visual Acuity (BSCVA) loss of 3 or more lines
 - b. Endophthalmitis

- c. Corneal decompensation
- d. Retinal detachment
- e. Severe choroidal hemorrhage
- f. Severe choroidal detachment and aqueous misdirection
2. The rate of ocular secondary surgical interventions (SSI)
3. The rate of ocular SSIs associated with CyPass[®] Micro-Stent placement and stability

Secondary effectiveness endpoints to be assessed through 36 months postoperatively in this study are:

1. Mean change in IOP
2. Proportion of subjects with IOP reduction $\geq 20\%$ while using the same or fewer ocular hypotensive medications
3. Proportion of subjects who are not using ocular hypotensive medication with IOP ≥ 6 mmHg and ≤ 18 mmHg

Additional endpoints are as follows:

- Increase from baseline IOP of 10 mmHg or greater at any time at/after 30 days postoperative
- BCVA loss of 2 or more lines compared to baseline
- BCVA loss of 2 or more lines in comparison with best recorded BCVA at any postoperative visit
- Device movement

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Reuschel, A., *et al.*, Comparison of endothelial changes and power settings between torsional and longitudinal phacoemulsification. *J Cataract Refract Surg*, 2010. 36(11): p. 1855-61.
2. Buys, Y.M., *et al.*, Prospective randomized comparison of one- versus two-site Phacotrabeculectomy two-year results. *Ophthalmology*, 2008. 115(7): p. 1130-1133 e1.