SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Artificial Iris
Device Trade Name:	CustomFlex™ Artificial Iris
Device Procode:	QBT
Applicant's Name and Address:	Clinical Research Consultants, Inc. 3308 Jefferson Avenue, Upper Level Cincinnati, OH 45220
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P170039
Date of FDA Notice of Approval:	May 30, 2018

Breakthrough Device: Granted breakthrough device status (formerly known as the Expedited Access Pathway, or EAP) on December 21, 2017 because it offers a more effective treatment of aniridia and there are no approved or cleared alternatives commercially available.

II. INDICATIONS FOR USE

The CustomFlex™ Artificial Iris is indicated for use in children and adults for the treatment of full or partial aniridia resulting from congenital aniridia, acquired defects, or other conditions associated with full or partial aniridia.

III. CONTRAINDICATIONS

The CustomFlex™ Artificial Iris device is contraindicated in eyes with any of the following conditions:

- Uncontrolled ocular inflammation (e.g., uveitis)
- Severe chronic uveitis
- Microphthalmus
- Untreated retinal detachment
- Untreated chronic glaucoma
- Rubella cataract
- Rubeosis of the iris
- Proliferative diabetic retinopathy
- Stargardt's retinopathy
- Pregnant women

- Intraocular infections

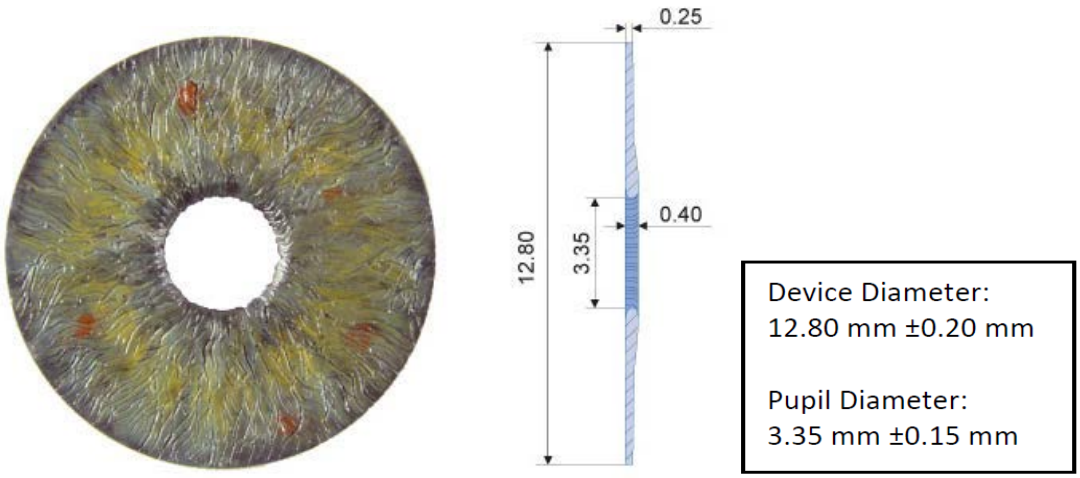
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CustomFlex™ Artificial Iris labeling.

V. DEVICE DESCRIPTION

The CustomFlex™ Artificial Iris device is a foldable iris prosthesis that is custom-made for each individual patient. The CustomFlex™ Artificial Iris prosthesis is manufactured from a commercially available ophthalmic silicone. Colorized silicone paste is applied by hand in a pattern to match the color of the natural iris using a photograph of the existing iris or, in the case of aniridia, the color of the photograph selected by the patient (Figure 1).

Figure 1: CustomFlex™ Artificial Iris Graphical Representation and Dimensions



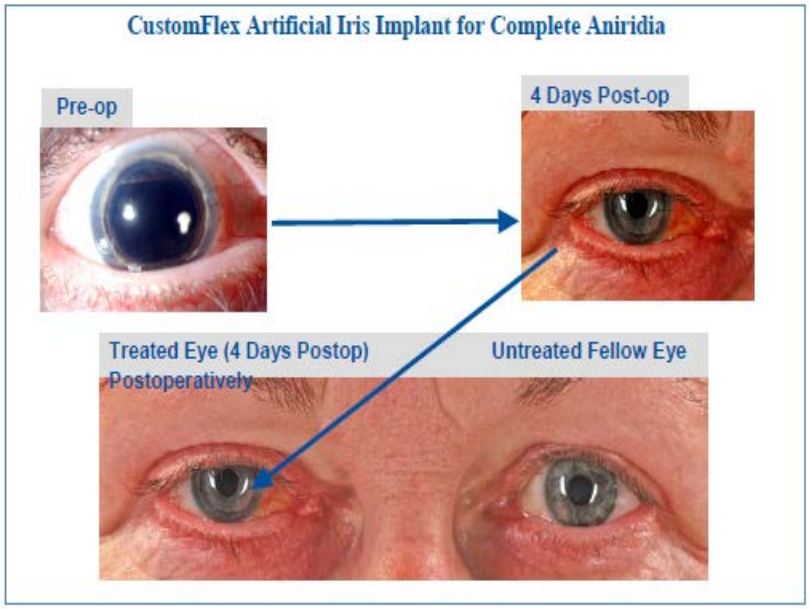
The CustomFlex™ Artificial Iris is available in two models: With Fiber or Fiber Free (Figure 2). The two (2) models are identical in every respect except that the With Fiber model has a polyester meshwork layer embedded in it to provide adequate tear strength to withstand suturing. The Fiber-Free model is suitable for sutureless implant techniques or can be sutured. The fiber-embedded device is more robust to tighter sutures and is less likely to induce cheese-wiring or tearing under higher suture tensions, though it is stiffer to fold.

Figure 2: CustomFlex™ Artificial Iris With Fiber and Fiber-Free Models

The CustomFlex™ Artificial Iris is implanted using the AMO Silver Series Intraocular Lens (IOL) Injector and the PSCST cartridge.

The CustomFlex™ Iris, implanted as a full device for complete aniridia, is shown in **Figure 3** below.

Figure 3: CustomFlex™ Artificial Iris preoperative and 4-day postoperative



The subjects receiving the CustomFlex™ Artificial Iris must be either pseudophakic (subjects with an IOL implanted), aphakic (subjects without a crystalline lens (e.g., after cataract extraction)), or eligible for crystalline lens extraction and implantation of an IOL.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently no iris prosthetic devices commercially available in the United States (US). Currently available alternative management options for patients with aniridia include:

- Tinted glasses
- Iris reconstruction

- Colored contact lenses
- Corneal tattooing

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 CustomFlex™ Artificial Iris has CE Mark and is commercially available in the European Union and all other countries that recognized the CE Mark. The CustomFlex™ Artificial Iris has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with the use of the device, surgical procedure, or IOL.

Device Related complications may include but may not be limited to:
- Worsening of photosensitivity and vision
- Elevated intraocular pressure (IOP)
- Decrease in Uncorrected Distance Vision (UCDVA)
- Decrease in Best Corrected Distance Visual Acuity (BSCVA)
- Eye infection/inflammation
- Device malpositioning, dislocations, and decentrations
- Secondary (additional) surgical intervention (SSI)

Intraocular Lens Related complications may include but may not be limited to:
- Anisometropia
- Glare/halos
- Diplopia
- IOL removal or replacement due to lens power calculation error

Surgery Related Adverse Events (AEs) may include but may not be limited to:
- Cystoid Macular Edema
- Hypopyon
- Endophthalmitis
- Device migration
- Pupillary Block
- Retinal Detachment
- Secondary surgical intervention (unplanned)
- Corneal Edema, persistent at 3 months or later
- Chronic iritis/anterior segment inflammation persistent at 3 months or later

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 (**Table 1**) was performed on the CustomFlex™ Artificial Iris in accordance with International Standard Organization (ISO) 11979-3:2006 Ophthalmic implants-Intraocular lenses-Part 5: Biocompatibility, 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, and - Part 10: Test for irritation and skin sensitization. Testing was conducted in compliance with Good Laboratory Practices.

Table 1: Biocompatibility Testing on the CustomFlex™ Artificial Iris

Test	Method	Acceptance Criteria	Results
Cytotoxicity	MEM Elution	Non-cytotoxic	Pass
Cytotoxicity	Direct contact	Non-cytotoxic	Pass
Sensitization	Guinea pig maximization study (saline and sesame oil extracts)	Non-sensitizer	Pass
Genotoxicity	Bacterial Reverse Mutation (Ames test; DMSO and saline extracts)	Non-genotoxic	Pass
Implantation	Intramuscular implantation (4 weeks) in rabbits	No significant biological local response	Pass

2. Physico-chemical Testing

Physico-chemical testing (**Table 2**) was conducted on the CustomFlex™ Artificial Iris to physically characterize and verify the stability. Physico-chemical testing was performed in accordance with ISO 11979-5: Ophthalmic implants- Intraocular lenses-part 5: Biocompatibility.

Table 2: Physico-Chemical Testing on the CustomFlex™ Artificial Iris

Test	Purpose	Acceptance Criteria	Results
Exhaustive extraction	Analysis of quantified extractable additives from aged and un-aged devices under exhaustive conditions	No significant release of leachables overtime	Pass
Leachables	Analysis of quantified extractable additives under physiological conditions	No significant release of leachables	Pass
Hydrolytic stability	Stability of material in aqueous environment	Stability of device over time	Pass
Photostability	Photostability of material when irradiated	Photostability	Pass

Test	Purpose	Acceptance Criteria	Results
Insoluble inorganics	Analysis of quantified release of inorganics	No significant release of inorganics	Pass

3. Mechanical Testing

The CustomFlex™ Artificial Iris was subjected to the mechanical testing in accordance with ISO 11979-3:2006 Ophthalmic implants - Intraocular lenses - Part 3: Mechanical properties and test methods. These tests are summarized in the **Table 3**.

Table 3: Mechanical Testing of the CustomFlex™ Artificial Iris

Test	Purpose	Acceptance Criteria	Results
Dimensional requirements	To determine if the device dimensions are within maximum tolerances	Described in ISO 11979-3	Pass
Topography	To determine the homogeneity of the textured anterior (colored) surface	Slightly curved peak lines and valleys, irregularly distributed, with predominant radial orientation	Pass
Recovery properties	To determine if the device maintains its dimensional properties and integrity after simulated surgical manipulation with forceps	Described in ISO 11979-3	Pass
Tear strength	To determine the tear strength of the device with prolene sutures (10-0)	50 mN and 500 mN for Fiber Free and With Fiber models, respectively	Pass
Injector compatibility	To determine if the device maintains its dimensional properties and integrity following simulated delivery with the AMO Silver Series Handpiece with PSCST cartridge	Described in ISO 11979-3	Pass

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

The CustomFlex™ Artificial Iris is sterilized by steam. The sterilization validation were performed in accordance with ISO 14937 Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices and ISO 17655-1 Sterilization of health care products - Moist heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices. The validation confirmed that the sterilization process achieves a Sterility Assurance Level (SAL) of 10^{-6}. Bacterial endotoxin testing was performed to

demonstrate that the CustomFlex™ Artificial Iris is non-pyrogenic using the Limulus Amebocyte Lysate (LAL) Kinetic turbimetric assay.

The CustomFlex™ Artificial Iris is placed into a polypropylene lens case that includes an inlay (also termed a "cover") which protects the CustomFlex™ Artificial Iris from hydroplaning during shipping and transportation. After the CustomFlex™ device is placed in the lens case, it is filled with 0.9% normal saline solution. The opening on the top is closed with an aluminum foil which is sealed to the polypropylene lens case container. The sealed lens case is then placed into a paper-film sterility bag, sealed and steam sterilized.

Packaging, shipping, and shelf life studies were conducted to verify that the packaging for CustomFlex™ Artificial Iris the maintains a sterile barrier and that the device performance meets product specification through a shelf life of 48 months. 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
Sterilization validation	Evaluate sterility	SAL of 10^{-6}	Pass
Bioburden Determination	Evaluate sterility	Action Limit: 60 CFU/device	Pass
Bacterial endotoxin	Evaluate sterility	≤0.2 EU/device	Pass
Package evaluation – Peel strength	Evaluate seal integrity over shelf life	Per ASTM F88	Pass
Package Evaluation – Bubble emission test	Evaluate whole package integrity over shelf life	Per ASTM F2096	Pass
Transport stability	Evaluate package integrity and device integrity following exposure to simulated climate and transport conditions	Package Integrity by Bubble emission test per ASTM F2096, Dye test per ASTM F1929 and Peel test per ASTM F88 Device Integrity by evaluation of surface & bulk homogeneity as described in ISO 11979-3	Pass

5. Magnetic Resonance Imaging (MRI) Safety Information

The CustomFlex™ Artificial Iris implant is MR Unsafe.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Prior Clinical Experience

The PMA approval is primarily based on the protocol AI-001 conducted under the IDE study (G100259). Prior to the initiation of the AI-001 study, the device had been implanted in the US in 64 patients through compassionate use requests. The data is summarized below and comprise of the first 64 CustomFlex™ Artificial Iris devices implanted in the US under FDA-granted compassionate use exemptions at Cincinnati Eye Institute. The indications for implantation were as follows:

Table 5: Indications for Treatment with the CustomFlex™ Artificial Iris in the Compassionate Use Requests (prior to the initiation of the AI-001 study)

INDICATION	NUMBER OF IMPLANTS (N)	AGE RANGE (years)
Congenital aniridia	28 eyes/15 patients	6 to 51
Post-tumor excision	6 eyes/6 patients	41 to 73
Trauma/Acquired iris defect	17 eyes/17 patients	4 to 82
ICE syndrome	1 eye/1 patient	56
Post-surgical trauma	5 eyes/5 patients	6 to 51
Post-epithelial ingrowth	2 eyes/2 patient	66 to 82
Severe aniridic keratopathy	5 eyes/3 patients	23 to 35

Each of the eyes implanted under FDA Compassionate Use approval achieved marked reduction or alleviation of their visual symptoms. All who had the potential for improved visual acuity achieved improvement in their measured Snellen visual acuity. Additionally, all patients are satisfied with the appearance of their prosthesis. None of the implanted eyes sustained any complications or AEs directly related to the CustomFlex™ Artificial Iris. A brief summary of these cases is presented below, stratified by the indication.

