CustomFlex™ Artificial Iris
Professional Use Information

CAUTION: U.S. Federal law restricts this device to sale by or on the order of a physician.

CAUTION: U.S. Federal law restricts this device to practitioners who have been trained and have experience in the surgical management and treatment of aniridia.

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The information contained in this Professional Use Information booklet is provided for the express purpose of informing users about the use of the CustomFlex™ Artificial Iris. The reproduction, copying, or distribution of this booklet for any use other than the express purpose of providing written professional use information is prohibited without the specific prior written consent of Clinical Research Consultants, Inc. and HumanOptics AG.

USING THE PROFESSIONAL USE INFORMATION BROCHURE

This Professional Use Information brochure provides essential information concerning the intended clinical use of the CustomFlex™ Artificial Iris as an iris prosthesis for the treatment of aniridia and other iris defects in adults and children.

Carefully read this brochure and all related documents and instructions prior to use of the CustomFlex™ Artificial Iris

Observe all contraindications, warnings and precautions as described in this brochure and all related documents. Failure to do so may result in patient and/or user complications.

Do not perform CustomFlex™ Artificial Iris treatments for cosmetic reasons only. The CustomFlex™ Artificial Iris is NOT intended for use for cosmetic color change and should only be implanted when medically necessary.

Do not implant the CustomFlex™ Artificial Iris in phakic eyes.

The CustomFlex™ Artificial Iris is not designed for placement in the anterior chamber.

If you have questions that are not addressed in this brochure contact the manufacturer or distributor at the information provided on page 2 of this brochure.

NOTICE TO USERS

RESTRICTED DEVICE

Caution: U.S. Federal law restricts this device to sale by or on the order of a physician.

U.S. Federal law restricts this device to practitioners who have been trained and have experience in the surgical management and treatment of aniridia.

DISCLAIMER

The physician is responsible for having sufficient medical knowledge for carrying out all surgical procedures.

The manufacturer is not liable for the implantation method or the operative technique used by the physician performing the procedure or for the selection of the implant in relation to the patient or his condition.

Read and understand this Professional Use Information before using the CustomFlex™ Artificial Iris.

The physician, or other trained personnel working under the physician's direction, is responsible for selection of the template photos for manufacturing the custom-made device. Poor quality photos may lead to a poor color match and unsatisfactory postoperative cosmesis.

The manufacturer reserves the right to reject any photos submitted for manufacturing that are of poor quality or do not conform to the requirements listed in the photo directives. The manufacturer is also not liable for postoperative difference in color between the natural iris tissue and the implanted CustomFlex™ Artificial Iris device.

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1.0 DEVICE DESCRIPTION

1.1 CustomFlex™ Artificial Iris

The CustomFlex™ Artificial Iris device is a foldable iris prosthesis that is custom-made for each individual patient by HumanOptics AG (Erlangen, Germany). 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). This custom color-match provides a cosmetically acceptable aesthetic restoration with high patient satisfaction.

FIGURE 1: CustomFlex™ Artificial Iris Dimensions

The CustomFlex™ Artificial Iris device is manufactured as a full 360º iris prosthesis with an overall diameter of 12.8 mm, which can be trephined as needed to custom-fit the device for placement in the ciliary sulcus or capsular bag. The device can also be cut into a suitable size and shape (fiber design only) and sutured to an iris remnant for treatment of partial aniridia or traumatic iris injury.

The CustomFlex™ Artificial Iris is available in two models, With Fiber or Fiber Free, as shown in Figure 2 below. The two 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.

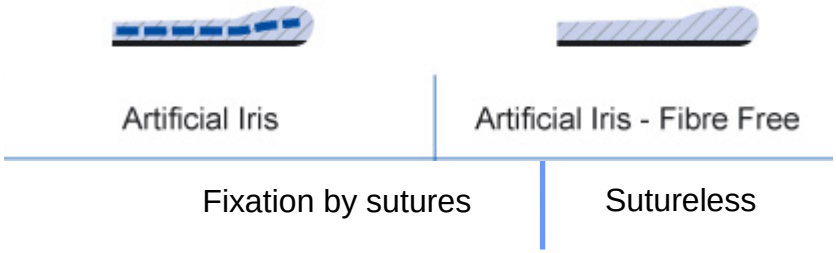

FIGURE 2: CustomFlex™ Artificial Iris With Fiber and Fiber-Free Models

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.

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

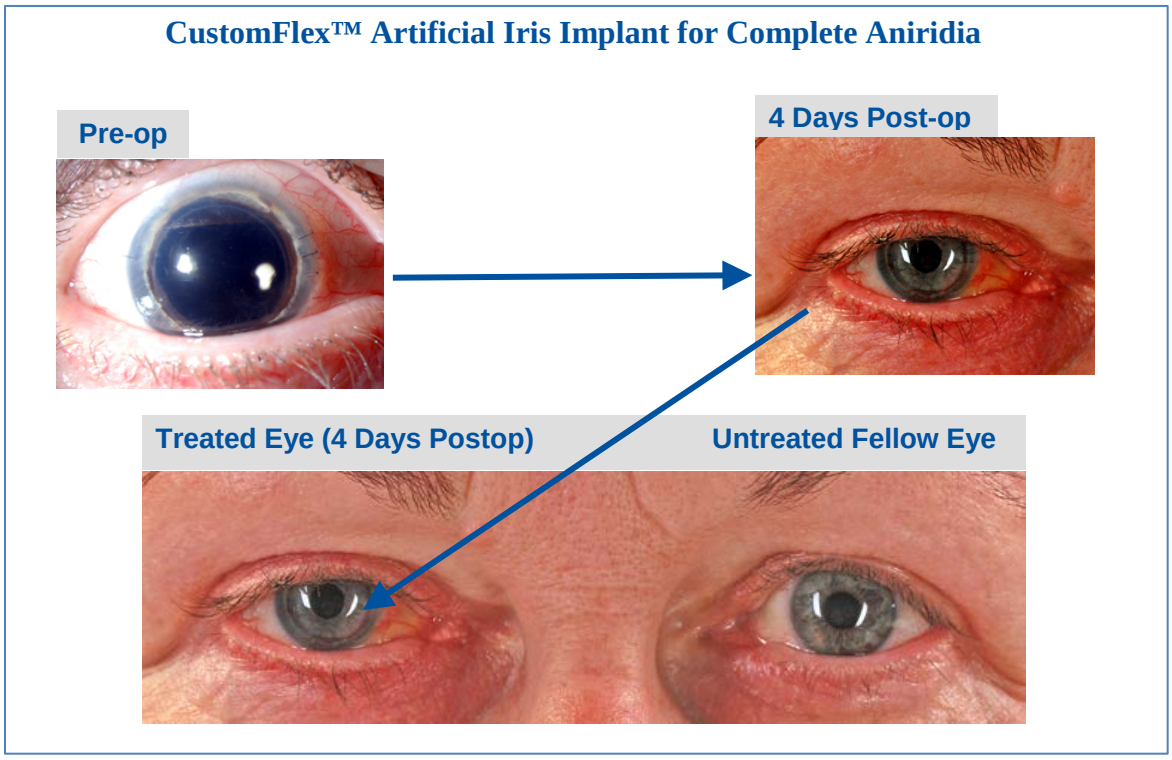

FIGURE 3: CustomFlex™ Artificial Iris Preoperative and 4-Days Postoperative

The term “CustomFlex™ Artificial Iris” as used throughout this brochure refers collectively to both the With Fiber and Fiber-Free models unless a particular model is specified. Although the CustomFlex™ Artificial Iris color is custom-matched to the template photo, the devices are described in this brochure as being blue, brown, gray, green, hazel or black in color for descriptive purposes.