Congenital Aniridia and Severe Aniridic Keratopathy
Twenty eight (28) eyes of 15 patients received the CustomFlex™ Artificial Iris for the treatment of congenital aniridia. In 23 eyes of 12 patients, the device was placed within the capsular bag. Five (5) eyes in three (3) patients in this subgroup have severe aniridic keratopathy. The artificial iris devices were implanted successfully; and all five (5) eyes have undergone, or will undergo, planned stem cell transplants for treatment of the aniridic keratopathy.

Post Melanoma Excision
Six (6) eyes of six (6) patients received the device for defects following iris melanoma removal.

Acquired Iris Defects

Seventeen (17) eyes of 17 patients received the CustomFlex™ Artificial Iris device for acquired iris defects resulting from trauma (N=15), HSV iritis (N=1), or toxic anterior segment syndrome (N=1). In five (5) eyes, the device was sutured to the scleral wall.

Iridocorneal endothelial (ICE) syndrome
One eye with ICE syndrome has received the CustomFlex™ Artificial Iris device. The implant was placed within the capsular bag.

Post-surgical and post-epithelial ingrowth-related iris defects
Seven (7) eyes in seven (7) patients have received the CustomFlex™ Artificial Iris device. All patients are doing well with no notable events.

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of implantation with CustomFlex™ Artificial Iris for the treatment of aniridia in the US under IDE # G100259 (protocol AI-001). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between November 26, 2013 and November 4, 2016. The database for this PMA reflected data collected through December 1, 2017 and included 447 eyes. FDA approved up to 14 investigators for participation in protocol AI-001 in the IDE study (G100259). A total of 12 investigators enrolled subjects in the PMA and Continued Access cohorts, and 10 investigators have enrolled subjects in the Compassionate Use cohort.

The study was a prospective, non- randomized, multicenter study to determine the safety and effectiveness of the CustomFlex™ Artificial Iris for the treatment of eyes having a diagnosis of congenital or acquired full or partial iris defect.

The study was comprised of 4 Cohorts enrolling up to 580 subjects, as follows:

- PMA Primary Eyes 180 subjects
- PMA Fellow Eyes (subset of PMA Primary Eye subjects)
- Continued Access 250 subjects
- Compassionate Use 150 subjects

Same day bilateral implantation of the CustomFlex™ Artificial Iris prosthesis was not permitted in the study. Fellow eye treatment was not performed sooner than 4 weeks (1 month) following the initial/first eye implant achieving medical stability. The fellow eye must also meet all inclusion and exclusion criteria for enrollment in the study or qualify for compassionate use treatment.

Sample Size:

Since the population with congenital aniridia, acquired defects, or other conditions associated with full or partial anirida is known to be small, the number of subjects suggested for the clinical investigation is not based on a statistical evaluation of an objective effectiveness outcome measure, but is based on demonstrating the cumulative device related AE rate is less than 5% for all AEs in the study and no individual AE should exceed a rate of 1%.

If the individual device related adverse rate is 1.0%, then the required sample size to achieve 80% power is 164 evaluable subjects. A sample size of 180 subjects was enrolled in the PMA cohort to provide for a 10% dropout rate. Each subject in the clinical trial served as their own control. Study outcomes were compared to baseline measures.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the AI-001 study was limited to subjects who met the following inclusion criteria:

   - 22 years of age or older.
   - Having a diagnosis of congenital or acquired full or partial iris defect in the study eye.
   - Having symptoms of light sensitivity, photophobia, and/or glare in the study eye.
   - Subjects should be pseudophakic, aphakic or require cataract extraction.
   - Signed and received a copy of the signed written informed consent.
   - Willingness and ability to comply with schedule for follow-up visits and postoperative evaluations.

   Subjects were not permitted to enroll in the AI-001 study if they met any of the following exclusion criteria:

   - Uncontrolled ocular inflammation (e.g., uveitis).
   - Preoperative intraocular pressure >21 mm Hg.
   - Subjects with a current condition that, in the investigator's opinion, would interfere with the treatment.
   - Subjects with any of the following conditions:
     - Severe chronic uveitis
     - Micro-ophthalmos
     - Untreated retinal detachment
     - Untreated chronic glaucoma
     - Rubella cataract
     - Rubeosis of the iris
     - Proliferative diabetic retinopathy
   - Female subjects who are pregnant or lactating at the time of surgery.
   - Subjects with a known sensitivity to required postoperative study medications (4^{th} generation fluoroquinolone or steroid anti-inflammatory), if an alternative medication is not available.

- Subjects under legal guardianship or who, in the investigator's opinion, lack the mental capacity to provide written informed consent for study participation.
- Stargardt's retinopathy.
- Subjects with gastric ulcers or diabetes mellitus in whom high doses of postoperative systemic steroids are required.
- Surgical difficulty of the planned surgery, which might increase the potential for complications.
- No useful vision or vision potential in the fellow eye.
- Clear crystalline lens (in eyes with intact natural, crystalline lens).
- Implantation of a CustomFlex™ Artificial Iris prosthesis in the contralateral eye within the previous 4 weeks.
- In the investigator's opinion, the presence of a condition or finding in the contralateral eye that would make it unsafe to implant a CustomFlex™ Artificial Iris prosthesis in the study eye.

2. Follow-up Schedule

   All subjects were scheduled to return for follow-up examinations at day 1, week 1, and months 1, 3, 6, and 12. The following examination schedule was followed from screening through 12 months of postoperative visits:

   - Screening/Photos (Within 30 Days Pre-Manufacturing, whenever practicable)
   - Manufacturing Period (~4 to 8 Weeks)
   - Preoperative (Day -30 to Day 0 Preoperatively)
   - Operative (Day 0)
   - Day 1: 1-3 days postoperatively (Day 1 Postoperatively)
   - Week 1: 4-14 days postoperatively (Week 1 Postoperatively)
   - Month 1: 21-60 days postoperatively (Month 1 Postoperatively)
   - Month 3: 70-120 days postoperatively (Month 3 Postoperatively)
   - Month 6: 150-210 days postoperatively (Month 6 Postoperatively)
   - Month 12: 330-420 days postoperatively (Month 12 Postoperatively/Final Exam)

   Preoperatively, the complete screening eye examination of the operative eye and subject histories included, where medically possible:

   - Demographics (date of birth, sex, ethnicity)
   - Ocular history, including pre-existing pathology and previous ocular surgery
   - Aniridic indication (indication for artificial iris implant)
   - Medical history
   - Medication history (current prescription and chronically used non-prescription medications)
   - Keratometry for corneal curvature
   - UCVA
   - BSCVA

- Manifest refraction
- IOP (applanation where possible; otherwise other methods)
- Gonioscopy
- Slit lamp biomicroscopy (including cornea, anterior chamber for cells and flare)
- Biometry (axial length, corneal curvature) and anterior chamber depth in phakic eyes only (Biometry method and device to be identified)
- Ocular motility
- Dilated fundus examination
- Ocular B-scan ultrasound when dilated fundus exam is not possible (e.g., post trauma)
- Endothelial cell density (ECD; when no corneal damage is present- non-contact specular or confocal microscopy with 3 images and calculating the average of central cell density)
- Digital ocular photos for iris device manufacturing (both eyes with bridge and right and left eyes alone)
- Subjective complaints for glare, halos and photophobia (day and night)
- Iris defect information (amount missing/location, partial/complete)
- Eye color
- Other optional diagnostic tests may be performed at the investigator's discretion (e.g., optical coherence tomography or ultrasonic biomicroscopy) to further evaluate the subject for iris

In addition, a preoperative evaluation was performed within 30 days of the scheduled implant surgery that included the following:

- BSCVA
- Manifest refraction
- IOP (applanation)
- Slit lamp biomicroscopy
- Interim ocular history
- National Eye Institute (NEI) Visual Function Questionnaire (VFQ-25) questionnaire
- Subjective complaint questionnaire
- Selection and dioptric power calculation of any optical (IOL) implant placed at the time of surgery

Postoperatively, the objective parameters measured at each visit **(**unless noted otherwise) during the study included:

- Documentation of interim medical, ocular, and medication histories since previous visit
- UCVA (omit on Day 1)
- BSCVA distance (Months 3, 6, 12)
- Manifest refraction (omit on Day 1, Week 1)

- IOP
- Slit lamp biomicroscopy (including cornea, anterior chamber for cells and flare at all visits; evaluate fundus status at Months 1, 3, 6, and 12)
- Evaluation of implant position (tilt, decentering, dislocation)
- ECD (when no corneal damage is present; Months 6 and 12)
- NEI VFQ-25 questionnaire (Month 6 and Month 12/Final Exam only)
- Subjective complaint questionnaire (omit on Day 1, Week 1)
- Global Aesthetic Improvement Scale (GAIS; omit on Day 1, Week 1)
- Digital ocular photos (Month 3; both eyes with bridge and operative eye alone)
- Other diagnostic tests (at investigator's discretion)
- AEs, complications, and visual disturbances

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety:

- Less than 5% of subjects without progressive stem cell disease (aniridic keratopathy) should lose more than 2 lines of BSCVA at 12 months postoperatively that is device related and unresolved;
- Less than 5% of subjects should have BSCVA of worse than 20/40 at 12 months postoperatively, if the preoperative BSCVA was 20/40 or better, and that is device related and unresolved;
- In subjects where an IOL has been implanted concurrently:
    - The cumulative rate of all lens-related AEs should be less than 5%; and no individual AE should exceed a rate of 1%; and,
    - The rates of cumulative and persistent surgery related complications should not exceed the threshold rates listed below when adjusted for the type of pre-existing condition for which the subjects are being treated.

With regards to effectiveness, parameters evaluated in the clinical study are:

- Changes over time in the subject's visual symptoms of light sensitivity and glare;
- Subject satisfaction with cosmesis as measured by the GAIS;
- Health related quality of life affected by vision assessed using the NEI VFQ-25 questionnaire total score.

With regard to success/failure criteria, no success/failure criteria were established because the study was not designed around effectiveness. It was designed to demonstrate safety.

B. Accountability of PMA Cohort

At the time of database lock, of 447 eyes enrolled in the PMA study, 75.8 % (n= 339) subjects were available for analysis at the completion of the study, the 12-month post-operative visit. The subject accountability is summarized in **Table 6**.

Table 6: Accountability by Eye for All Eyes Combined Treated with the CustomFlex™ Artificial Iris

Status	Screening		Operative		1D		1W		1M		3M		6M		12M	
Enrolled (N)	447		447		447		447		447		447		447		447	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Available for Analysis	447	100.0	447	100.0	447	100.0	442	98.9	431	96.4	406	90.8	394	88.1	339	75.8
Discontinued					0	0.0	0	0.00	0	0.0	1	0.2	1	0.2	1	0.2
Active (Not Eligible for Interval)					0	0.0	3	0.67	11	2.5	22	4.9	43	9.6	88	19.7
Lost to Follow-up					0	0.0	0	0.00	2	0.4	4	0.9	4	0.9	15	3.4
Missed Visit (Accounted for)					0	0.0	2	0.45	3	0.7	14	3.1	5	1.1	4	0.9
% Accountability						100.0%		99.5%		98.9%		95.8%		97.8%		94.7%

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a PMA clinical study performed in the US and are summarized in **Table 7**.

Table 7: Demographic Characteristics for All Eyes Treated – By Cohort

Characteristic	Parameter	Primary Eyes	Secondary Eyes	Compassionate Use Eyes	Continued Access Eyes	All Eyes Combined
N (Eyes)		180	28	89	150	447
Age (Years)	Mean	53.68	45.00	33.81	51.56	48.51
	Std. Dev.	15.76	15.40	20.98	16.88	18.79
	Median	55.00	43.00	23.00	53.00	50.00
	Minimum	22.0	22.0	6.0	21.0	6.0
	Maximum	86.0	74.0	75.0	94.0	94.0
Sex n (%)	Male	112 (62.22)	17 (60.71)	56 (62.92)	101 (67.33)	286 (63.98)
	Female	68 (37.78)	11 (39.29)	33 (37.08)	49 (32.67)	161 (36.02)
Race n (%)	Caucasian	164 (91.11)	25 (89.29)	74 (83.15)	135 (90.00)	398 (89.04)
	African American	4 (2.22)	0 (0.0)	4 (4.49)	0 (0.0)	8 (1.79)
	Hispanic	6 (3.33)	1 (3.57)	6 (6.74)	5 (3.33)	18 (4.03)
	Asian	4 (2.22)	1 (3.57)	1 (1.12)	7 (4.67)	13 (2.91)
	American Indian	0 (0.0)	0 (0.0)	2 (2.25)	0 (0.0)	2 (0.45)
	Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.67)	1 (0.22)
	Other[1]	2 (1.11)	1 (3.57)	2 (2.25)	2 (1.33)	7 (1.57)

The indications for treatment of the enrolled subjects are presented below in **Table 8.**

1 Chinese (n=1), Russian (n=2), Middle Eastern (n=1), Caucasian/Hispanic (n=1)

Table 8: Indications for Treatment with the CustomFlex™ Artificial Iris by Cohort

Characteristic	**Primary Eyes**	**Secondary Eyes**	**Compassionate Use Eyes**	**Continued Access**	**All Combined**
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
N (Eyes)	180	28	89	150	447
Congenital Aniridia	21 (11.67)	20 (71.43)	29 (32.58)	36 (24.00)	106 (23.71)
Post-Epithelial ingrowth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Post-Melanoma excision	6 (3.33)	0 (0.0)	0 (0.0)	1 (0.67)	7 (1.57)
Post-Surgical Defect	28 (15.56)	1 (3.57)	14 (15.73)	15 (10.00)	58 (12.98)
Traumatic Iris Defect	94 (52.22)	0 (0.0)	42 (47.19)	80 (53.33)	216 (48.32)
ICE syndrome	5 (2.78)	0 (0.0)	0 (0.0)	3 (2.00)	8 (1.79)

The ocular history was obtained by a review of the subject's medical chart as well as from subject self-reports. The tabulated summary of the screening (baseline) ocular history (**Table 9**) shows that glaucoma is present in 39.2% (175/447) of the overall study population and 11.6% (52/447) of eyes have had previous glaucoma filtering surgery. The incidence of nystagmus (19.9%, 89/447), macular hypoplasia (14.3%, 64/447), amblyopia (12.5%, 56/447), and previous retinal detachment (14.1%, 63/447).

Table 9: Ocular History at Screening for All Eyes Treated with CustomFlex™ Artificial Iris By Cohort

		Primary Eyes	Secondary Eyes	Compassionate Use Eyes	Continued Access	All Eyes Combined
	N (eyes)	**180**	**28**	**89**	**150**	**447**
		n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Visit	**Characteristic**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Screening	Amblyopia	24 (13.33)	7 (25.00)	17 (19.32)	8 (5.30)	56 (12.53)
	Diabetic Retinopathy	1 (0.56)	0 (0.0)	1 (1.14)	1 (0.66)	3 (0.67)
	Pseudoexfoliation	2 (1.11)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.45)
	Previous Glaucoma Filtering Surgery	24 (13.33)	4 (14.29)	13 (14.77)	11 (7.28)	52 (11.63)
	Glaucoma	82 (45.56)	13 (46.43)	38 (43.18)	42 (27.81)	175 (39.15)
	Macular Hypoplasia	17 (9.44)	17 (60.71)	18 (20.45)	12 (7.95)	64 (14.32)
	Macular Degeneration	10 (5.56)	1 (3.57)	1 (1.14)	2 (1.32)	14 (3.13)
	Nystagmus	18 (10.00)	16 (57.14)	32 (36.36)	23 (15.23)	89 (19.91)
	Poor Pupil Dilation	10 (5.56)	1 (3.57)	5 (5.68)	4 (2.65)	20 (4.47)
	Previous Retinal Detachment	26 (14.44)	1 (3.57)	16 (18.18)	20 (13.25)	63 (14.09)
	Uveitis	8 (4.44)	0 (0.0)	1 (1.14)	1 (0.66)	10 (2.24)

Regarding the model and color of the device implanted, the frequency of use of the two CustomFlex™ Artificial Iris models and the various device colors are presented in **Table 10**.

Table 10: Device Models and Colors in All Eyes Treated with CustomFlex™ Artificial Iris in Pediatric and Adult Cohorts

Operative Category	**Characteristic**	**Parameter**	**Pediatric Eyes Compassionate Use n (%)**	**Adult Eyes Compassionate Use n (%)**	**Adult Eyes Other Cohorts n (%)**	**All Combined n (%)**
Device Information	Model	Fiber	22 (50.00)	24 (53.33)	153 (42.86)	199 (44.62)
		Fiber-free	22 (50.00)	21 (46.67)	204 (57.14)	247 (55.38)
	Color	Blue	15 (34.09)	20 (44.44)	165 (46.09)	200 (44.74)
		Brown	18 (40.91)	20 (44.44)	114 (31.84)	152 (34.00)
		Gray	0 (0.0)	0 (0.0)	1 (0.28)	1 (0.22)
		Green	3 (6.82)	1 (2.22)	17 (4.75)	21 (4.70)
		Hazel	7 (15.91)	3 (6.67)	43 (12.01)	53 (11.86)
		Black	1 (2.27)	1 (2.22)	18 (5.03)	20 (4.47)

D. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the overall cohort of 447 eyes procedures available for the 12 month evaluation. The key safety outcomes for this study are presented in the **Tables 11** and **12**. Adverse effects are reported in **Table 13**.

Table 11: Key AI-001 Study Safety Endpoints at 12 Months Postoperatively in Eyes Treated with CustomFlex™ Artificial Iris by Cohort

Device Related Adverse Events at 12 Months	**Threshold Rate (*)**	**PMA Primary Eyes n (%)**	**Secondary Eyes n (%)**	**Compassionate Use Eyes n (%)**	**Continued Access Eyes n (%)**	**All Eyes Combined n (%)**
N (at 12 Months)		172	26	62	79	339
• >2 Line (>10 Letters) Loss of BSCVA that is device related	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
N (20/40 or better at 12 Months)		59	3	17	26	105
• BSCVA of worse than 20/40 that is device related, if the Preoperative BSCVA was 20/40 or better	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
N (cumulative)	**Threshold Rate**	180	28	89	150	447
Cumulative Lens	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Anisometropia	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Glare/halos	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Diplopia	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• IOL removal or replacement due to lens power calculation error	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative Surgery						
• Cystoid Macular	18.8%	7 (3.9%)	0 (0.0%)	0 (0.0%)	6 (4.0%)	13 (2.9%)
• Hypopyon	3.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Endophthalmitis	3.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Device migration	5.4%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Pupillary block	7.8%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Retinal detachment	5.4%	2 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	3 (0.7%)
• Secondary surgical intervention (unplanned)	8.5%	4 (2.2%)	1 (3.6%)	0 (0.0%)	1 (0.7%)	6 (1.3%)
• Corneal edema, persistent at 3 months or later	4.2%	4 (2.2%)	0 (0.0%)	0 (0.0%)	3 (2.0%)	7 (1.6%)
• Chronic anterior segment inflammation, persistent at 3 months or later (chronic iritis)	5.0%	3 (1.7%)	0 (0.0%)	0 (0.0%)	5 (3.3%)	8 (1.8%)

[*] Threshold rate is the minimum rate detectable as statistically significantly different from the safety endpoint, when adjusted for the type of pre-existing condition for which the subjects are being treated, as specified in International Standard Organization 11979-7:2006.

Table 12: Key AI-001 Study Safety Endpoints at 12 Months Postoperatively in All Treated Eyes by Pediatric and Adult Cohorts

Device Related Adverse Events at 12 Months	**Threshold Rate ([*])**	**Pediatric Compassionate Use Eyes n (%)**	**Adult Compassionate Use Eyes n (%)**	**All Other Adult Eyes n (%)**	**All Eyes Combined n (%)**
N		44	45	358	447
• >2 Line (>10 Letters) Loss of BSCVA that is device related	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• BSCVA of worse than 20/40 if the pre-op BSCVA was 20/40 or better (device related)	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative Lens Related Adverse Events	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Anisometropia	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Glare/halos	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Diplopia	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• IOL removal or replacement due to lens power calculation error	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative Surgery Related Adverse Events	**Threshold Rate**				
• Cystoid Macular Edema	18.8%	0 (0.0%)	0 (0.0%)	13 (3.6%)	13 (2.9%)
• Hypopyon	3.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Endophthalmitis	3.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Device migration	5.4%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Pupillary block	7.8%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Retinal detachment	5.4%	0 (0.0%)	0 (0.0%)	3 (0.8%)	3 (0.7%)
• Secondary surgical intervention (unplanned)	8.5%	0 (0.0%)	0 (0.0%)	6 (1.7%)	6 (1.3%)
• Corneal edema, persistent at 3 months or later	4.2%	0 (0.0%)	0 (0.0%)	7 (2.0%)	7 (1.6%)
• Chronic anterior segment inflammation, persistent at 3 months or later (chronic iritis)	5.0%	0 (0.0%)	0 (0.0%)	8 (2.2%)	5 (1.8%)

[*] Threshold rate is the minimum rate detectable as statistically significantly different from the safety endpoint, when adjusted for the type of pre-existing condition for which the subjects are being treated, as specified in International Standard Organization 11979-7:2006.

Because the CustomFlex™ Artificial Iris is not a refractive device, the primary outcome measures are safety related or related to effectiveness in resolving debilitating visual symptoms. Subjects who may benefit from this device have comorbid ocular pathologies. There is a progressive decline in vision, progressive elevation in IOP requiring glaucoma treatments, surgical interventions such as corneal transplants, and/or corneal-limbal stem cell transplants especially in cases of congenital aniridia. The co-morbidities associated to aniridia, and especially congentital aniridia, need to be considered in the safety analysis and profile of the CustomFlex™ Artificial Iris. The rates

of complications and AEs need to be interpreted with respect to the presenting pathologies leading to the surgical implantation of the CustomFlex™ Artificial Iris.

Slit lamp exam (SLE) findings of clinical significance were as expected in this subject population especially since multiple surgical procedures were performed. However, there were no alarming findings even among the slit lamp findings of greater than 2+ with a frequency greater than 2%. The only IOL related finding greater than 2% was posterior capsular opacity (2.9%, 13/447) in the lens field. Other infrequent SLE findings were endothelial pigment deposit, 2.2% (10/447); punctate epithelial keratopathy, 2.9% (13/447), punctate epithelial keratopathy 2.9% (13/447), and in the orbit/lids (ptosis), 2.9% (13/447).

ECD changes were a major safety analysis in the outcomes of this study. When evaluating the endothelial cell data, it should be noted that subjects who require iris prostheses are a very heterogeneous group of subjects, even for those sharing a common diagnosis. This population has complex ocular pathology and co-morbidities that can significantly affect the ability to capture reliable or repeatable endothelial cell measurements in this group of study subjects. Coexisting endothelial compromise is common and may stem from the primary pathology, trauma, or surgical interventions. In this subject population, cell count assessments have an even higher variability than healthy eyes. Other corneal pathologies such as stromal scarring (i.e. from trauma) or epitheliopathy (i.e., from aniridic stem cell disease) can further impact the variability of endothelial cell counts. Never-the-less, the mean ECD remained stable with no clinically significant loss over the 12 months of the study in the pediatric and adult eyes. The summary analyses by each individual study cohort as well as the overall cohort for ECD is as follows:

- All Eyes Analysis
  - Mean percentage changes are 0.84% and -6.36% at 6 and 12 months postoperatively. The generally accepted surgical loss rate is 10% and less than the 13.9% rate of loss for combined cataract extraction and pars plana vitrectomy procedures
- Primary Cohort Analysis (n=126)
  - Mean changes of -0.78% and -6.14% at 6 and 12 months, respectively
- Continued Access Cohort Analysis (n=86)
  - Mean changes of -6.19% and -9.94% at 6 and 12 months, respectively
- Compassionate Use Cohort (n=47)
  - 25.15% and 4.30% at 6 and 12 months, respectively
- Fellow Eye Cohort (n=20)
  - -15.89% and -19.95% at 6 and 12 months, respectively
- Mean change in ECD from 6 months to 12 months is
  - -2.98% for the overall population

The mean percentage change in ECD from 6 Months to 12 Months in pediatric eyes with paired data was a gain of 7.23% (n=25) and 1.43% (n=6), respectively. These gains are compared to mean percentage losses in ECD of -2.98% at 6 months and -2.81% at 12 months in the total eyes treated. ECD differences from baseline to 6 and 12 months for the aniridic indications are similar to those observed in the individual study cohorts and overall study population. Likewise, ECD loss for post-surgical defects are similar to those for the treatment of traumatic injuries. Congenital aniridics seemed to trend a slightly higher loss, recognizing small group numbers and a much higher variability between measures than from the group as a whole.

Endothelial cell losses >10% were evaluated to more fully characterize this subject population. A review of the ocular history, operative procedure, and postoperative course revealed that each of these cases involved one or more surgical procedures performed in the same surgical setting at the time of the artificial iris implant. Every case demonstrated either co-morbidities or non-device related postoperative complications that predisposed the eyes to significant loss of endothelial cells.

Adverse effects that occurred in the PMA clinical study:
The most frequent AE for all eyes treated was increased IOP greater than 30 mm Hg resulting from multiple causes. IOP spikes greater than 30 mm Hg also tended to occur within the first day to 1-month postoperatively. There were no reports of IOP >30 mm Hg that were IOL related and only one (0.2%) report that was related to the artificial iris device (1/447 eyes). Overall, 7.8% (35/447) of treated eyes had elevations of IOP >30 mm Hg that were surgically related; 6.0% (27/447) of eyes had drug related elevations of IOP >30 mm Hg; and, IOP spikes greater than 30 mm Hg resulted from other known causes in 9.4% (42/447) of the study population (e.g., routine pressure spikes in pre-existing glaucoma or glaucoma due to Rieger's syndrome, ICE syndrome, congenital glaucoma, or prior trauma). Most AEs occurred in the first 3 months postoperatively. Corneal edema cleared by Month-1 with only rare cases reported after 1 month. Vitreal hemorrhage and hyphema are both complications of the surgical procedure and resolved after 1 month in all cases.

The adverse effects are reported in the **Table 13** and include surgical complications, device-related and IOL-related complications. The device-related complications were infrequent and consisted of device decentration (1.8%, 8/447), device dislocations (2.5%, 11/447) and secondary surgical interventions to reposition the dislocated or decentered devices (2.2%, 6/447).