1.2 Principle of Operation and Potential Benefits of CustomFlex™ Artificial Iris

The CustomFlex™ Artificial Iris functions as an iris prosthesis. It is manufactured from medical-grade silicone and has a fixed aperture of 3.35 mm, with an opaque perimeter and a black posterior surface to absorb light completely, reducing photic phenomena. The device closely mimics the appearance of the natural iris, creating an excellent cosmetic effect, at the same time it reduces the symptoms associated with aniridia. The small central aperture might increase visual acuity, increase depth of field, and increase contrast sensitivity (pinhole effect).

The CustomFlex™ Artificial Iris can be cut to a size that will fit a specific capsular bag or ciliary sulcus with a trephine. It can be implanted in addition to or at the same time as most commercially available intraocular lenses (IOL's) with the exception of active accommodating IOL's. The CustomFlex™ Artificial Iris is flexible, allowing it to be folded and inserted manually using forceps or injected using the AMO silver series IOL injector. The device can be implanted using a sutured or sutureless technique. It can be used for either intracapsular, sulcus, or suture fixation, depending on pre-existing anatomy and the evolution of the individual patient's surgical procedure. Furthermore, secondary suture fixation is possible late after the primary procedure in case progressive zonulopathy causes dislocation of the device.

The device has the potential to improve the quality of life by reducing visual symptoms and improving the cosmetic appearance of the eye.

2.0 INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

2.1 Intended Use/Indications for Use

The CustomFlex™ Artificial Iris is intended for use as an iris prosthesis for the treatment of iris defects. 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.

2.2 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

2.3 Warnings

Implantation of the CustomFlex™ Artificial Iris is not recommended in patients with the following conditions and situations:

- Children who are less than 3 years of age because their eyes are still in a stage of major growth development that would be disrupted by ocular surgery
- Preoperative intraocular pressure (IOP) above 21 mm Hg that does not respond to pressure-lowering medication, unless the IOP is known to be above 21 mm Hg and is well-controlled with glaucoma treatment
- Any other condition that would interfere with the planned surgical procedure to implant the artificial iris
- Post-partum women who are nursing or lactating and for whom postoperative medications are contraindicated
- Patients with gastric ulcers or diabetes mellitus in whom high doses of orally administered systemic steroids are required postoperatively

- Patients with severe endothelial corneal dystrophy should not be implanted with the CustomFlex™ Artificial Iris as potential surgical trauma associated with implantation of this device may lead to damage of the cornea such that the potential benefits of implantation do not outweigh the risks
- No useful vision or vision potential in the fellow eye, unless the patient has debilitating visual symptoms so that the potential benefits of CustomFlex™ Artificial Iris implantation clearly outweigh the risks
- Presence of a condition or finding in the contralateral eye that would make it unsafe to implant a CustomFlex™ Artificial Iris prosthesis in the eye to be treated
- Allergy to any of the planned postoperative antibiotic or anti-inflammatory medications, unless a suitable alternative medication can be prescribed

2.4 Precautions

The CustomFlex™ Artificial Iris should be used with caution in the following situations:

- A clear natural crystalline lens
- The vision potential in the fellow eye cannot be evaluated preoperatively (e.g., poor visual acuity due to cataract)
- Preoperative IOP > 21 mm Hg that is known to be stable and well controlled with glaucoma treatment (e.g., medication, tubes or shunts)
- Presence of any other medical condition that might be expected to make the patient an unsuitable candidate for CustomFlex™ Artificial Iris implantation
- Anticipated complexity of the planned surgical procedure that might increase the potential for complications
- Implantation in the fellow eye before stabilization of the first implanted eye (typically 1 month or more)
- Safety and effectiveness of intraocular lenses has not been established in pediatric patients in the U.S.

2.5 MRI Safety Information

The CustomFlex™ Artificial Iris implant is MR Unsafe. 

3.0 RISKS OF CUSTOMFLEX™ ARTIFICIAL IRIS

Potential risks and possible complications can be caused by the CustomFlex™ Artificial Iris device, by the surgical implant procedure, or by the IOL that is pre-existing or is implanted at the same time as the CustomFlex™ Artificial Iris device. As with any surgical procedure, the risks and benefits of using the CustomFlex™ Artificial Iris to treat the patient's aniridia should be evaluated carefully by the surgeon and discussed in detail with the patient before the decision is made to implant the device. If a concurrent IOL replacement is performed simultaneously with the artificial iris surgical procedure, complications related to the IOL that could affect vision should also be considered.

Below is a list of the probable adverse events (AEs) and complications associated with the use of the device, surgical procedure or IOL.

Device Related complications may include, but may not be limited to:

- Worsening or photosensitivity and vision
- Elevated intraocular pressure (IOP)
- Decrease in Uncorrected Visual Acuity (UCVA)
- 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 5.7, below.

The CustomFlex™ Artificial Iris is not a refractive device. Patients may experience improvement in vision that results from the reduction of visual symptoms or the concurrent IOL. In some cases, implantation of the CustomFlex™ Artificial Iris and/or IOL may make the patient's best-corrected or uncorrected distance vision worse than it was before surgery.

Most patients experience an improvement in the severity of visual symptoms; however, visual symptoms may be worse in some patients after implantation of the CustomFlex™ Artificial Iris and/or IOL.

The CustomFlex™ Artificial Iris With Fiber device is more robust to tighter sutures and is less likely to induce cheese-wiring or tearing under higher suture tensions, although it is stiffer to fold. When suturing the CustomFlex™ Artificial Iris With Fiber model, the suture pass should be at least 1 mm away from the edge in order to guarantee the stability of the device after suturing and minimize the risk of device decentration or dislocation.

Patients with aniridia frequently have other co-morbidities that increase the risk of complications from those other conditions or may require additional medical or surgical interventions to treat those co-morbidities. Postoperative management of eyes implanted with the CustomFlex™ Artificial Iris includes a tapering regimen of anti-inflammatory and steroid ophthalmic drops, which can cause steroid-induced increases in IOP, especially in patients whose IOP is known to be "steroid-responsive."

Please refer to the clinical results in Section 5 of this brochure for an evaluation of the risks and benefits associated with the implantation of the CustomFlex™ Artificial Iris, the surgical procedures, the concurrent IOL, and other known causes related to co-morbidities or postoperative medications.

Even though the CustomFlex™ Artificial Iris has a 3.5 mm pupil aperture, viewing, imaging, or treating other eye conditions or structures may be difficult due to the presence of the artificial iris. Surgery in the anterior chamber or posterior chamber may be possible with the artificial iris in place. However, you may choose to remove the artificial iris before such surgery. If the artificial iris is removed, the decision to replace the artificial iris device must be made on a case-by-case basis.

4.0 SURGICAL PLANNING AND PROCEDURES

The following should be considered in addition to the previously described contraindications, warnings and precautions to evaluate whether a patient is a good candidate for CustomFlex™ Artificial Iris for the treatment of the patient's congenital or acquired aniridia or iris defect.