Table 13: Cumulative Frequency of Occurrence of Unique Reports of AEs in Pediatric, Adult and All Eyes by Cohort

CUMULATIVE ADVERSE EVENT REPORTS	Pediatric Eyes		Adult Compassionate Use Eyes		Adult All Other Eyes		All Eyes Combined	
N	44		45		358		447	
	n	%	n	%	n	%	n	%
Surgical Complications								
Edema, cystoid macular	0	0.0%	0	0.0%	13	3.6%	13	2.9%
Retinal detachment	0	0.0%	0	0.0%	3	0.8%	3	0.7%
Cyclitic membrane	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Edema, corneal (at 1 month or later)	0	0.0%	2	4.4%	9	2.5%	11	2.5%
Edema, corneal persistent	0	0.0%	0	0.0%	7	2.0%	7	1.6%
Iritis (at 1 month or later)	0	0.0%	1	2.2%	14	3.9%	15	3.4%
Iritis, chronic	0	0.0%	0	0.0%	8	2.2%	8	1.8%
Synechiae	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Secondary glaucoma	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Vitritis	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Endophthalmitis	0	0.0%	0	0.0%	0	0.0%	0	0.0%
IOP > 30 mm Hg	0	0.0%	3	6.7%	32	8.9%	35	7.8%
BSCVA loss (>2 lines lost at 3 months or later)	0	0.0%	0	0.0%	6	1.7%	6	1.3%
Reaction to Anesthetic	0	0.0%	0	0.0%	0	0.0%	0	0.0%
OTHER								
Adhesions, fibrin	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Capsular tear	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Conjunctival dehiscence	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Corneal blood staining	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Dry eye	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Epithelial defect, corneal	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Fibrin strands in anterior chamber	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Flashes of light	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Heme, vitreous	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Hemorrhage, retrobulbar	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Hemorrhage, vitreous	2	4.5%	0	0.0%	17	4.7%	19	4.3%
Hyphema	3	6.8%	1	2.2%	14	3.9%	18	4.0%
Hypotony	0	0.0%	0	0.0%	3	0.8%	3	0.7%

Table 13: Cumulative Frequency of Occurrence of Unique Reports of AEs in Pediatric, Adult and All Eyes by Cohorts (continued)

CUMULATIVE ADVERSE EVENT REPORTS	Pediatric Eyes		Adult Compassionate Use Eyes		Adult All Other Eyes		All Eyes Combined	
N	44		45		358		447	
IOL Dislocation	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Iris remnant prolapse	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Macular pucker	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Retinal tear	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Secondary Surgery:	0							
• Iris remnant revision	0	0.0%	0	0.0%	1	0.3%	1	0.2%
• Wound revision	0	0.0%	0	0.0%	1	0.3%	1	0.2%
• Patch graft for exposed suture	0	0.0%	0	0.0%	4	1.1%	4	0.9%
Superficial punctate keratopathy	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Suture, exposed (without patch graft)	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Suture, trimmed	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Wound leak	0	0.0%	0	0.0%	6	1.7%	6	1.3%
Device Related Complications								
Device decentration	1	2.3%	0	0.0%	7	2.0%	8	1.8%
Device dislocation	1	2.3%	1	2.2%	9	2.5%	11	2.5%
Pupillary block	0	0.0%	0	0.0%	0	0.0%	0	0.0%
IOP > 30 mm Hg	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Iritis (at 1 month or later)	0	0.0%	0	0.0%	3	0.8%	3	0.7%
Synechiae	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Secondary surgical interventions (artificial iris):								
• Repositioning	1	2.3%	1	2.2%	8	2.2%	10	2.2%
• Replacement	0	0.0%	0	0.0%	1	0.3%	1	0.2%
• Removal	0	0.0%	0	0.0%	0	0.0%	0	0.0%
OTHER								
• Device Defect	0	0.0%	0	0.0%	1	0.3%	1	0.2%
• Fibrin Strands in Anterior Chamber	0	0.0%	0	0.0%	0	0.0%	1	0.3%
IOL Related Complications								
Anisometropia	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Glare/halos	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Diplopia	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Table 13: Cumulative Frequency of Occurrence of Unique Reports of AEs in Pediatric, Adult and All Eyes by Cohorts (continued)

CUMULATIVE ADVERSE EVENT REPORTS	Pediatric Eyes		Adult Compassionate Use Eyes		Adult All Other Eyes		All Eyes Combined	
N	44		45		358		447	
IOL removal or replacement due to lens power calculation error	0	0.0%	0	0.0%	0	0.0%	0	0.0%
OTHER								
Debris, inflammatory	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Haze, capsular	3	6.8%	0	0.0%	5	1.4%	8	1.8%
Hemorrhage, vitreous	1	2.3%	0	0.0%	0	0.0%	1	0.2%
IOL haptic malpositioned	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Retinal detachment	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Secondary Surgery:								
• Patch graft for exposed IOL haptic	0	0.0%	0	0.0%	1	0.3%	1	0.2%
• IOL haptic repositioned	0	0.0%	0	0.0%	2	0.6%	2	0.4%
• IOL removal	1	2.3%	0	0.0%	0	0.0%	1	0.2%
• Device/IOL replacement	0	0.0%	0	0.0%	1	0.3%	1	0.2%
• Uveitis	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Complications, Other Known Cause								
Abrasion, corneal	0	0.0%	0	0.0%	3	0.8%	3	0.7%
AEK re-bubble	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Aniridia fibrosis syndrome	0	0.0%	1	2.2%	0	0.0%	1	0.2%
Band keratopathy	0	0.0%	0	0.0%	2	0.6%	2	0.4%
BSCVA loss (>2 lines lost at 3 months or later)	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Capsulorhexis break	1	2.3%	0	0.0%	10	2.8%	11	2.5%
Conjunctivitis	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Corneal neovascularization	0	0.0%	1	2.2%	0	0.0%	1	0.2%
Death, motor vehicle accident	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Dellen	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Diplopia	0	0.0%	0	0.0%	1	0.3%	1	0.2%
DSAEK detachment	0	0.0%	1	2.2%	0	0.0%	1	0.2%
DSAEK graft misaligned or loose	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Dysphotopsia, negative	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Edema, corneal (at 1 month or	0	0.0%	1	2.2%	3	0.8%	4	0.9%

Table 13: Cumulative Frequency of Occurrence of Unique Reports of AEs in Pediatric, Adult and All Eyes by Cohorts (continued)

CUMULATIVE ADVERSE EVENT REPORTS	Pediatric Eyes		Adult Compassionate Use Eyes		Adult All Other Eyes		All Eyes Combined	
N	44		45		358		447	
later)								
Edema, corneal persistent	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Edema, cystoid macular	0	0.0%	0	0.0%	4	1.1%	4	0.9%
Epiciliary fibrosis	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Epiretinal membrane	1	2.3%	1	2.2%	12	3.4%	14	3.1%
Epithelial cell migration onto surface of IOL and device	0	0.0%	0	0.0%	3	0.8%	3	0.7%
Epithelial defect, corneal	0	0.0%	0	0.0%	15	4.2%	15	3.4%
Epithelial downgrowth	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Fibrin strands in anterior chamber	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Fibrotic strand	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Fibrovascular proliferation	1	2.3%	3	6.7%	3	0.8%	7	1.6%
Floater	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Graft rejection	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Haze, capsular	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Hemorrhage, subconjunctival (1 month or later)	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Hemorrhage, vitreous	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Hyphema	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Hypotony	0	0.0%	0	0.0%	1	0.3%	1	0.2%
IOL decentration	0	0.0%	0	0.0%	1	0.3%	1	0.2%
IOP > 30 mm Hg	0	0.0%	1	2.2%	2	0.6%	3	0.7%
Iritis (1 month or later)	0	0.0%	0	0.0%	5	1.4%	5	1.1%
Iritis, chronic	0	0.0%	3	6.7%	13	3.6%	16	3.6%
Lens capsule posterior opacification	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Peripheral vision disturbance, transient	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Posterior vitreous detachment	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Pseudophakodonesis	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Ptosis	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Residual capsule/cortical material	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Retinal detachment	0	0.0%	0	0.0%	3	0.8%	3	0.7%
Retinal tear	0	0.0%	0	0.0%	1	0.3%	1	0.2%

Table 13: Cumulative Frequency of Occurrence of Unique Reports of AEs in Pediatric, Adult and All Eyes by Cohorts (continued)

CUMULATIVE ADVERSE EVENT REPORTS	Pediatric Eyes		Adult Compassionate Use Eyes		Adult All Other Eyes		All Eyes Combined	
N	44		45		358		447	
Secondary Surgery:								
Device/IOL reposition pre-corneal transplant	0	0.6%	0	0.6%	1	0.6%	1	0.6%
Device/IOL removal	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Fibrous tissue removal	1	0.6%	0	0.6%	0	0.6%	1	0.6%
Patch graft for exposed suture	0	0.0%	2	0.0%	4	0.0%	6	0.0%
Wound revision	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Superficial punctate keratopathy	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Suture, package mislabeled	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Thin intracapsular membrane	1	2.3%	0	0.0%	0	0.0%	1	0.2%
Vitritis, non-infectious	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Wound leak	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Complications, Drug Related								
Debris, inflammatory	0	0.0%	2	4.4%	0	0.0%	2	0.4%
Drug allergy	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Edema, cystoid macular	0	0.0%	0	0.0%	1	0.3%	1	0.2%
Hypotony	0	0.0%	0	0.0%	2	0.6%	2	0.4%
IOP > 30 mm Hg	1	2.3%	4	8.9%	22	6.1%	27	6.0%
Ocular Hypertension	0	0.0%	0	0.0%	2	0.6%	2	0.4%
Superficial punctate keratopathy	0	0.0%	0	0.0%	1	0.3%	1	0.2%

2. Effectiveness Results

   As presented in Table 5 and in the Accountability of PMA Cohort section (page 14 above), a total of 447 eyes implanted with the CystomFlex™ device. Of these, 339 eyes were available for analysis of effectiveness at the 12-month time point. Key effectiveness outcomes are presented in the **Tables 14 and 15** below.

Table 14: Key AI-001 Study Effectiveness Endpoints at 12 Months Postoperatively in Eyes Treated with CustomFlex™ Artificial Iris by Cohort

Visual Symptoms of Photosensitivity	PMA Primary Eyes	PMA Secondary Eyes	Compassionate Use	Continued Access	All Eyes Combined
N (at 12 Months)	172	26	62	79	339
	Difference in Marked-Severe	Difference in Marked-Severe	Difference in Marked-Severe	Difference in Marked-Severe	Difference in Marked-Severe
• Decrease in severity of day-time light sensitivity	-62.4	-67.6	-58.8	-54.9	-59.7
• Decrease in severity of night-time light sensitivity	-44.1	-42.9	-38.6	-39.8	-41.5
• Decrease in severity of glare during day	-52.3	-64.0	-53.3	-52.6	-53.1
• Decrease in severity of glare at night	-50.2	-50.0	-37.2	-53.6	-48.5
Health Related Quality of Life	Total score	Total score	Total score	Total score	Total score
• Improvement in NEI-VFQ total score	16.91	15.83	12.56	14.08	15.36
Cosmesis satisfaction	GAIS score	GAIS score	GAIS score	GAIS score	GAIS score
• Satisfaction with cosmesis (GAIS rated as improved, much improved, or very much improved)	159/172	25/26	61/62	73/79	318/339

Table 15: Key AI-001 Study Effectiveness Endpoints at 12 Months Postoperatively in Treated Eyes by Pediatric and Adult Cohorts

Visual Symptoms of Photosensitivity	**Pediatric Compassionate Use Eyes**	**Adult Compassionate Use Eyes**	**All Other Adult Eyes**	**All Eyes Combined**
N (at 12 Months)	33	29	277	339
	Difference in Marked-Severe (%)	**Difference in Marked-Severe (%)**	**Difference in Marked-Severe (%)**	**Difference in Marked-Severe (%)**
• Decrease in severity of day-time light sensitivity	-54.5	-61.2	-60.1	-59.7
• Decrease in severity of night-time light sensitivity	-26.5	-52.3	-42.2	-41.5
• Decrease severity of glare during the day	-50.0	-54.4	-53.3	-53.1
• Decrease in severity of glare at night	-25.8	-49.9	-51.3	-48.5
Health Related Quality of Life	**Total Score**	**Total Score**	**Total Score**	**Total Score**
• Improvement in NEI-VFQ total score	9.66	15.87	16.00	15.36
Cosmesis Satisfaction	**GAIS Score**	**GAIS Score**	**GAIS Score**	**GAIS Score**
• Satisfaction with cosmesis (GAIS rated as improved, much improved, or very much improved)	33/33	28/29	257/277	318/339

Each cohort experienced clinically significant decreases in both daylight and night-time light sensitivity and glare. The reduction in severity of night-time light sensitivity and the improvement in NEI VFQ-25 total scores were significant at 6 months for all of the cohorts. The continued access cohort is ongoing during the PMA review cycle so 12 month data are not available.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: A poolability analysis of the data consisting of an analysis of demographics to determine homogeneity of the subject population across sites was conducted to address significant differences in the number of individuals enrolled and treated at each study site. The various study sites were grouped according ranges of subjects enrolled and treated. These groupings were referred to as pseudosites for the purposes of this analysis. A separate analysis was performed by pseudo-sites which were organized as the high (>40 eyes), medium (20 to 40 eyes) and low (<20 eyes) enrolling sites based on total eyes enrolled by each site in the total PMA Cohort.