4.1 Patient Selection

- Recommended CustomFlex™ Artificial Iris patient profile:
  - Adults or children at least 3 years of age or older -- there is no upper age limit for treatment
  - Having a diagnosis of congenital or acquired full or partial iris defect in the eye to be treated
  - Having symptoms of light sensitivity, photophobia, and/or glare in the study eye or other medically necessary indication for treatment ; the CustomFlex™ Artificial Iris is NOT indicated for cosmetic color change
  - The eye to be treated should be pseudophakic, aphakic or scheduled to undergo cataract extraction before or concurrently with the artificial iris surgical procedure
  - Implantation of the CustomFlex™ Artificial Iris is not contraindicated or not recommended

4.2 Preoperative Assessment

A comprehensive eye examination should be performed to determine if the patient is a candidate for CustomFlex™ Artificial Iris surgery to treat the patient's aniridia or iris defect. The comprehensive examination should include a detailed history and evaluation for conditions that could contraindicate use of the artificial iris device or result in increased risk or poor outcomes.

Slit lamp examination must be performed to evaluate the status of the natural, crystalline lens. Phakic eyes should undergo slit lamp biomicroscopy and dioptric power calculation of any optical implant placed before, or concurrently with, the artificial iris implant surgery.

An evaluation and rating of the patient's baseline visual symptoms and activities of daily living are also recommended.

4.3 Iris Photographs

The color composition of the CustomFlex™ Artificial Iris is custom designed on the basis of a photo printout. Therefore, utmost care should be taken to achieve the highest quality photograph and printout for each eye, as the manufacturer relies on these photographs to manufacture the device.

Digital ocular photos are obtained according to the manufacturer's directions and submitted with the CustomFlex™ Artificial Iris order form. The photo instructions and order form are provided in Appendices I and II of this brochure. Digital ocular photos of both eyes with bridge, and the right and left eyes alone should be taken. Ideally these should be standardized pictures of the size 9x13 cm (3½x5") showing the iris with a diameter of approx. 4 – 6 cm (1.5 – 2.5").

For a color-matched device, the doctor and the patient should select the hardcopy photo printout that is the best match for the target color. This will be used as the template to custom manufacture the artificial iris. Aniridia patients who have no native iris available to use as a template will submit the photo of another person's eye (e.g., family, friends) to use as the template photo. Photos from magazines or other digital sources are not acceptable. The photo that is to be used for production must be signed and dated by the doctor. It is also preferable to have the patient sign and date the selected template photo.

Photos cannot be submitted electronically as digital files since the color of every computer screen and printer shows different results of a photo. If the clinic/doctor is not set up for high quality photography and photo printouts, it recommended that the patient be sent to a professional photographer of their choice to provide the patient and doctor with high quality photos and printouts.

4.3.1 Tips for Obtaining Good Quality Photos

- Use a good quality camera; slit lamps, fundus cameras or any video cameras are not suitable for taking good pictures
- Illumination is essential:
    - Good, even illumination of the eye is essential; try not to use flash since it can overexpose the photo and cause reflections off the cornea
    - Illuminate the eye of the patient evenly in order not to produce shadows on the iris.
- Make a white balance with your camera at the exact place where you want to take the photo of the patient‘s eye (use of a white balance chart or gray balance chart may be helpful).
- Take care that the iris of the patient is completely visible and in focus.
- Use a good quality printer and paper for the printout:
    - Laser printers are usually not as good as ink-jets
    - Photo paper shows better results than normal copy paper
- Evaluate the photos for quality before submitting the photos with the artificial iris device order:
    - When evaluating a printout, it is best to hold the printout right next to the patient's eye.

  - Check if the color composition and patterns of the printout match the color composition and pattern of the natural iris when compared under the same illumination.
  - Check that the conjunctiva on the printout is white.
- The doctor must sign and date the template photo that is to be used for production. The patient may also sign the template photo to document his or her satisfaction thereof.

4.3.2 Custom Manufacturing

The CustomFlex™ Artificial Iris order form should be completed and submitted with 1) hardcopy paper printouts of both eyes and 2) the photo selected for color matching that will be used as the template for production of the artificial iris. The production template photo printout must be signed and dated by the doctor, and preferably, also by the patient.

The manufacturer will perform a quality review on the submitted photos to determine acceptability for manufacturing the custom-made artificial iris device. Repeat template eye photos may need to be obtained from the patient if the manufacturer deems the submitted template photos are of unacceptable quality for manufacturing.

Manufacturing and delivery time is generally ~4 to 8 weeks from the time of receipt of the CustomFlex™ Artificial Iris order form and acceptable photos. Upon receipt of the order form, the manufacturer will provide an estimated time of delivery for the custom-manufactured device that can be used by the surgeon to schedule the artificial device implant surgery.

4.4 Surgical Implant Techniques

The general surgical procedures for implanting the CustomFlex™ Artificial Iris that can be used to implant the artificial iris device are described below. The selection of the surgical technique should be dictated by the preoperative iris and anterior segment anatomy and pathology.

CustomFlex™ Artificial Iris devices that are to be implanted using an injector can only be used with the AMO Silver Series IOL Injector and PSCST cartridge, as the mechanical effects of folding and passage of the CustomFlex™ Artificial Iris through an injector have only been validated with this injector system.

Selection of the CustomFlex™ Artificial Iris Fiber-Free or With Fiber models should be based on the planned surgical technique. Both models are 12.8 mm in diameter. The Fiber-Free model can be implanted as a full diaphragm either within the ciliary sulcus or within the capsular bag. The With Fiber model is generally used when the planned surgical technique uses suture fixation.

- Capsular Bag Trephination: When placed within the capsular bag, the CustomFlex™ Artificial Iris should be trephinated *ex vivo* to an appropriate size for the intended bag. For an adult eye of average sized natural lens, this typically is approximately 10.0 mm in diameter, though can vary from patient to patient. The capsular bag diameter should be estimated based on the size of the evacuated capsular bag once a capsular tension ring (CTR) has been placed, especially in smaller eyes, pediatric eyes or larger myopic or megalo-ophthalmic eyes.
- Ciliary Sulcus Trephination: For passive placement into a suitably intact ciliary sulcus, the artificial iris device should be trephinated to the estimated smallest meridian sulcus diameter.

Always use sharp, sterile instruments for trephinating the CustomFlex™^{TM} Artificial Iris with Fiber

4.4.1 Capsular Bag Placement

For planned placement of the artificial iris device within the capsular bag, the anterior segment should be appropriately prepared by cataract removal, synechiolysis, and/or vitrectomy, as dictated by the preoperative anterior segment anatomy and pathology. A capsular tension ring should be placed if the capsular bag and capsulorhexis remain intact. The desired intraocular lens (IOL) will be placed within the capsular bag. Anterior capsule staining with trypan Blue or indocyanine green should be performed at the beginning of the surgical procedure, and additional dye can be painted or instilled along the anterior capsule margin just prior to implantation if the initial dye has faded. The limbal-corneal wound should be of adequate size (typically ~2.75 mm) for implantation of the iris device, either by forceps or by injection. The anterior chamber should be adequately deepened and, in fact, slightly hyper-deepened by a cohesive ophthalmic viscosurgical device (OVD) to allow adequate space for the artificial iris device to unfold without undue contact or pressure on the other intraocular structures.