The demographics were analyzed for poolability of age, sex, and race. The outcome parameters were further divided into analyses of the poolability of:

(1) Changes in daytime light sensitivity
(2) Changes in daytime glare
(3) Satisfaction with cosmesis, as measured by GAIS

Age

There were no significant differences in the distribution of ages across the pseudo-sites (p=0.0289). The distribution of ages across the individual sites and within the cohorts are as expected given the indications for treatment and age subpopulations that comprise each cohort and that affect the age distribution (i.e., the enrollment of congenital aniridics in the PMA Secondary Eye cohort and enrollment of pediatric subjects in the Compassionate Use cohort).

Sex

The results of this analysis indicated that there were no differences in the proportion of males and females across the pseudo-sites (p=0.6853). The sex distribution for the pseudo-sites parallels that of the overall study population, with ~63% males and ~37% females enrolled in the study.

Racial Distribution

There were no differences in the proportion of races across the sites (p=0.4519). The racial distribution for the pseudo-sites parallels that of the overall study population, with ~89% Caucasian and ~5% Hispanic enrolled in the study.

Pseudo-site 2 includes Site 6, which has the highest enrollment of Hispanic study subjects of any of the investigative sites. Geographically, Site 6 is located in Los Angeles, California; California has the largest Hispanic population of any state in the US, and enrollment at Site 6 is representative of local geographic demography. Published literature evaluating racial differences have demonstrated there are no significant differences between the Hispanic and Caucasian populations for corneal curvature, central corneal thickness, refractive measurements, preoperative astigmatism, or intraocular pressure.[1, 2]

Analyses of the ethnicity of the enrolled subjects was not performed.

Study Outcome Measures

The percentages of eyes that changed from Marked-Severe at baseline to None-Moderate at 12 Months was the same for Day Light Sensitivity with all being around 65% +/ 2%. Since these responses are clinically significant and from previous analysis statistically significant, these are acceptable responses for poolability of these data across pseudo-sites. For the Glare During the Day variable, two (2) of the Pseudo sites (1 and 3) were at 60% and the other site (2) was at 48%. Even though pseudo site 2 was slightly lower than the other sites, this is acceptable for poolability because these responses are clinically

significant, and from previous analysis statistically significant; therefore, these are acceptable responses for poolability of these data across pseudo sites.

- ***Satisfaction with Cosmesis (GAIS)***
  Satisfaction with cosmesis was high across the pseudo-sites, with 71.6% of the eyes at Pseudo-site 1 rating postoperative cosmesis as "very much improved" or "much improved," compared to 80.4% of eyes at Pseudo-site 2 and 85.3% of eyes at Pseudo-site 3.

- ***Device Model & Color***
  The two (2) models are identical in every respect except that the With Fiber model has a polyester meshwork layer embedded in it to provide additional strength. Model type was analyzed to determine if With Fiber or Fiber-Free devices exhibited a difference in the outcome measures for light sensitivity in daylight and daytime glare. The results of this analysis indicated that the With Fiber and Fiber-Free devices each achieved a significant decrease in symptoms ($p=<0.0001$). Device color was also analyzed to see if there was a color effect on the outcome measures for light sensitivity in daylight and daytime glare. This analysis indicated that each color group achieved a significant decrease in symptoms ($p<0.0001$).

Compassionate Use (Pediatric Subset)
The poolability analysis of the pediatric subset is based on 35 eyes of 29 subjects enrolled at 7 investigative sites. The pediatric subset of the Compassionate Use cohort was compared to the adult subset of the Compassionate Use cohort and to the PMA Cohort (primary and secondary eyes combined) to determine if pediatric subjects exhibited a difference from adults in the outcome measures for light sensitivity in daylight and daytime glare and for satisfaction with cosmesis as rated using the GAIS. The results of the analysis indicate that the pediatric subset achieved improvements in both light sensitivity in daylight and in daytime glare. The Compassionate Use adult subset and PMA Cohort eyes also achieved improvement in both light sensitivity and glare symptoms. Satisfaction was highest in the pediatric subset, with 88.9% of the eyes rating postoperative cosmesis as "very much improved" or "much improved" compared to 82.6% of the Compassionate Use adult subset and 79.3% of the PMA Cohort eyes.

4. Pediatric Extrapolation
   This section is not applicable to this PMA. Pediatric data was generated to support the studied patient population.

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 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Pediatric Subpopulation

An analysis of the pediatric outcomes was performed for the 44 eyes of 35 subjects who have been treated with the CustomFlex™ Artificial Iris as of the data cutoff (December 1, 2017) for this report. Sponsor intends for these data to support the indication for use in children as well as adults, and to identify any trends in the pediatric data that differ from the adult population. In this analysis, outcomes of the pediatric subset (n = 44 eyes) are compared to those of the adult population in the Compassionate Use cohort (n = 45 eyes) and to the rest of the adult population treated in the AI-001 clinical study (i.e., the PMA Primary, Secondary, and Continued Access eyes (n = 358 eyes) and All Eyes Combined cohort (n = 447 eyes)).

The age in the pediatric subset, age ranged from 6 years to 21 years of age. The mean age in the pediatric group is 16.2 years, with young adults 16 to 21 years of age comprising 59% of the pediatric subset and the remainder being equally distributed between adolescents (12 to 15 years) and children (3 to 11 years of age). Of the 44 pediatric eyes, 45.45% (n=20) were in females and 54.55% (n=24) in males. Of these, 77.3% (n=27) were Caucasian, 4.55% (n=1) African-American, 6.82% (n=2) Hispanic, 2.27% Asian (n=7), 4.55% (n=1) American Indian, and 4.5% (n=1) other.

Pediatric Aniridic and Operative Characteristics

Congenital aniridia was the main reason for treatment with the CustomFlex™ Artificial Iris in 47.7% (21/44) of the pediatric eyes compared to 17.8% (8/45) of the adult compassionate eyes and 21.5% (77/358) of all other adults. Treatment for an iris defect resulting from trauma was the second most common indication in the pediatric subset. In the adult populations, these two (2) indications were also the most common indications for implantation of the CustomFlex™ Artificial Iris although trauma was the leading cause followed by congenital aniridia. An iris defect resulting from ocular surgery was the third most common indication for treatment with the CustomFlex™ Artificial Iris device in both the pediatric and adult populations, occurring with similar frequency in both age groups.

Table 16: Indications for Treatment by Pediatric and Adult Cohorts

Characteristic	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	All Combined
N (eyes)	44	45	358	447
Congenital Aniridia	21 (47.73)	8 (17.78)	77 (21.51)	106 (23.71)
Post-Epithelial ingrowth	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Post-Melanoma excision	0 (0.0)	0 (0.0)	7 (1.96)	7 (1.57)
Post-Surgical Defect	6 (13.64)	8 (17.78)	44 (12.29)	58 (12.98)
Traumatic Iris Defect	16 (36.36)	26 (57.78)	174 (48.60)	216 (48.32)
ICE syndrome	0 (0.0)	0 (0.0)	8 (2.23)	8 (1.79)
Other	1 (2.27)	3 (6.67)	48 (13.41)	52 (11.63)

Surgical Procedure Characteristics

Placement in the capsular bag and suture fixation to the scleral wall were the most common techniques in all four (4) cohort groups. Implantation of the Fiber-Free device in the capsular bag was the preferred surgical technique for congenital aniridic eyes, and the frequency of capsular bag placement (47.7%; 21/44) (**Table 17**) correlates with the proportion of congenital aniridic eyes (47.7%; 21/44) in the pediatric subset eyes (**Table 16**). Delivery via an injector was used slightly more often than forceps in each of the groups. The frequency and type of other surgical procedures performed along with the iris prosthesis implant were similar amongst the pediatric eyes and adult eyes, except the pediatric eyes had a slightly higher rate of vitrectomy (31.8%; n=14) and synechiolysis (15.9%; n=7) than did the adult population (**Table 18**).

Table 17: Surgical Techniques for Implantation of the CustomFlex™ Artificial Iris by Pediatric and Adult Cohorts

Operative Category	**Characteristic**	**Parameter**	**Pediatric Eyes Compassionate Use n (%)**	**Adult Eyes Compassionate Use n (%)**	**Adult Eyes Other Cohorts n (%)**	**All Combined n (%)**
Surgical Technique	Capsular Bag	No	21 (47.73)	28 (62.22)	205 (57.26)	254 (56.82)
		Yes	23 (52.27)	17 (37.78)	153 (42.74)	193 (43.18)
	• In the Capsular Bag	Yes	22 (100.0)	15 (100.0)	143 (100.0)	180 (100.0)
	Passive Sulcus fixation without suture	No	43 (97.73)	44 (97.78)	316 (88.27)	403 (90.16)
		Yes	1 (2.27)	1 (2.22)	42 (11.73)	44 (9.84)
	Suture Fixation to scleral wall	No	26 (59.09)	18 (40.00)	218 (60.89)	262 (58.61)
		Yes	18 (40.91)	27 (60.00)	140 (39.11)	185 (41.39)
	Partial artificial iris segment	No	44 (100.0)	45 (100.0)	358 (100.0)	447 (100.0)
	PCIOL sutured to artificial iris	No	31 (70.45)	36 (80.00)	278 (77.65)	345 (77.18)
		Yes	13 (29.55)	9 (20.00)	80 (22.35)	102 (22.82)
	Other Placement	No	44 (100.0)	44 (97.78)	336 (93.85)	424 (94.85)
		Yes	0 (0.0)	1 (2.22)	22 (6.15)	23 (5.15)

Table 18: Representative Other Procedures Performed with Implantation of the CustomFlex™ Artificial Iris by Pediatric and Adult Cohorts

Operative Category	Characteristic	Parameter	Pediatric Eyes Compassionate Use n (%)	Adult Eyes Compassionate Use n (%)	Adult Eyes Other Cohorts n (%)	All Combined n (%)
Other Procedure	IOL Reason	Cataract Extraction	25 (60.98)	18 (46.15)	186 (62.84)	229 (60.90)
		IOL Exchange	2 (4.88)	7 (17.95)	25 (8.45)	34 (9.04)
		Secondary IOL	14 (34.15)	14 (35.90)	85 (28.72)	113 (30.05)
	Vitrectomy	No	30 (68.18)	31 (68.89)	267 (74.58)	328 (73.38)
		Yes	14 (31.82)	14 (31.11)	91 (25.42)	119 (26.62)
	Synechiolysis	No	37 (84.09)	42 (93.33)	316 (88.27)	395 (88.37)
		Yes	7 (15.91)	3 (6.67)	42 (11.73)	52 (11.63)
	Partial Repair of Iris	No	43 (97.73)	41 (91.11)	331 (92.46)	415 (92.84)
		Yes	1 (2.27)	4 (8.89)	27 (7.54)	32 (7.16)
	Other Procedure	No	10 (22.73)	6 (13.33)	107 (29.89)	123 (27.52)
		Yes	34 (77.27)	39 (86.67)	251 (70.11)	324 (72.48)

Pediatric Operative Day Complications

The frequency of complications in the pediatric population was infrequent and similar to the adult. Anterior segment bleeding was the most commonly reported surgical complication, occurring in 6.8% (3/44) of the pediatric compassionate eyes compared to 17.8% (8/45) of the adult compassionate eyes and 7.6% (34/447) of all implant surgeries. The high frequency of anterior segment bleeding in the adult Compassionate Use cohort is attributed to the type of surgery performed, other surgical procedures performed and the complexity of the procedures.

Pediatric Key Safety and Effectiveness Endpoints Safety

There were no reports (0.0%) of device-related loss of BSCVA in the study at Month 12 postoperatively in any of the pediatric or adult eyes treated with the CustomFlex™ Artificial Iris. There were also no reports (0.0%) of any IOL-related related AEs that comprise the key safety endpoints in any of the pediatric or adult eyes. Surgery related AEs in the pediatric population were limited to retrobulbar hemorrhage (2.3%; 1/44), vitreous hemorrhage (4.5%; 2/44), and hyphema (6.8%; 3/44). There was only one report of retrobulbar hemorrhage occurring in the entire study. The reports of vitreous hemorrhage are similar, although slightly higher, than in the remainder of the study population (4.7%, 17/358 for all adult eyes combined). There were no reports in the

pediatric or adult compassionate eyes of any cumulative surgery related AEs that are key safety endpoints. Specifically, cystoid macular edema occurred in none (0.0%) of the pediatric eyes compared to 2.9% of all eyes treated (13/447 eyes), all of which occurred in the other adult eyes. Retinal detachments occurred in none of the pediatric eyes (0.0%) and in 3 out of 358 (0.8%) of other adult eyes treated in the study. Persistent corneal edema and chronic iritis were also rare in the study, with no reports (0.0%) in the pediatric eyes compared to 7 (2.0%) other adult eyes reports of persistent corneal edema and 8 out of 358 reports (2.2%) of chronic iritis in the all other adult eyes group. There were no unplanned secondary surgical interventions in the pediatric eyes, and no reports of surgery related hypopyon, endophthalmitis, device migration, pupillary block, in any of the eyes in the study.

Device related AEs in the pediatric eyes were limited to one observation of device decentration (2.3%; 1/44)) and one report of device dislocation (2.3%; 1/44) which required surgical repositioning (2.3%; 1/44). This frequency of AEs related to the CustomFlex™ Artificial Iris is quite similar to the adult eyes and the overall study cohort. IOL related AEs were also infrequent, consisting primarily of capsular haze in 3 eyes (6.8%; 3/44)).

Table 19: Key AI-001 Study Safety Endpoints at 12 Months Postoperatively in All Treated Eyes by Pediatric and Adult Cohorts

Device Related Adverse Events at 12 Months	**Threshold Rate**	**Pediatric Compassionate Use Eyes**	**Adult Compassionate Use Eyes**	**All Other Adult Eyes**	**All Eyes Combined**
N		44	45	358	447
• >2 Line (>10 Letters) Loss of BSCVA that is device related	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• BSCVA of worse than 20/40 if the pre-op BSCVA was 20/40 or better (device related)	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative Lens Related Adverse Events	<5%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Anisometropia	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Glare/halos	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Diplopia	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• IOL removal or replacement due to lens power calculation error	<1%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cumulative Surgery Related Adverse Events	**Threshold Rate**				
• Cystoid Macular Edema	18.8%	0 (0.0%)	0 (0.0%)	13 (3.6%)	13 (2.9%)
• Hypopyon	3.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Endophthalmitis	3.0%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Device migration	5.4%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Pupillary block	7.8%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
• Retinal detachment	5.4%	0 (0.0%)	0 (0.0%)	3 (0.8%)	3 (0.7%)
• Secondary surgical intervention (unplanned)	8.5%	0 (0.0%)	0 (0.0%)	6 (1,7%)	6 (1.3%)
• Corneal edema, persistent at 3 months or later	4.2%	0 (0.0%)	0 (0.0%)	7 (2.0%)	7 (1.6%)
• Chronic anterior segment inflammation, persistent at 3 months or later (chronic iritis)	5.0%	0 (0.0%)	0 (0.0%)	8 (2.2%)	5 (1.8%)

Effectiveness

For the pediatric eyes, daytime light sensitivity and daytime and night-time glare during the day both demonstrated decreases in the proportion of eyes that had marked-severe symptoms. The reduction in light sensitivity at night was substantial and clinically meaningful. The

smaller differences in night-time symptoms of light sensitivity and glare are not unexpected since the proportion of pediatric eyes with marked to severe night-time symptoms preoperatively was lower than in the adult eyes.

Table 20: Visual Symptoms Recorded via Self-Administered Questionnaire in All Eyes Treated by Pediatric Cohort

PMA Cohort	Visit	Operative Category	Characteristic	N	None n (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Severe n (%)
Pediatric Eyes Compassionate Use	Preoperative	Complaint Survey	Day-time light sensitivity	44	1 (2.27)	4 (9.09)	11 (25.00)	8 (18.18)	20 (45.45)
			Night-time light sensitivity	44	10 (22.73)	13 (29.55)	8 (18.18)	8 (18.18)	5 (11.36)
			Difficulty Driving at Night	44	5 (11.36)	2 (4.55)	2 (4.55)	2 (4.55)	6 (13.64)
			Reading Difficulty	44	7 (15.91)	6 (13.64)	6 (13.64)	2 (4.55)	21 (47.73)
			Double Vision	44	27 (61.36)	7 (15.91)	3 (6.82)	4 (9.09)	2 (4.55)
			Fluctuation in Vision	44	22 (50.00)	10 (22.73)	6 (13.64)	2 (4.55)	4 (9.09)
			Glare during the Day	44	3 (6.82)	7 (15.91)	12 (27.27)	9 (20.45)	13 (29.55)
			Glare during the Night	44	11 (25.00)	8 (18.18)	11 (25.00)	6 (13.64)	8 (18.18)
			Halos during the Day	44	19 (43.18)	11 (25.00)	6 (13.64)	4 (9.09)	4 (9.09)
			Halos during the Night	44	19 (43.18)	8 (18.18)	6 (13.64)	7 (15.91)	4 (9.09)
			Starbursts	44	20 (45.45)	6 (13.64)	7 (15.91)	8 (18.18)	3 (6.82)
			Dryness	44	22 (50.00)	13 (29.55)	8 (18.18)	0 (0.0)	1 (2.27)
			Pain	44	26 (59.09)	16 (36.36)	2 (4.55)	0 (0.0)	0 (0.0)
			Foreign Body Sensation	44	28 (63.64)	11 (25.00)	5 (11.36)	0 (0.0)	0 (0.0)
			Other	44	11 (25.00)	0 (0.0)	1 (2.27)	0 (0.0)	0 (0.0)
Pediatric Eyes Compassionate Use	12 Month	Complaint Survey	Day-time light sensitivity	33	6 (18.18)	16 (48.48)	8 (24.24)	3 (9.09)	0 (0.0)
			Night-time light sensitivity	33	17 (51.52)	14 (42.42)	1 (3.03)	1 (3.03)	0 (0.0)
			Difficulty Driving at Night	33	11 (33.33)	3 (9.09)	0 (0.0)	1 (3.03)	1 (3.03)
			Reading Difficulty	33	4 (12.12)	11 (33.33)	8 (24.24)	4 (12.12)	6 (18.18)
			Double Vision	33	24 (72.73)	5 (15.15)	3 (9.09)	0 (0.0)	0 (0.0)

Table 20: Visual Symptoms Recorded via Self-Administered Questionnaire in All Eyes Treated by Pediatric Cohort (continued)

PMA Cohort	Visit	Operative Category	Characteristic	N	None n (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Severe n (%)
			Fluctuation in Vision	33	20 (60.61)	11 (33.33)	2 (6.06)	0 (0.0)	0 (0.0)
			Glare during the Day	33	12 (36.36)	12 (36.36)	9 (27.27)	0 (0.0)	0 (0.0)
			Glare during the Night	33	16 (48.48)	11 (33.33)	4 (12.12)	2 (6.06)	0 (0.0)
			Halos during the Day	33	25 (75.76)	8 (24.24)	0 (0.0)	0 (0.0)	0 (0.0)
			Halos during the Night	33	20 (60.61)	7 (21.21)	4 (12.12)	2 (6.06)	0 (0.0)
			Starbursts	33	21 (63.64)	10 (30.30)	1 (3.03)	1 (3.03)	0 (0.0)
			Dryness	33	14 (42.42)	14 (42.42)	4 (12.12)	1 (3.03)	0 (0.0)
			Pain	33	26 (78.79)	7 (21.21)	0 (0.0)	0 (0.0)	0 (0.0)
			Foreign Body Sensation	33	23 (69.70)	9 (27.27)	1 (3.03)	0 (0.0)	0 (0.0)
			Other	33	8 (24.24)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 21: Visual Symptoms Recorded via Self-Administered Symptom Questionnaire in Eyes Treated by All Eyes Combined Cohort

PMA Cohort	Visit	Operative Category	Characteristic	N	None N (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Severe n (%)
All Combined	Preoperative	Complaint Survey	Day-time light sensitivity	446	16 (3.59)	23 (5.16)	77 (17.26)	101 (22.65)	227 (50.90)
			Night-time light sensitivity	446	56 (12.56)	68 (15.25)	106 (23.77)	87 (19.51)	127 (28.48)
			Difficulty Driving at Night	446	43 (9.64)	37 (8.30)	64 (14.35)	49 (10.99)	145 (32.51)
			Reading Difficulty	446	46 (10.31)	36 (8.07)	69 (15.47)	33 (7.40)	255 (57.17)
			Double Vision	446	273 (61.21)	50 (11.21)	47 (10.54)	29 (6.50)	43 (9.64)
			Fluctuation in Vision	446	215 (48.21)	81 (18.16)	71 (15.92)	39 (8.74)	36 (8.07)
			Glare during the Day	446	40 (8.97)	42 (9.42)	76 (17.04)	88 (19.73)	198 (44.39)
			Glare during the Night	446	50 (11.21)	57 (12.78)	80 (17.94)	87 (19.51)	169 (37.89)
			Halos during the Day	446	208 (46.64)	70 (15.70)	63 (14.13)	39 (8.74)	60 (13.45)
			Halos during the Night	446	144 (32.29)	54 (12.11)	74 (16.59)	60 (13.45)	109 (24.44)
			Starbursts	446	193 (43.27)	49 (10.99)	61 (13.68)	45 (10.09)	92 (20.63)
			Dryness	446	189 (42.38)	107 (23.99)	72 (16.14)	36 (8.07)	40 (8.97)
			Pain	446	290 (65.02)	88 (19.73)	39 (8.74)	18 (4.04)	8 (1.79)
			Foreign Body Sensation	446	268 (60.09)	87 (19.51)	56 (12.56)	17 (3.81)	15 (3.36)
			Other	446	146 (32.74)	8 (1.79)	8 (1.79)	2 (0.45)	3 (0.67)

Table 21: Visual Symptoms Recorded via Self-Administered Symptom Questionnaire in Eyes Treated by All Eyes Combined Cohort (continued)

PMA Cohort	Visit	Operative Category	Characteristic	N	None n (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Severe n (%)
All Combined	12 Month	Complaint Survey	Day-time light sensitivity	339	71 (20.94)	140 (41.30)	80 (23.60)	34 (10.03)	14 (4.13)
			Night-time light sensitivity	339	152 (44.84)	119 (35.10)	45 (13.27)	13 (3.83)	10 (2.95)
			Difficulty Driving at Night	339	115 (33.92)	62 (18.29)	37 (10.91)	12 (3.54)	36 (10.62)
			Reading Difficulty	339	92 (27.14)	85 (25.07)	72 (21.24)	24 (7.08)	65 (19.17)
			Double Vision	339	254 (74.93)	44 (12.98)	23 (6.78)	10 (2.95)	7 (2.06)
			Fluctuation in Vision	339	193 (56.93)	94 (27.73)	35 (10.32)	7 (2.06)	10 (2.95)
			Glare during the Day	339	126 (37.17)	117 (34.51)	57 (16.81)	25 (7.37)	13 (3.83)
			Glare during the Night	339	131 (38.64)	121 (35.69)	56 (16.52)	17 (5.01)	14 (4.13)
			Halos during the Day	339	267 (78.76)	48 (14.16)	15 (4.42)	1 (0.29)	8 (2.36)
			Halos during the Night	339	199 (58.70)	81 (23.89)	33 (9.73)	13 (3.83)	13 (3.83)
			Starbursts	339	223 (65.78)	68 (20.06)	26 (7.67)	12 (3.54)	10 (2.95)
			Dryness	339	122 (35.99)	116 (34.22)	66 (19.47)	17 (5.01)	18 (5.31)
			Pain	339	245 (72.27)	65 (19.17)	17 (5.01)	7 (2.06)	5 (1.47)
			Foreign Body Sensation	339	234 (69.03)	70 (20.65)	24 (7.08)	5 (1.47)	5 (1.47)
			Other	339	123 (36.28)	5 (1.47)	1 (0.29)	3 (0.88)	1 (0.29)

The changes in the degree of severity of subjective visual complaints from baseline to 12 month postoperative visits are summarized below in **Table 22** for the pediatric compassionate eyes. For comparison, the changes in degree of severity changes in visual symptoms at 12 Months are presented in **Table 23** for all eyes treated.

Table 22: Changes in Degree of Severity of Visual Symptoms in All Eyes Treated by Pediatric Cohort

Visit	Operative Category	Characteristic	Percent Baseline None-Moderate	Percent Baseline Marked-Severe	Percent Visit None-Moderate	Percent Visit Marked-Severe	Difference in Marked-Severe
12 Month	Complaint Survey	Day-time light sensitivity	36.36	63.64	90.91	9.09	-54.5
		Night-time light sensitivity	70.45	29.55	96.97	3.03	-26.5
		Difficulty Driving at Night	52.94	47.06	87.50	12.50	-34.6
		Reading Difficulty	45.24	54.76	69.70	30.30	-24.5
		Double Vision	86.05	13.95	100.0	0.00	-14.0
		Fluctuation in Vision	86.36	13.64	100.0	0.00	-13.6
		Glare during the Day	50.00	50.00	100.0	0.00	-50.0
		Glare during the Night	68.18	31.82	93.94	6.06	-25.8
		Halos during the Day	81.82	18.18	100.0	0.00	-18.2
		Halos during the Night	75.00	25.00	93.94	6.06	-18.9
		Starbursts	75.00	25.00	96.97	3.03	-22.0
		Dryness	97.73	2.27	96.97	3.03	0.76
		Pain	100.0	0.00	100.0	0.00	0.00
		Foreign Body Sensation	100.0	0.00	100.0	0.00	0.00
		Other	100.0	0.00	100.0	0.00	0.00

Table 23: Changes in Degree of Severity of Visual Symptoms in All Eyes Treated by All Eyes Combined Cohort

Visit	Operative Category	Characteristic	Percent Baseline None-Moderate	Percent Baseline Marked-Severe	Percent Visit None-Moderate	Percent Visit Marked-Severe	Difference in Marked-Severe
12 Month	Complaint Survey	Day-time light sensitivity	26.19	73.81	85.84	14.16	-59.7
		Night-time light sensitivity	51.69	48.31	93.22	6.78	-41.5
		Difficulty Driving at Night	42.43	57.57	81.68	18.32	-39.2
		Reading Difficulty	34.47	65.53	73.67	26.33	-39.2
		Double Vision	83.67	16.33	94.97	5.03	-11.3
		Fluctuation in Vision	83.22	16.78	94.99	5.01	-11.8
		Glare during the Day	35.67	64.33	88.76	11.24	-53.1
		Glare during the Night	42.31	57.69	90.86	9.14	-48.5
		Halos during the Day	77.45	22.55	97.35	2.65	-19.9
		Halos during the Night	61.59	38.41	92.33	7.67	-30.7
		Starbursts	68.79	31.21	93.51	6.49	-24.7
		Dryness	82.84	17.16	89.68	10.32	-6.83
		Pain	94.12	5.88	96.46	3.54	-2.34
		Foreign Body Sensation	92.76	7.24	97.04	2.96	-4.28
		Other	97.01	2.99	96.99	3.01	0.01

NEI VFQ-25

An analysis of the NEI VFQ-25 health related quality of life outcomes was performed on the pediatric and adult subsets, in which the postoperative differences from baseline in each NEI VFQ-25 subscale and the total scores were calculated. A difference from baseline that has a positive numeric value indicates both an improvement in the subscale and less dysfunction (**Table 24**).