The artificial iris device should be folded or placed in the injection cartridge with the colored side outward to reduce the risk of endothelial cell contact during the unfolding procedure posteriorly. The leading edge of the folded artificial iris device should be placed under the distal capsule margin, visualized by noting the trypan blue or indocyanine green over the iris device, before the iris device is unfolded. A spatula or second hand instrument can guide the unfolding or injecting process. Once the iris device is unfolded, the edges can be completely tucked into the capsular bag, taking special care to avoid undue pressure on the bag margins, especially in congenital aniridics. The iris device can be manipulated either by hooks or a micrograsping small-gauge intraocular forceps. If the iris device does not go into the bag easily, grasping it with an intraocular microforceps at the pseudopupil margin and overflowing it can markedly improve the ease of placement through the capsulorhexis and into the bag. Once IOL and iris device

centration and stability are confirmed, the OVD can be removed. If the chamber shallows, the iris device may “pop” out at one margin or another of the bag and require repeat positioning. In view of the multiple comorbid pathologies of the eyes requiring such an iris device, it can often be easier to remove the OVD in a bimanual approach to maintain a deep chamber. The wound should be sealed and secured according to surgeon preference. Instillation of intraocular carbachol is advised to reduce the risk for post-operative pressure elevation, which can occur in these already vulnerable eyes.

4.4.2 Passive Sulcus Fixation

For placement of the iris device in the ciliary sulcus without suture fixation, either the fiber or fiber free device is acceptable. The anterior segment will be appropriately prepared by cataract removal, IOL placement, synechiolysis, and/or vitrectomy, as dictated by the preoperative anterior segment anatomy and pathology. The iris device should be trephinated to the estimated sulcus size, as measured by ultrasound or intraoperative direct measurement (of the pressurized globe). The limbal-corneal wound should be of adequate size (typically ~2.75mm) for implantation of the iris device, either by forceps or by injection. The anterior chamber should be adequately deepened and, in fact, slightly hyper-deepened by a cohesive OVD to allow adequate space for the iris device to unfold without undue contact or pressure on the other intraocular structures.

The iris device should be folded or placed in the injection cartridge with the colored side outward to reduce the risk of endothelial cell contact during the unfolding procedure for unfolding posteriorly. The iris device can be manipulated either by hooks or with a micro-grasping small-gauge intraocular forceps. The iris device should be placed within the ciliary sulcus, and an adequately snug fit should be confirmed. If the iris device appears to buckle or fit too tightly, it may need to be removed and trephinated to a smaller size. If the iris device is freely mobile within the sulcus due to a smaller than estimated size, use the stand-by and renew sizing; or, gentle suspension sutures can be placed through the scleral wall at the ciliary sulcus to prevent movement. The sutures should be tied with only enough tension to prevent movement and achieve centration. Over-tightening the sutures can cause cheese-wiring of the iris device if a fiber-free device is utilized. In view of the multiple comorbid pathologies of the eyes requiring such an iris device, it can often be easier to remove the OVD in a bimanual approach to maintain a deep chamber. The wound should be sealed and secured according to surgeon preference. Instillation of intraocular carbachol is advised to reduce the risk for post-operative pressure elevation, which can occur in these already vulnerable eyes. Patch graft material can be placed over fixation sutures externally, as deemed necessary by the operating surgeon.

4.4.3 Planned Suture Fixation to the Scleral Wall

For sutured placement of the iris device in the ciliary sulcus, the iris device with polyester fiber is advisable. The anterior segment will be appropriately prepared by cataract removal (if present), IOL placement (e.g. sulcus placement or transscleral suture of the IOL), synechiolysis, and/or vitrectomy, as dictated by the anterior segment anatomy and pathology. The iris device should be trephinated to the estimated sulcus size, as measured by ultrasound or intraoperative direct measurement (of the pressurized globe). The limbal-corneal wound should be of adequate size (typically ~2.75 mm) for implantation of the iris device, either by forceps or by injection. The anterior chamber should be adequately deepened and, in fact, slightly hyper-deepened by a cohesive OVD to allow adequate space for the iris device to unfold without undue contact or pressure on the other intraocular structures. The iris device should be folded or placed in the injection cartridge with the colored side outward to reduce the risk of endothelial cell contact during the unfolding procedure. The iris device can be manipulated either by hooks or with a micrograsping small-gauge intraocular forceps. Sutures should be placed before intraocular placement. The iris device should be placed within the ciliary sulcus, and an adequately snug fit should be confirmed. If the iris device appears to buckle or fit too tightly, it may need to be removed and trephinated to a smaller size. The sutures should be tied with only enough tension to prevent movement and achieve centration. Over-tightening the sutures can cause cheese-wiring of the iris device if a fiber free device is utilized. In view of the multiple comorbid pathologies of the eyes requiring such an iris device, it can often be easier to remove the OVD in a bimanual approach to maintain a deep chamber. The wound should be sealed and secured according to surgeon preference. Instillation of intraocular carbachol is advised to reduce the risk for post-operative pressure elevation, which can occur in these already vulnerable eyes. Patch graft material can be placed over fixation sutures externally, as deemed necessary by the operating surgeon.

4.4.4 Placement of a Device with PCIOL Sutured Ex Vivo to the Iris Device

There are three viable methods to achieve fixation in this setting:

1) The IOL may be sutured to the iris device (with fibers) and then the entire complex secured to the scleral wall with transcleral sutures of the iris device.
2) The iris device may be secured with sutures to a PCIOL, which, in turn, can be secured to the eye wall with transcleral sutures.
3) The iris device and PCIOL may be each independently secured to the eye wall with transcleral sutures.

Note: Glued IOLs are not recommended.

In view of the multiple co-morbid pathologies of the eyes requiring such an iris device, it can often be easier to remove the OVD in a bimanual approach to maintain a deep chamber. The wound should be sealed and secured according to surgeon preference. Instillation of intraocular

carbachol is advised to reduce the risk for post-operative pressure elevation, which can occur in these already vulnerable eyes.

CAUTION: Do not use the artificial iris if the package has been damaged. The sterility of the artificial iris may have been compromised.

The surgeon should have at least one stand-by device available during the surgical procedure in addition to the device that is to be implanted.

4.5 Postoperative Procedures

The early postoperative course should be managed similarly to other complex anterior or posterior chamber surgical procedures, and management will be dictated by the patient's clinical course. Postoperative examinations should include IOP measurement, visual acuity, and slit lamp examination of the cornea, anterior chamber for cells and flare, and evaluation of the implant position (tilt, decentering, and dislocation). Postoperative photos of the treated and fellow eyes may be obtained after the initial postoperative wound healing is complete. An evaluation of the patient's visual symptoms and activities of daily living is also recommended.

Postoperatively, antibiotic eye drops should be administered according to manufacturer's directions for at least 7 days or until the ocular surface has fully stabilized. A fourth-generation fluroquinolone, or antibiotic with a similar spectrum, is recommended. Corticosteroid or anti-inflammatory eye drops should be administered frequently (e.g. 3 times/day) for at least 1 week, with a tapering regimen over no less than 4 weeks. Additional medications including, but not limited to, ocular antihypertensives and non-steroidal anti-inflammatories should be prescribed at the discretion of the operating surgeon.

Frequent postoperative follow-up examinations must be performed for at least the first year following implantation to evaluate the patient's postoperative complications and adverse events. We recommend the following postoperative follow-up schedule, at a minimum, during the first year following implantation of the artificial iris: 1 day, 1 to 2 weeks, 1 month, 6 months and 12 months. An eye care professional must monitor the patient's vision and ocular health regularly thereafter, as long as the artificial iris is implanted.