Table 24 : Postoperative Differences from Baseline in NEI-VFQ-25 Questionnaire Scores at 12 Months by Pediatric and Adult Cohorts

			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	General Health	n	33	29	275	33	29	277	33	29	275
		Mean	73.48	68.10	69.09	70.45	67.24	70.94	-3.03	-0.86	1.82
		Std. Dev.	23.33	23.99	22.59	21.15	22.26	20.62	20.50	18.28	18.65
		Median	75.00	75.00	75.00	75.00	75.00	75.00	0.00	0.00	0.00
		Minimum	25.0	25.0	0.0	25.0	25.0	0.0	-25	-50	-50
		Maximum	100	100	100	100	100	100	50.0	25.0	100
			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	General Vision	n	33	29	274	33	29	277	33	29	274
		Mean	62.42	57.93	57.45	72.12	68.97	73.57	9.70	11.03	16.06
		Std. Dev.	20.47	24.11	20.35	15.76	21.10	16.87	19.44	21.77	21.90
		Median	60.00	60.00	60.00	80.00	80.00	80.00	0.00	0.00	20.00
		Minimum	20.0	20.0	0.0	40.0	20.0	20.0	-20	-20	-40
		Maximum	100	100	100	100	100	100	60.0	60.0	80.0

Table 24: Postoperative Differences from Baseline in NEI-VFQ-25 Questionnaire Scores at 12 Months by Pediatric and Adult Cohorts (continued)

			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Ocular Pain	33	29	275	33	29	277	33	29	275	33
		80.68	79.74	77.36	85.61	87.07	83.66	4.92	7.33	6.18	80.68
		17.70	17.81	22.56	16.27	13.97	19.55	21.64	13.58	22.10	17.70
		87.50	87.50	87.50	87.50	87.50	87.50	0.00	12.50	0.00	87.50
		25.0	50.0	12.5	50.0	50.0	12.5	-38	-25	-63	25.0
		100	100	100	100	100	100	75.0	37.5	75.0	100
			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Near Activities	n	33	29	275	33	29	277	33	29	275
		Mean	72.47	58.05	59.74	82.32	72.70	77.77	9.85	14.66	17.89
		Std. Dev.	22.87	25.05	24.14	14.09	21.23	20.86	17.86	18.72	22.68
		Median	75.00	58.33	58.33	83.33	75.00	83.33	8.33	16.67	16.67
		Minimum	25.0	16.7	0.0	50.0	33.3	0.0	-25	-17	-25
		Maximum	100	100	100	100	100	100	50.0	50.0	100

Table 24: Postoperative Differences from Baseline in NEI-VFQ-25 Questionnaire Scores at 12 Months by Pediatric and Adult Cohorts (continued)

			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12Months	Distance Activities	n	33	29	275	33	29	277	33	29	275
		Mean	66.67	64.94	61.59	82.07	77.87	79.35	15.40	12.93	17.61
		Std. Dev.	22.73	22.64	24.05	14.60	21.16	20.52	15.18	17.62	21.18
		Median	75.00	66.67	58.33	83.33	83.33	83.33	8.33	8.33	16.67
		Minimum	25.0	33.3	0.0	50.0	33.3	12.5	-8.3	-8.3	-63
		Maximum	100	100	100	100	100	100	58.3	50.0	91.7
			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Vision Specific: Social Functioning	n	33	29	275	33	29	277	33	29	275
		Mean	83.71	70.69	79.09	91.29	86.21	91.34	7.58	15.52	12.18
		Std. Dev.	21.53	24.15	23.31	13.44	16.14	16.05	21.18	23.30	20.97
		Median	87.50	75.00	87.50	100.00	87.50	100.00	0.00	12.50	0.00
		Minimum	12.5	25.0	0.0	62.5	50.0	0.0	-25	-13	-63
		Maximum	100	100	100	100	100	100	87.5	75.0	100

Table 24: Postoperative Differences from Baseline in NEI-VFQ-25 Questionnaire Scores at 12 Months by Pediatric and Adult Cohorts (continued)

			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Vision Specific: Mental Health	n	33	29	275	33	29	277	33	29	275
		Mean	59.47	45.26	51.52	74.05	73.06	75.74	14.58	27.80	24.11
		Std. Dev.	28.82	30.24	28.14	25.15	24.10	25.93	23.37	25.47	25.96
		Median	68.75	43.75	50.00	87.50	75.00	87.50	12.50	25.00	18.75
		Minimum	0.0	0.0	0.0	18.8	18.8	0.0	-38	-31	-44
		Maximum	100	93.8	100	100	100	100	93.8	75.0	100
			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Vision Specific: Role Difficulties	n	33	29	275	33	29	277	33	29	275
		Mean	64.02	56.03	58.09	77.65	78.88	79.96	13.64	22.84	21.73
		Std. Dev.	29.27	30.18	29.85	23.75	22.93	25.70	31.15	27.15	26.22
		Median	75.00	50.00	62.50	87.50	87.50	87.50	12.50	12.50	25.00
		Minimum	0.0	0.0	0.0	12.5	12.5	0.0	-50	-25	-38
		Maximum	100	100	100	100	100	100	75.0	75.0	100

Table 24: Postoperative Differences from Baseline in NEI-VFQ-25 Questionnaire Scores at 12 Months by Pediatric and Adult Cohorts (continued)

			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Vision Specific: Dependency	n	33	29	275	33	29	277	33	29	275
		Mean	70.45	65.52	70.52	78.03	83.91	88.03	7.58	18.39	17.45
		Std. Dev.	24.92	30.92	29.52	23.65	21.35	21.49	18.56	24.84	24.82
		Median	75.00	75.00	83.33	83.33	91.67	100.00	8.33	16.67	8.33
		Minimum	8.3	0.0	0.0	25.0	33.3	0.0	-33	-25	-50
		Maximum	100	100	100	100	100	100	66.7	83.3	91.7
			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Driving	n	12	19	208	21	19	223	11	19	202
		Mean	75.00	74.34	70.79	79.76	87.50	86.21	17.05	13.16	16.71
		Std. Dev.	18.46	21.44	21.25	26.36	15.59	16.58	15.08	15.85	19.22
		Median	75.00	87.50	75.00	87.50	87.50	87.50	25.00	12.50	12.50
		Minimum	37.5	25.0	12.5	25.0	50.0	25.0	0.0	-13	-50
		Maximum	100	100	100	100	100	100	37.5	50.0	75.0

Table 24: Postoperative Differences from Baseline in NEI-VFQ-25 Questionnaire Scores at 12 Months by Pediatric and Adult Cohorts (continued)

			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Color Vision	n	33	29	275	33	29	275	33	29	273
		Mean	93.94	84.48	90.45	95.45	94.83	96.36	1.52	10.34	5.86
		Std. Dev.	16.57	22.57	19.16	13.19	12.28	12.10	20.67	21.67	19.59
		Median	100.00	100.00	100.00	100.00	100.00	100.00	0.00	0.00	0.00
		Minimum	25.0	25.0	0.0	50.0	50.0	0.0	-50	-50	-100
		Maximum	100	100	100	100	100	100	75.0	50.0	100
			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Peripheral Vision	n	32	29	275	33	29	274	32	29	272
		Mean	63.28	50.00	58.55	77.27	68.97	78.65	15.63	18.97	19.67
		Std. Dev.	27.67	24.09	28.73	22.85	26.44	24.96	20.82	28.86	28.40
		Median	62.50	50.00	50.00	75.00	75.00	75.00	25.00	0.00	25.00
		Minimum	25.0	25.0	0.0	25.0	25.0	0.0	-25	-50	-50
		Maximum	100	100	100	100	100	100	50.0	75.0	100

			Baseline Results			Visit Results			Difference		
Time	Characteristic	Parameter	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts	Pediatric Eyes Compassionate Use	Adult Eyes Compassionate Use	Adult Eyes Other Cohorts
12 Months	Total Score	n	33	29	275	33	29	277	33	29	275
		Mean	71.64	63.48	66.42	81.30	79.35	82.51	9.66	15.87	16.00
		Std. Dev.	14.49	19.60	18.52	11.92	15.15	16.09	11.86	15.26	15.50
		Median	74.54	69.20	69.85	82.73	81.70	87.88	7.29	12.92	13.18
		Minimum	29.3	32.6	17.8	50.5	47.5	15.5	-14	-9.1	-35
		Maximum	93.4	93.8	97.4	98.2	99.2	100	35.6	48.1	68.1

GAIS

GAIS is a one-item questionnaire in which the subject rates his/her satisfaction with the postoperative cosmetic result achieved after the CustomFlex™ Artificial Iris implant surgery according to one of the following five category descriptions:

Rating	Description
Very much improved	Optimal cosmetic result from the implant in this subject
Much improved	Marked improvement in appearance from the initial condition but not completely optimal
Improved	Obvious improvement in appearance from the initial condition, but a touch-up is indicated
No change	The appearance is essentially the same as the original condition
Worse	The appearance is worse than the original condition

Table 25: GAIS Ratings of Postoperative Cosmetic Appearance by Pediatric and Adult Cohorts

Visit	Operative Category	Characteristic	Parameter	Pediatric Eyes Compassionate Use n (%)	Adult Eyes Compassionate Use n (%)	Adult Eyes Other Cohorts n (%)	All Combined n (%)
1 Month	GAIS	Rating	Very Much Improved	17 (40.48)	19 (47.50)	189 (54.47)	225 (52.45)
			Much Improved	19 (45.24)	10 (25.00)	85 (24.50)	114 (26.57)
			Improved	4 (9.52)	9 (22.50)	49 (14.12)	62 (14.45)
			No Change	2 (4.76)	1 (2.50)	18 (5.19)	21 (4.90)
			Worse	0 (0.0)	1 (2.50)	6 (1.73)	7 (1.63)
3 Month	GAIS	Rating	Very Much Improved	16 (40.00)	19 (51.35)	183 (55.62)	218 (53.69)
			Much Improved	14 (35.00)	11 (29.73)	89 (27.05)	114 (28.08)
			Improved	9 (22.50)	6 (16.22)	36 (10.94)	51 (12.56)
			No Change	1 (2.50)	1 (2.70)	18 (5.47)	20 (4.93)
			Worse	0 (0.0)	0 (0.0)	3 (0.91)	3 (0.74)
6 Month	GAIS	Rating	Very Much Improved	17 (45.95)	21 (56.76)	182 (57.05)	220 (55.98)
			Much Improved	16 (43.24)	10 (27.03)	79 (24.76)	105 (26.72)
			Improved	3 (8.11)	4 (10.81)	37 (11.60)	44 (11.20)
			No Change	0 (0.0)	1 (2.70)	19 (5.96)	20 (5.09)
			Worse	1 (2.70)	1 (2.70)	2 (0.63)	4 (1.02)
12 Month	GAIS	Rating	Very Much Improved	16 (48.48)	14 (48.28)	166 (59.93)	196 (57.82)
			Much Improved	12 (36.36)	11 (37.93)	59 (21.30)	82 (24.19)
			Improved	5 (15.15)	3 (10.34)	32 (11.55)	40 (11.80)
			No Change	0 (0.0)	0 (0.0)	15 (5.42)	15 (4.42)
			Worse	0 (0.0)	1 (3.45)	5 (1.81)	6 (1.77)

The pediatric subset of eyes and each of the adult groups of eyes achieved improvements in the NEI VFQ-25 total score. The pediatric subset also had the greatest proportion of eyes in which postoperative cosmesis was rated as “improved,” “much improved,” or

"very much improved" in 100% of the pediatric eyes compared to 96.6% (28/29) of the adult compassionate eyes, 93.0% (257/277) of the all other adult eyes group, and 94.0% (318/339) of the overall study cohort (please refer to **Table 14** above for additional details).

Pediatric Changes in BSCVA

The proportion of pediatric eyes gaining lines of BSCVA was slightly lower than the adult eyes with 41.9% (13/31) gaining 2 or more lines of vision compared to 48.3% (14/29) in the adult compassionate eyes, 53.7% (145/270) in the other adult eyes, and 52.1% (n=172/330) in the overall cohort. The results were similar for each of the groups when the eyes that gained lines or had no change in BSCVA. In this category, 90.3% (28/31) of the pediatric eyes had no change or gained 1 or more lines of BSCVA compared to 89.6% (26/29) of the adult compassionate eyes, 87.8% (237/270) of the other adult eyes, and 88.2% (291/330) of the overall eyes treated with CustomFlex™ Artificial Iris. The percentage of eyes that lost more than 2 lines of BSCVA was similar in each of the groups, with 6.5% (2/31) of the pediatric eyes, 3.5% (1/29) of the adult compassionate eyes, 5.6% (15/270) of the other adult eyes, and 5.5% (18/330) of the overall cohort losing more than 2 lines of BSCVA. There were no device-related losses of BSCVA in any of the study populations; and, any loss in BSCVA that resulted from other causes is not unexpected since many of these eyes have complex ocular pathology.

In addition to the clinical data presented in this summary, the CustomFlex™ Artificial Iris has been implanted internationally in approximately 530 eyes to date in the past 9 years in 41 different countries. Of these, ~295 implants are the with-fiber design; and, ~236 eyes have been implanted with the fiber-free design which became available in 2005. Data have not been collected under a formal clinical study.

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 there were no questions of safety or effectiveness for which Panel input was required. This is a Breakthrough Device Designation for a population of patients for which there is no other suitable treatment available.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

This clinical summary report was submitted to support a Pre-market Approval for the CustomFlex™ Artificial Iris. This is the first of a kind medical device to be marketed for the indication of treatment of full or partial aniridia resulting from congenital aniridia, acquired defects, or other conditions associated with full or partial aniridia.