5.0 CLINICAL RESULTS

The AI-001 study was a prospective, non-masked, non-randomized multicenter study to determine the safety and effectiveness of the CustomFlex™ Artificial Iris for the treatment of full or partial iris defects. The study included subjects with a history of congenital aniridia and acquired iris defects, including but not limited to traumatic iris defects and traumatic mydriasis.

This study was composed of four cohorts: PMA, PMA Fellow Eye, Compassionate Use, and Continued Access. A total of 447 eyes treated with the CustomFlex™ Artificial Iris and enrolled across 12 sites were included in the data analysis for the PMA submission. The data cutoff for the analysis was based on the completion of the 12 month end of study visit by the last subject in the original PMA cohort. Data for all PMA Secondary Eyes, Compassionate Use, and Continued Access subjects treated with the CustomFlex™ Artificial Iris between November 26, 2013 and December 1, 2017 and all postoperative visits occurring between those dates, are included in this analysis.

Analyses were completed that demonstrated the gender, race, age, and outcome measures for the study cohorts are homogenous across the investigative sites. Analyses further confirmed that neither the color of the device nor device model type (With Fiber or Fiber-Free) implanted in the AI-001 study eyes affected the homogeneity of the study data. The analysis dataset includes 44 pediatric eyes enrolled in the Compassionate Use cohort. Analyses confirmed that the outcome measures for the Compassionate Use pediatric subset (age <22 years) were homogenous with the Compassionate Use adult subset and the remainder of the adult population.

As a result of these analyses, the entire 447-eye cohort can be combined and is presented in this reporting of the clinical study results. Results from the pediatric subset are also presented where appropriate.

5.1 Study Design

Subjects enrolled in the AI-001 study were evaluated initially to determine if the subject had a condition for which treatment with an iris prosthesis was medically indicated. Treatment for cosmetic reasons, i.e., for iris color change, was not permitted in the study; and, eyes receiving an iris prosthesis must have been either pseudophakic, aphakic, or eligible for lens extraction with an IOL replacement. Subjects who had an eligible condition and agreed to participate in the study provided informed consent.

Visual acuity measurements, IOP, gonioscopy, fundus examination, endothelial cell density, and depth of the anterior chamber (phakic patients only) were obtained at the screening examination, when medically possible, along with other tests and measurements necessary to evaluate the subject's candidacy for the artificial iris implant and any concomitant IOL replacement

procedure. Baseline measurements were obtained preoperatively within 30 days of the operative day. Postoperatively, subjects were evaluated at 1 day, 1 week, and 1, 3, 6, and 12 months postoperatively. Ophthalmic evaluations (when possible) included measurements of best spectacle-corrected visual acuity (BSCVA), manifest refraction, slit lamp evaluation, IOP, endothelial cell density, and position of the iris device along with other tests or measurements as medically necessary to evaluate the artificial iris device.

Safety monitoring throughout the study included observations at appropriate times for visual symptoms via a subjective complaints questionnaire, complications, adverse events, and any clinically significant findings on ophthalmic examination, including slit lamp and fundus examination, IOP measurement, and endothelial cell counts. Quality of vision was evaluated preoperatively and postoperatively via a vision related quality of life questionnaire (NEI VFQ-25). Postoperative satisfaction with cosmesis was evaluated using the Global Aesthetic Improvement Scale (GAIS).

5.2 Demographics

The demographic characteristics are presented in Table 5.2-1 below for each of the cohorts and for all eyes treated in the AI-001 study. Subjects must be at least 22 years old to be enrolled in the PMA or Continued Access cohorts, and all pediatric subjects 21 years of age or younger are enrolled in the Compassionate Use cohort. Mean age is 53.7 and 51.6 years for the adult PMA and Continued Access cohorts, respectively. The mean age in the Compassionate Use cohort is 33.8 years, and the younger age in this cohort is not unexpected considering the pediatric subset age ranges from 6 to 21 years and comprises half (n = 44/89 eyes; 49.4%) of the Compassionate Use cohort. The mean age for the PMA Secondary Eyes is 45.0 years and consists primarily of subjects with congenital aniridia who by nature of their indication are a younger population. The mean age for the entire study population is 48.5 years, which reflects the inclusion of the younger pediatric subjects and PMA Secondary Eye cohort.

The gender and racial distributions are similar to those observed in the investigators' general population of aniridic patients. Gender for all eyes treated showed a predominance of males (64.0%; 286/447) compared to females (36.0%; 161/447), and the distribution within the cohorts is very similar to the overall population enrolled in the AI-001 study. Enrollment across the entire cohort is 89.0% (398/447) Caucasian, with smaller numbers of Hispanic (4.0%; 18/447), Asian (2.9%; 13/447), and African-American (1.8%; 8/447) subjects participating in the study. Five subjects preferred to describe themselves in terms of their heritage or nationality instead of race, and two subjects were self-described as a mixed race.

Table 5.2-1: 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
Gender 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)

5.3 Aniridic Indications

The indications for treatment for the pediatric eyes and those in the adult groups are presented in Table 5.3-1 below. 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 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.

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

Table 5.3-1: 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)

5.4 Device Model and Color

The frequency of use of the two CustomFlex™ Artificial Iris models and the various device colors are presented in Table 5.4-1 below. The With-Fiber and Fiber-Free models of the CustomFlex™ Artificial Iris were implanted with equal frequency in the pediatric Compassionate Use eyes; whereas, the With Fiber model was used more frequently in the adult Compassionate Use eyes and the Fiber-Free model was used more commonly in the other adult eyes and overall study cohort in the AI-001 study.

Blue and brown were the predominant eye colors for the implanted devices in both the pediatric and adult eye groups, followed by hazel. Black devices were manufactured and implanted in eyes which had albinism with a non-pigmented iris that was translucent and poorly functioning for blocking light transmission, resulting in a deep blue iris color postoperatively due to the contrast between the existing translucent iris and black implant.

Table 5.4-1: Device Models and Colors in All Eyes Treated with 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 (%)**
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)

5.5 Key Effectiveness Endpoints

The primary effectiveness parameters evaluated in the AI-001 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; and, health related quality of life affected by vision is assessed using the NEI VFQ-25 questionnaire.

Effectiveness endpoints established for the AI-001study are:

- Improvement in visual symptoms of photosensitivity, as measured by the self-reported subjective visual symptoms questionnaire, specifically:
    - Decrease in severity of day-time light sensitivity symptoms
    - Decrease in severity of night-time light sensitivity symptoms
    - Decrease in severity of glare during the day
    - Decrease in severity of glare at night
- Improvement in health related quality of life, as measured by the NEI VFQ-25 total score
- Subject satisfaction with cosmesis, as measured by the proportion of subjects rating postoperative cosmesis as improved, much improved, or very much improved on the GAIS scale

It should be noted, the analysis was not designed to test the cosmesis comparison as a statistical hypothesis. Furthermore, it is recognized that each subject has a varying potential for improvement in visual acuity; and, since the CustomFlex™ Artificial Iris is not a refractive device, visual acuity itself is not a primary success criterion for effectiveness.

The established key effectiveness endpoints are summarized below in Table 5.5-1 for the pediatric and adult eyes and for the total study cohort.

Table 5.5-1: 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

Decreases in daylight and night-time light sensitivity and glare during the day and at night were achieved for each cohort, and for each of the adult eye groups. For the pediatric eyes, day-time light sensitivity and glare during the day both demonstrated decreases in the proportion of eyes that had marked-severe symptoms (-54.4% and -50.0%, respectively). The reductions in light sensitivity and glare at night were substantial and clinically meaningful.

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% of the adult compassionate eyes, 93.0% of the all other adult eyes group, and 94.0% of the overall study cohort.

5.6 Safety Endpoints

Complications and adverse events are the primary safety outcomes evaluated in the AI-001 clinical study. Safety assessments include a tabulation of adverse events, changes in BSCVA, changes in endothelial cell density, IOP and slit lamp biomicroscopy of the cornea and anterior chamber.

Safety endpoints established are:

- Less than 5% of eyes 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 eyes 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 eyes where an IOL has been implanted concurrently:
    - The cumulative rate of all lens-related adverse events should be less than 5%; and no individual adverse event 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.

A comparison of the study outcomes achieved and the established key safety endpoint threshold rates are presented in Table 5.6-1 below for the pediatric and adult eyes and the total study cohort.

Table 5.6-1: 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[2]**	**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%)

[2] 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.

• 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%)

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. All reports of BSCVA loss at 12 months resulted from other known causes or co-morbidities, and there were no reports of device-related loss of BSCVA in the study at Month 12 postoperatively in any of the eyes treated with the CustomFlex™ Artificial Iris. Similarly, any eyes with a pre-op BSCVA of 20/40 or better that was worse than 20/40 at 12 months postoperatively had co-morbidities or other known causes for the BSCVA loss, and none were device related.

There were also no reports (0.0%) of any IOL-related related adverse events that comprise the key safety endpoints in any of the pediatric or adult eyes. There were no reports in the pediatric or adult compassionate eyes of any cumulative surgery related adverse events 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 All Other group of adult eyes. Retinal detachments occurred in no pediatric eyes (0.0%) and in three of the All Other adult eyes (0.8%) 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 reports (2.0%) of persistent corneal edema and 8 reports (2.2%) of chronic iritis in the all other adult eyes group. There were no reports of surgery related hypopyon, endophthalmitis, device migration, pupillary block, or unplanned secondary surgical interventions in the study.

5.7 Cumulative Frequency of Adverse Events

The cumulative frequency of unique occurrences of reportable adverse events and complications that occurred in the AI-001 study is presented Table 5.7-1 for the pediatric and adult eyes and the overall study cohort. The adverse event listings in this table consist of the first occurrence of each new or recurrent event throughout the study (operative through postoperative Month 12).

Reportable events in the table are tabulated by causality and presented as those related to the surgical procedure, artificial iris device, IOL, other known cause, or medications for each cohort (PMA Primary, Secondary, Compassionate Use, and Continued Access eyes) and for all eyes treated with the CustomFlex™ Artificial Iris. Ocular adverse events associated with non-study surgical procedures performed in conjunction with the artificial iris or IOL implant surgery, or that resulted from causes unrelated to either the artificial iris, IOL, or surgical procedure, are tabulated under the “Other Known Cause” listing in the adverse event tables for each of the cohorts. Since concomitant medication was a somewhat frequently listed causality, the table includes a listing of medication related adverse events (e.g., steroid induced IOP increase, drug allergy).

Table 5.7-1: Cumulative Frequency of Occurrence of Unique Reports of Adverse Events in Pediatric, Adult, and All Eyes Treated 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%

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%

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%

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%

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%

The most frequent adverse events 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 (0/447 eyes; 0%) and only one report that was related to the artificial iris device (1/447 eyes; 0.2%). Overall, 7.8% of the eyes treated in the study had elevations of IOP > 30 mm Hg that were surgically related; 6.0% 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% 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).

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 related to vitreous heme, vitreous, or retained viscoelastic are also expected 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 study protocol proscribed 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. Increased IOP is a known side effect from the use of prednisolone or other steroidal eye drops.[3] The causality for the single report of device related IOP >30 is unclear whether it is truly device related or caused by the steroid drops administered for the treatment of iritis.

Adverse events related to the artificial iris device were infrequent. Complications related to device positioning consisted of device decentrations (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) or replace the device (0.2%; 1/447). The repositioning and replacement surgeries were successful in all cases.

Several pediatric subjects had pre-existing conditions that complicated their postoperative course, and adverse events tended to be clustered in these individuals.

Surgery related adverse events in the pediatric population were limited to reports of retrobulbar hemorrhage (2.3%), vitreous hemorrhage (4.5%), and hyphema (6.8%). The retrobulbar hemorrhage was the only report occurring in the entire study; and, the reports of vitreous hemorrhage are similar, although slightly higher, than was observed in the remainder of the study population.

Device related adverse events 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 adverse events related to the CustomFlex™ Artificial Iris is quite similar to the adult eyes and the overall study cohort. IOL related adverse events were also infrequent, consisting primarily of capsular haze in 3 eyes (6.8%). Other adverse events occurring in the pediatric eyes occurred with similar frequency as the adult population; and, there were fewer medication related adverse events in the pediatric eyes than the adult eyes.

[3] Player U, Ursell P, Rama P. Intraocular pressure effects of common corticosteroids for post-cataract inflammation: Are they all the same? Ophthalmol Ther.2013; Dec. 2(2):55-72.

Overall, the majority of adverse events in the study occurred in the first 3 months postoperatively. Corneal edema occurring within the first month after surgery is considered to be part of the normal postoperative wound healing process. Corneal edema cleared by Month 1 in the majority of eyes with only rare cases reported after 1 month. Vitreal hemorrhage and hyphema are both complications of the surgical procedure and resolved after 1 month postoperatively in all cases. IOP spikes greater than 30 mm Hg also tended to occur within the first day to 1 month postoperatively. Later reports of increased IOP were most commonly steroid induced or in eyes with concomitant glaucoma or other co-morbidities that predisposed the eyes to IOP increases.

5.8 Patient Reported Outcomes

Patient reported outcomes were evaluated using three different instruments.

Subjective visual complaints were obtained from each subject using a self-administered 12 item questionnaire to record symptoms. Subjects were asked to rate the presence or absence of each visual complaint in their CustomFlex™ Artificial Iris implanted eye at the preoperative baseline visit before the implant surgery and at each postoperative visit, beginning with the Month 1 visit. Subjects were instructed to rate the absence of a complaint as *"none"* and the presence of a complaint as *"mild," "moderate," "marked,"* or *"severe"*.

The NEI Visual Function Questionnaire (VFQ-25) was used in the study to capture the influence of vision on multiple dimensions of health related quality of life, including emotional well-being and social functioning, in persons with low vision problems of any cause, and was not designed for one specific condition.[4]

The subject's satisfaction with postoperative cosmesis was measured using the Global Aesthetic Improvement Scale[5] (GAIS), 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.

5.8.1 Frequency and Severity of Subjective Visual Complaints

Responses to the subjective questionnaire at the preoperative baseline and at Month 12 are summarized below by symptom in Table 5.8.1-1 for the pediatric compassionate eyes. For

[4] Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25 item National Eye Institute 25-Item Visual Function Questionnaire. Arch Ophthalmol. 2001; 119:1050-1058.

[5] Adapted from: Narins R et al. A randomized, double-blind, multicenter comparison of the effectiveness and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg 2003; 29: 588-95

comparison, the preoperative and Month 12 subjective questionnaire responses for all eyes treated are presented in Table 5.8.1-2.