The applicant provided data for 447 treated eyes to demonstrate reasonable assureness of safety and effectiveness. The study collected patient reported outcomes related to functional visual activities and demonstrated a marked improvement in visual health related quality of life. Reduced photosensitivity to daytime and nighttime lighting and associated glare lead not only to improved visual comfort, but also improved visual acuity due to presence of an artificial pupil combined with intraocular lens implantation for correction of refractive errors.

- There was a decrease in the severity of night-time symptoms of light sensitivity, glare, halos and starbursts:

  - 6.8% (n=23/339) of the eyes had symptoms of light sensitivity at night that were marked or severe after the artificial iris surgery compared to 48.0% (n=214/443) of eyes before the surgery
  - 9.1% (n=31/339) of the eyes had symptoms of glare at night that were marked or severe after the artificial iris surgery compared to 57.4% (n=256/443) of eyes before the surgery
  - 7.7% (n=26/339) of the eyes had symptoms of halos at night that were marked or severe after the artificial iris surgery compared to 37.9% (n=169/443) of eyes before the surgery
  - 6.5% (n=22/339) of the eyes had symptoms of starbursts at night that were marked or severe after the artificial iris surgery compared to 30.7% (n=137/443) of eyes before the surgery

- Reading was improved with 26.3% (n=89/339) of eyes having marked to severe reading difficulty after CustomFlex^{TM} Artificial Iris treatment compared to 64.6% (n=288/339) before the treatment.

- Difficulty driving at night also improved with 14.2% (n=48/339) of subjects who were driving reporting marked to severe difficulty driving after CustomFlex^{TM} Artificial Iris treatment compared to 43.5% (n=194/339) who had marked to severe difficulty driving before the treatment.

- There was a three-fold improvement in the subjects' ability to complete normal vision-related activities of daily living, as measured by a standardized health related quality of life questionnaire. The mean score on the questionnaire before CustomFlex^{TM} Artificial Iris surgery was 66.7 compared to 15.4 after the surgery, where a lower score indicates improvement in health related quality of life and less dysfunction.

- Satisfaction with the cosmetic appearance was high, with 93.8% (n=318/339) of subjects rating their appearance as improved to very much improved after implantation of the CustomFlex^{TM} Artificial Iris.

- Although the CustomFlex^{TM} Artificial Iris is not designed to improve vision, 67.2% (n=170/253) of the eyes had better uncorrected visual acuity (vision

without glasses or contact lenses) after the artificial iris surgery; and, 27.7% (n=70/253) of the eyes had uncorrected vision that was unchanged.

B. **Safety Conclusions**

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

- Postoperative inflammation resolved by 1 month. 92% or more of the pediatric and adult eyes had no or trace cell or flare, 90% of pediatric and adult eyes had no corneal stromal edema; and, at least 96% of pediatric and adult eyes had no corneal wound edema at 1month.

- Intraocular pressure was well controlled in the majority of eyes; mean postoperative IOP was within 1.5 mm Hg of mean preoperative IOP at all visits for the overall cohort and within 2.6 mm Hg for the pediatric eyes.

- Spikes of IOP >30 mm Hg were the most commonly reported postoperative AEs. Surgery related IOP increases >30 mm Hg occurred in less than 8% (35/447) of all the treated eyes and in none of the pediatric eyes.

- Although the CustomFlex™ Artificial Iris is not a refractive device, 65% (215/330) of all eyes and 55% (24/44) of pediatric eyes gained 1 or more lines of BSCVA; 67% (170/253) of all eyes and 64% (16/25) of pediatric eyes gained 1 or more lines of UCVA; and, mean MRSE was -0.36 D for all eyes and -0.83 D for pediatric eyes at 12 Months postoperatively.

- Few eyes lost BSCVA; 6.5% (2/31) of pediatric and 7.9% (26/330) of the overall study eyes lost 2 or more lines of BSCVA postoperatively compared to their preoperative vision at 12 months; and, none of the losses were related to the device per se.

- ECD changes were a major safety analysis in the outcomes of this study. The mean endothelial cell density remained stable with no clinically significant loss over the 12 months of the study in the pediatric and adult eyes.

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.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

Because the CustomFlex™ Artificial Iris is a permanent implant, the natural lens of the eye has to be removed before or at the same time as the artificial iris surgery and an IOL

will be implanted. Therefore, the assessment of risks includes the risk associated from the CustomFlex™ Artificial Iris, surgery and IOL.

The most frequent AEs across the entire study population were reports of increased IOP greater than 30 mm Hg (IOP >30 mm Hg) resulting from multiple causes. It is important to note that in the entire study, there were no reports of IOP >30 mm Hg that were IOL related and only one report that was related to the artificial iris device (0.2%; 1/447). More than half of surgically related elevations in IOP occurred at Day 1 or within the first week after surgery. Elevated IOP in the first week after surgery is a known and expected complication from surgery of this type, especially in eyes with pre-existing glaucoma or other co-morbidities which can be exacerbated by surgical procedures and that complicate the clinical management of these eyes.

Surgically related IOP spikes above 30 mm Hg were related to vitreous heme or vitreous hemorrhage in 4/447 (n=0.9%) of the treated eyes and were expected exacerbations of glaucoma secondary to the trauma from the surgery. The drug related IOP spikes were primarily due to non-compliance with glaucoma medications or a response to postoperative steroids. All eyes in the study received a regimen of steroid drops three times a day for at least 1 week followed by a tapering regimen over no less than 4 weeks after implantation of the CustomFlex™ Artificial Iris and any accompanying IOL procedure(s). Increased IOP is a known side effect from the use of prednisolone or other steroidal eye drops.

Device-related complications occurring at a frequency of 3% or less were all related to device positioning and consisted of device decentration (1.8%, 8/447), device dislocation (2.5%, 11/447) and secondary surgical interventions to reposition the dislocated devices (2.2%, 6/447) or replace the device (0.2%, 1/447).

Capsular haze was IOL related complication and occurred at a rate of 1.8% (8/447).

1. Patient Perspectives
   Patient perspectives considered during the review included NEI VFQ-25 and the GAIS questionnaire.

   Aniridia, regardless of etiology, creates visually debilitating symptoms such as decreased visual acuity, disabling glare, and photophobia. Reducing or eliminating these functional visual disabilities is the intended use of the CustomFlex™ Artificial Iris. The study measured subjects' self-reported decrease in severe sensitivity to light and glare post-procedure, health-related quality of life, and satisfaction with the cosmetic improvement or appearance of the prosthesis.

   At 12 months after implantation there was an overall improvement in the vision related quality of life and photosensitivity symptoms in pediatric and adult subjects as determined by administration of the NEI VFQ-25 and GAIS questionnaires.

Over 70% of subjects reported decreases in light sensitivity and glare. For all study eyes (447 eyes combined), subjects reported a decrease in severity in day-time light sensitivity (-59.7%), night-time light sensitivity (-41.5%), glare during the day (-53.1%), glare at night (-48.5%). They also reported an increase in health related quality of life following the procedure through the NEI-VFQ-25 questionnaire. In addition, 94% percent of all subjects were satisfied with the artificial iris' appearance. The GAIS assessment results showed that cosmesis was aesthetically pleasing, with 94% (318/339) of subjects rating the cosmesis as improved, much improved, or very much improved.

The CustomFlex™ Artificial iris offers the benefit of being implantable through a small surgical incision and can be implanted using different techniques, depending on patient's anatomy and the surgical procedure. The positive clinical outcomes indicate that the CustomFlex™ reduces the symptoms associated with complete or partial aniridia and very closely mimics the natural iris, thus providing very high quality cosmesis. The incidence of AEs, complications, and other ocular or vision-related observations is small. Visual symptoms are reduced, and visual function is increased after CustomFlex™ Artificial Iris implantation compared to baseline. The CustomFlex™ Artificial Iris meets all key safety endpoints for device-related, IOL-related-, and surgery-related AEs. Moreover, all effectiveness endpoints demonstrated a decrease in the severity of photosensitivity visual symptoms and improvement in health-related quality of life.

In conclusion, given the available information above, the data support that for the treatment of full or partial aniridia resulting from congenital or acquired defects, the probable benefits outweigh the probable risks.

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 CustomFlex™ Artificial Iris study is the first and the largest known study for an iris prosthesis. From the surgeon perspective, the CustomFlex™ Artificial Iris offers the benefit of being implantable through a small surgical incision. The device is available in two (2) models (With Fiber and Fiber-Free) and can be implanted using different surgical techniques (intra-capsular, sulcus, or suture fixation), depending on native patient anatomy and the evolution of the individual patient's surgical procedure. In addition, secondary suture fixation is possible late after the primary procedure should progressive zonulopathy develop (a common comorbid pathology in congenital aniridia).

The CustomFlex™ Artificial Iris study data indicates that the CustomFlex™ Artificial Iris reduces the symptoms associated with complete or partial aniridia and

very closely mimics the natural iris, thus providing very high quality cosmesis. The incidence of AEs, complications, and other ocular or vision-related observations is small. Visual symptoms are reduced, and visual function is increased after CustomFlex™ Artificial Iris implantation compared to baseline. The CustomFlex™ Artificial Iris meets all key safety endpoints for device related, IOL related, and surgery related AEs and all key effectiveness endpoints for decrease in the severity of photosensitivity visual symptoms, improvement in health-related quality of life affected by vision, and satisfaction with cosmeses that were established *a priori* for the approved IDE study. These outcomes were similar in each of the study cohorts, the pediatric eyes and the overall study population.

XIV. CDRH DECISION

CDRH issued an approval order on May 30, 2018. The final conditions of approval cited in the approval order are described below.

1. ODE Lead PMA Post-Approval Study – Post-Approval Study of Adult and Pediatric Subjects Implanted with the CustomFlex™ Artificial Iris: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study will be conducted as per the protocol agreed upon between ODE and Clinical Research Consultants. The study protocol outline is as follows:

   The study is a prospective, nonrandomized, multi-center, safety study in adults and pediatric subjects in which the postoperative outcomes are compared to its preoperative baseline. The study is designed to evaluate the long term safety (up to postoperative 3 years for adults and 5 years for pediatrics) of the CustomFlex™ Artificial Iris for the treatment of iris defects in adult and pediatric subjects. The study is limited to adult and pediatric subjects who participated in the 12-month AI-001 clinical trial and are implanted with the CustomFlex™ Artificial Iris for less than 36 months (adults) or less than 60 months (pediatrics). Up to 580 subjects (180 subjects of the PMA cohort, 250 subjects of the Continued Access, and 150 subjects of the Compassionate Use cohort) enrolled in one of four AI-001 study cohorts will be evaluated through 36 months for adults and 60 months for pediatrics for safety. Eligible subjects who are enrolled in the study will be followed postoperatively for 3 years for adults and 5 years for pediatrics, with the following frequency of assessments: postoperative at 12, 24, and 36 months for adults, and postoperative 3, 12, 24, 36, 48, 60 months for pediatrics.

   The study will evaluate: secondary surgical interventions, implant position, device or surgery related complications, and device malfunction or defects. Specifically, the primary safety outcome is to evaluate device related adverse events at postoperative 12 months (i.e., <5% experience a >2 lines best spectacle-corrected visual acuity (BSCVA) loss that is device related, and <5% experience BSCVA worse than 20/40, if preoperative BSCVA was 20/40 or better). The secondary safety outcome is to evaluate cumulative rate of lens (IOL) related adverse events at 12 months (i.e.,

anisometropia, glare/halos, diplopia, and IOL removal or replacement due to lens power calculation error <1%). Other study outcomes include: cumulative rate of surgery related adverse events, endothelial cell density (ECD) changes, device malfunction or defects, and device related complications.

2. OSB Lead PMA Post-Approval Study - Pediatric Artificial Iris New Enrollment PAS: The Office of Surveillance and Biometrics (OSB) will have the lead for the study initiated after device approval. This study will be conducted as per the protocol agreed upon between OSB and Clinical Research Consultants. The study protocol outline is as follows:

   Clinical Research Consultants will conduct a prospective, single-arm, multi-center, new enrollment, safety study, in which the postoperative outcomes of the subjects are compared to their preoperative baselines. The study is designed to evaluate the long-term safety of the CustomFlex™ Artificial Iris in pediatric subjects for the treatment of full or partial aniridia resulting from congenital and acquired iris defects, including but not limited to traumatic iris defects, traumatic mydriasis, and post inflammatory iris sequelae. A total of 125 pediatric eyes are to be enrolled, where 77 eyes are from the new enrollment PAS and 48 eyes are from the AI-001 compassionate use study. The sample size is based on an 80% follow-up rate to ensure that there are 100 evaluable eyes at 5 years post-operative. The study sites will be the same sites as those in the AI-001 study with the possibility of the additional non-IDE sites. A minimum of 7 sites with pediatric subjects is required for the study. Eligible subjects will be followed for five years post implantation with the following frequency of assessments: preoperative, the operative day and postoperative at 3, 12, 24, 36, 48, 60 months.

   The study will evaluate: secondary surgical interventions, implant position, device or surgery related complications, and device malfunction or defects. Specifically, the primary safety outcome is to evaluate device related adverse events at postoperative 12 months (i.e., <5% experience a >2 lines best spectacle-corrected visual acuity (BSCVA) loss that is device related, and <5% experience BSCVA worse than 20/40, if preoperative BSCVA was 20/40 or better). The secondary safety outcome is to evaluate cumulative rate of lens (IOL) related adverse events at 12 months (i.e., anisometropia, glare/halos, diplopia, and IOL removal or replacement due to lens power calculation error <1%). Other study outcomes include: cumulative rate of surgery related adverse events, endothelial cell density (ECD) changes, device malfunction or defects, and device related complications.

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

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