The pediatric eyes had a lesser degree of preoperative visual complaints than the other adult group of eyes, as well as the overall study cohort. Day-time light sensitivity was rated as marked to severe in 63.6% (28/44) of the pediatric eyes, compared to 75.0% in the adult compassionate use eyes, 74.9% in the other adult eyes and 73.6% (328/446) in the overall treatment group. Similarly, glare during the day was less problematic in the pediatric group with 50.0% (22/44) of eyes rating symptoms as marked to severe compared to 68.2% of the adult compassionate use eyes, 65.6% of the other adult eyes and 64.3% (286/446) of the overall cohort. Night-time symptoms were all substantially less in the pediatric population with 29.5% (13/44) of the pediatric eyes reporting marked to severe symptoms of night-time light sensitivity and 31.8% (14/44) reporting glare at night, compared to the overall cohort of eyes in which 48.3% (214/446) had marked to severe night-time light sensitivity and 57.6% (256/446) had marked to severe glare at night. Preoperatively, reading difficulty was marked to severe in 52.3% (23/44) of the pediatric eyes compared to 64.8% (288/446) of the overall study population.

Postoperatively, visual symptoms related to light sensitivity and glare were substantially improved at the Month 1 visit in the pediatric eyes. None of the eyes (0.0%) rated symptoms for daytime or night-time light sensitivity and glare at night as being “severe,” and only 7.1% of the pediatric eyes (3/42 eyes) rated daytime light sensitivity as “marked”, 2.4% (1/42 eyes) reported daytime glare as “severe,” 2.4% (1/42 eyes) reported daytime glare as “marked”, and 4.8% (2/42 eyes) reported night-time light sensitivity and glare at night as being “marked.” Improvement in reading also occurred with 19.1% of the eyes having marked to severe difficulty reading compared to 52.3% (23/44) preoperatively.

Visual symptoms continued to improve across time, and at 12 months none (0.0%) of the pediatric eyes rated any of the visual symptoms as “severe,” except reading difficulty in 18.2% (6/33) and driving at night in 3.0% (1/33) of the pediatric eyes. Visual symptoms in the pediatric eyes related to photosensitivity that were rated as “marked” were also quite low for day-time light sensitivity (9.1%; 3/33), night-time light sensitivity (3.0%;1/33), and glare during the day (0.0%) and at night (6.1%; 2/33). Improvement in reading was also evident at 12 months but not to the same degree as observed at Month 1, with 30.3% (10/33) of eyes reporting marked to severe reading difficulty.

Table 5.8.1-1: Visual Symptoms Recorded via Self-Administered Symptom Questionnaire in All Treated Pediatric Eyes

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)

PMA Cohort	Visit	Operative Category	Characteristic	N	None n (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Severe n (%)
			Double Vision	33	24 (72.73)	5 (15.15)	3 (9.09)	0 (0.0)	0 (0.0)
			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 5.8.1-2: Visual Symptoms Recorded via Self-Administered Symptom Questionnaire in All Eyes Treated

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)
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)

PMA Cohort	Visit	Operative Category	Characteristic	N	None n (%)	Mild n (%)	Moderate n (%)	Marked n (%)	Severe n (%)
			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)

5.8.2 Changes in Severity of Visual Complaints

The changes in the degree of severity of subjective visual complaints from baseline to the 1, 3, 6, and 12 month postoperative visits are summarized below in Table 5.8.2-1 for the pediatric compassionate eyes. For comparison, the changes in degree of severity changes in visual symptoms at 12 Months are presented in Table 5.8.2-2 for all eyes treated.

In the pediatric subset, all categories of complaints showed a reduction in severity of complaints after the artificial iris was implanted compared to baseline at all postoperative visits, except eye dryness, pain and foreign body sensation had a slight increase in the proportion of eyes with marked-severe symptoms that returned to baseline by Month 12. At Month 1, reductions in daytime and night-time light sensitivity, glare during the day and at night, reading difficulty, daytime and night-time halos, and starbursts were reported; and there was an increase in foreign body sensation. By Month 12, the proportion of eyes with marked to severe symptoms was substantially reduced for all visual symptoms, except eye dryness which was slightly increased, and pain and foreign body sensation which had returned to baseline. Foreign body sensation and pain returned to baseline with no reports of moderate to severe symptoms. The decreases in severity of visual complaints paralleled the outcomes of the adult population, except that each adult cohort also achieved decreases in difficulty driving at night and reading difficulty.

In the overall study population, decreases in each visual complaint were achieved at each time point. The reduction in severity of light sensitivity during the day and at night, difficulty night driving, reading difficulty, glare and halos during the day and at night and starbursts are especially important in the overall study cohort as these are the symptoms associated with aniridia that most affect the subject's quality of life. The IOL procedure performed at the same time as the iris prosthesis implant may have contributed to the improvements in reading difficulty and night driving; however, the dramatic improvement in the degree of severity during the day and at night of light sensitivity, glare, and halos clearly demonstrates the effectiveness of the CustomFlex™ Artificial Iris in each of the cohorts.

The reduction in severity of visual symptoms related to photosensitivity are clinically significant in the pediatric population as these symptoms can be quite debilitating and interfere with the pediatric subjects' activities of daily living, including the ability to tolerate class-room lighting, participate in outdoor athletic activities, and other vision related social activities. Improvement in driving is less relevant in the pediatric cohort because over half of the subjects are not of legal driving age.

Questionnaires administered from 1 to 12 months after surgery not only confirmed that visual symptoms improved quickly after the artificial iris was implanted, but they showed the improvement was long term in the pediatric and adult eyes.

Table 5.8.2-1: 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 5.8.2-2: 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

5.8.3 NEI VFQ-25 Questionnaire

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.

Descriptive statistics for the NEI VFQ-25 subscale and total scores, and postoperative differences from baseline subscale and total scores, are summarized below in Table 16 at 6 months for the pediatric Compassionate Use subset, adult Compassionate Use subset, and all other adult eyes. At 12 months postoperatively, mean improvement in the total composite score was reported in each group, with a mean improvement of 9.66 points for the pediatric eyes, 15.87 points for the adult Compassionate Use eyes, and 16.00 points for the remainder of the adult eyes treated. Although the trends are similar, there were differences amongst the pediatric and adult groups in the individual subscores at 12 months postoperatively, with the pediatric subset achieving improvement in each of the subscales except General Health, Ocular Pain, and Color Vision; whereas, the adult population also achieved improvement in Ocular Pain and Color Vision. Any differences observed in the pediatric population compared to adults most likely results from the inclusion of questions in the NEI VFQ-25 that are more reflective of adult activities. For example, the VFQ-25 asks questions related to driving, reading newspapers, etc. These activities may not be applicable to the pediatric subjects enrolled in the study, where subjects less than 16 years of age cannot drive, and subjects in this age group obtain their news from digital sources rather than print sources.

Nevertheless, from the NEI VFQ-25 analysis, it can be concluded that the CustomFlex™ Artificial Iris demonstrated animprovement (reduction in symptoms) in total score and multiple dimensions of health related quality of life, including emotional well-being and social functioning, affected by vision for the pediatric eyes as well as the adult eyes.

Table 5.8.3-1: Postop Differences from Baseline in NEI-VFQ-25 Questionnaire Scores at 6 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

			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

			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

			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

			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

			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

5.8.4 Global Aesthetic Improvement Scale (GAIS)

The CustomFlex™ Artificial Iris is indicated for implant only when medically indicated. Implantation for cosmetic reasons to change iris color is contraindicated. Although the CustomFlex™ Artificial Iris is not a cosmetic-only implant, subject's satisfaction with cosmesis is an additional measure of the subject's satisfaction with the postoperative result. The Global Aesthetic Improvement Scale[6] (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

In this study, the GAIS was administered at each postoperative visit, beginning with Month 1, to rate the cosmetic result according to one of the five category descriptions. The GAIS results are summarized in Table 5.8.4-1 below for the pediatric and adult eyes and the total study cohort.

[6] Adapted from: Narins R et al. A randomized, double-blind, multicenter comparison of the effectiveness and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg 2003; 29: 588-95

Table 5.8.4-1: Global Aesthetic Improvement Scale 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)

At 12 months postoperatively, half of the eyes in each of the cohorts were rated as having a postoperative cosmetic result that was “Very Much Improved;” and, more than 80% of the pediatric and adult eyes were rated as being either “Very Much Improved” or “Much Improved” at each of the postoperative visits. The pediatric eyes had the highest satisfaction with cosmesis, with 84.8% (28/33) of the pediatric eyes having a postoperative cosmetic result that was rated as either “Very Much Improved” or “Much Improved” at the 12-Month postoperative visit compared to 86.2% (25/29) of the adult Compassionate Use eyes, 81.2% (225/277) of the other adult eyes, and 82.0% (278/339) of the overall study population. At 12 months, all of the pediatric eyes were rated as “Improved” to “Very Much Improved,” with only 2 eyes at 1 month and 1 eye at 3 months rated as “Unchanged”, and only 1 eye at 6 months rated as “Worse”. Results were similar for the adult Compassionate Use eyes, which had 1 report of “No Change” at 1, 3, and 6 months postoperatively and 1 report of “Worse” at 1, 6 and 12 months postoperatively. In both the remainder of the adult eyes and All Eyes Combined cohorts, “No Change” was reported in ~5% (15/339) of the eyes and reports of “Worse” in ~2% (6/339) of the eyes.

Four adult eyes were rated as having a “Worse” cosmetic result. When queried, each subject confirmed his/her ratings of “Worse” but indicated the rating was based on their impression of the changes in the postoperative eye condition and vision, not the cosmetic result. Upon further questioning, each subject indicated satisfaction with the cosmetic appearance of the device but elected to keep the rating as “Worse” irrespective of the cosmetic satisfaction.

Non-albino subjects who received black iris devices for treatment of iris pigment epithelial defects without stromal or aesthetic defects would not be expected to have any changes in cosmesis. Nevertheless, all four non-albino subjects who received a black iris device rated their postoperative cosmesis as “Improved” or “Very Much Improved.”

This analysis confirms the cosmetic effect obtained after receiving the CustomFlex™ Artificial Iris is esthetically pleasing in the study subjects, and particularly so in the pediatric population. Cosmesis is important in that it particularly can affect psycho-social development and interaction in the pediatric population.

5.9 Study Conclusions

This study is significant in that it represents the first controlled clinical trial of the CustomFlex™ Artificial Iris and is the largest known case series world-wide of eyes treated with an iris prosthesis.

Based on this summary evaluation, the CustomFlex™ Artificial Iris, when implanted for the treatment of full or partial aniridia, performs as intended as an iris prosthesis. The results exceed all of the AI-001 protocol target safety and effectiveness criteria. The incidence of adverse events, complications, and other ocular or vision-related observations was small. Visual symptoms were reduced, and visual function was increased compared to baseline after the CustomFlex™ Artificial Iris was implanted. There are no emerging safety or effectiveness concerns from this cohort of subjects treated with the CustomFlex™ Artificial Iris. Specifically, at 12 months after CustomFlex™ Artificial Iris implantation:

- There was an overall improvement in photosensitivity symptoms, quality of life and vision in pediatric and adult subjects.
- The CustomFlex™ Artificial Iris implant was correctly positioned in at least 95% of the pediatric and adult eyes throughout the 12-month study.
- Overall, there was a decrease in the proportion of eyes with marked to severe ratings for each of the evaluated visual symptoms: day-time light sensitivity, night-time light sensitivity, difficulty driving at night, reading difficulty, double vision, fluctuation in vision, glare during the day, glare at night, halos during the day, halos at night, starbursts, eye dryness, pain, and foreign body sensation after CustomFlex™ Artificial Iris implantation compared to before surgery. For pediatric eyes, there was a decrease in the proportion of eyes with marked to severe ratings for each visual symptom, except eye dryness increased. There were no pediatric eyes with marked to severe pain or foreign body sensation preoperatively or at 12 months.
- There was an improvement in health related quality of life, as measured by the NEI VFQ-25, in the pediatric and adult eyes.
- Postoperative cosmesis was aesthetically pleasing, with 94% of the overall cohort and 100% of the pediatric subjects rating the appearance of their eyes as improved, much improved, or very much improved.
- Postoperative inflammation resolved by 1 month in the majority of all eyes treated, as well as the pediatric eyes; 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.

- Mean endothelial cell density remained stable with no clinically significant loss over the 12 months of the study in the pediatric and adult eyes.
- IOP 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 adverse events following surgery, device or IOL 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 CustomFlex™ Artificial Iris.
- Visual symptoms generally improved at 1 month postoperatively. Furthermore, these outcome measures were maintained or improved with further follow-up through 12 months postoperatively.
- Pediatric subjects had postoperative safety and effectiveness outcomes that were equivalent or better than adults.

All key safety and effectiveness endpoints were met and achieved statistical significance for all eyes treated and for the pediatric eyes. Results for the key safety and effectiveness endpoints and other study outcomes were similar in the pediatric eyes, adult eyes, and the overall study population.

6.0 ADDITIONAL DEVICE INFORMATION

6.1 How Supplied

The CustomFlex™ Artificial Iris is manufactured from a hydrophobic silicone elastomer with embedded color pigments.

Each CustomFlex™ Artificial Iris is supplied in a container sealed within a single sterile pouch, sterilized by steam. Check the contents of the package to ensure the seal is intact before opening. The package should be opened only under sterile conditions.

6.2 Reprocessing

The CustomFlex™™ Artificial Iris is for single use only. Reprocessing or re-sterilization of the CustomFlex™™ Artificial Iris is strictly prohibited, and may compromise device performance, which could cause serious harm to the patient's health and safety.

6.3 Reporting

Adverse events and/or potentially sight-threatening complications that may reasonably be regarded as artificial iris related and that are not previously expected in nature, severity or rate of occurrence must be reported to the manufacturer or the manufacturer's representative in the United States. Any device defects must also be reported. This information is being requested from all surgeons in order to document potential long-tern effects of artificial iris implantation.

6.4 Expiration Date

The expiration date on the artificial iris package is located on each CustomFlex™ Artificial Iris box and packaging. The artificial iris should not be implanted after the indicated expiration date.

Reprocessing or re-sterilization of the CustomFlex™ Artificial Iris is strictly prohibited. Reprocessing or re-sterilization can cause serious patient harm or injury.

6.5 Return/Exchange Policy

A refund or credit is not possible if cancellation of an order occurs after production of the custom-made device has begun.