FDA Executive Summary P170040

Prepared for the
November 9, 2020 meeting of the
Ophthalmic Devices Panel

P170040
VisAbility Micro Insert System
Refocus Group, Inc.

Introduction

This is the FDA Executive Summary for the VisAbility Micro Insert System. The device is a scleral implant and is intended to improve unaided near vision in presbyopic eyes. The clinical trial to study the device was approved by the Agency on November 14, 2014 under IDE (b) (4) On December 15, 2017, Refocus Group, Inc. (hereinafter referred to as the "applicant") submitted a Premarket Approval Application (PMA) requesting marketing approval of the device under P170040. This submission has been reviewed by the Division of Ophthalmic Devices, Office of Health Technology 1, Office of Product Evaluation and Quality (OPEQ) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This memorandum will summarize FDA's review of the PMA highlighting the areas for which we are seeking your expertise and input. These topics will include the device performance and clinical experience to date, and the results of the trial obtained from the IDE cohort. At the conclusion of your review and discussion of the data presented, FDA will ask for your recommendation regarding your interpretation of the benefit-risk assessment.

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1 Proposed Indications for Use (IFU)

The applicant has proposed the following Indications for Use (IFU) statement:

> The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes, and require a minimum near correction of at least +1.25 D reading add.

2 Device Description

The VisAbility Micro Insert System is a scleral implant that is comprised of the following:

- VisAbility Micro Insert: a scleral implant
- VisAbility Scleratome: a surgical instrument used for creating scleral tunnel incisions in which the VisAbility Micro Insert is placed
- VisAbility Feeder Tube: tubing used to assist in placing the VisAbility Micro Insert into the scleral tunnel

In addition, a Docking Station is to be used in conjunction with the VisAbility Micro Insert System.

2.1 VisAbility Micro Insert

The VisAbility Micro Insert (Model SGP-046) is a curved scleral implant that is injection molded from polymethylmethacrylate (PMMA). Each VisAbility Micro Insert consists of 2 pieces, a main body segment with 2 legs and a locking segment. The locking segment has trans-longitudinal grooves on both sides that correspond to 2 small "rails" on the interior edges of the legs of the main body segment. These features allow the locking segment to be snapped into place in the main body segment. The VisAbility Micro Inserts include stabilization feet at each end intended to fixate at the entrance and exit sides of the scleral tunnel incision, which are intended to prevent displacement or migration of the implanted VisAbility Micro Insert. The VisAbility Micro Inserts are provided sterile in a Tyvek peel pouch. See **Figure 1**.

Four VisAbility Micro Inserts are placed in a single presbyopic eye. Each VisAbility Micro Insert is implanted in a scleral tunnel approximately 4.0 mm posterior to the corneal limbus through scleral incisions centered at the 1:30, 4:30 7:30, and 10:30 oblique quadrants. See **Figure 2**.

FDA Commentary: The applicant has studied two versions of the device. The first version was previously referred to as the PresVIEW Scleral Implant (PSI) Model PSI-001, did not include a locking segment, and was studied under IDE (b) (4) *as discussed below in* ***Section 6.2*** (b) (4) ***– Pivotal Clinical Trial of PSI-001 (Protocol P-277-5)****. Later in the same IDE,* (b) (4) *, the applicant modified the device to include the locking segment, which was the second version of the device, PSI Model SGP-046. The second version was also studied under IDE* (b) (4) *as discussed below in* ***Section 6.4*** (b) (4) ***– Pivotal Clinical Trial of VisAbility Micro Insert System (Protocol VIS-2014)****. The proposed device for marketing, the VisAbility Micro Insert (Model SGP-046), is the same as the PSI Model SGP-046 that was studied under the pivotal trial* (b) (4) *.*

2.2 VisAbility Scleratome

The VisAbility Scleratome (REF 87562800) is a custom designed disposable device used to create the scleral tunnel incisions into which the VisAbility Micro Inserts are placed. Ultrasound imaging is recommended as part of the patient screening examination to confirm that the thickness of the sclera in the region of placement of the VisAbility Micro Inserts meets the requirements for making the scleral incisions.

The VisAbility Scleratome (REF 87562800) is provided sterile in a disposable plastic tray with a Tyvek cover and is for single patient use only. See **Figure 3**.

The VisAbility Scleratome (REF 87562800) is prepared for use by turning the integrated winding knob in the clockwise direction. After placing the VisAbility Scleratome in position on the sclera aided by the Docking Station, the actuator button on the VisAbility Scleratome handle is pressed, extending and retracting the blade and creating the scleral tunnel. The VisAbility Scleratome is then reloaded for the next actuation by turning the integrated winding knob in the clockwise direction.

FDA Commentary: The applicant has studied three versions of the Scleratome. The first version was previously referred to as the PresbyDrive System, which was electrically powered, reusable, and was studied under IDE (b) (4) *as discussed below in* ***Section 6.1*** (b) (4) ***– Feasibility Clinical Trial of PSI-001*** *and* ***Section 6.2*** (b) (4) ***– Pivotal Clinical Trial of PSI-001 (Protocol P-277-5)****.*

Later in the same IDE, (b) (4) *, the applicant modified the PresbyDrive System to be smaller, lighter, mechanically powered and disposable, and the applicant referred to this second version as the Scleratome. This version also required the end-user/investigator to assemble the blade guard, footplate, and blade prior to use.*

After receiving preliminary results with this second version, the applicant decided to further modify the Scleratome to be fully assembled and eliminate assembly by the end-user/investigator. This third version was studied under (b) (4) *as discussed below in*

Section 6.4 (b) (4) ***– Pivotal Clinical Trial of VisAbility Micro Insert System (Protocol VIS-2014)****. This third version of the Scleratome is the subject device, VisAbility Scleratome (REF 87562800).*

2.3 VisAbility Feeder Tube

After the scleral tunnels have been formed, the VisAbility Micro Inserts are inserted using the VisAbility Feeder Tube. The VisAbility Feeder Tube is made of PTFE (Teflon). The PTFE tubing provides the means of traversing the lamellar scleral tunnel and is intended to minimize external stress on surrounding tissue. Each VisAbility Micro Insert main body segment can be loaded into a VisAbility Feeder Tube by the surgical assistant prior to transport from the assistant's sterile workspace to the surgeon for implantation.

The main body segment of the VisAbility Micro Insert is compressed into the end of the VisAbility Feeder Tube. The VisAbility Feeder Tube is then passed through the scleral tunnel, pulling with it the compressed main body segment of the VisAbility Micro Insert. As the tube exits the tunnel, the trailing stabilization feet on the legs of the VisAbility Micro Insert main body segment catch the entrance of the tunnel and hold it in place as the tubing is removed, and the forward locking stabilization feet open to engage the exit incision. Final assembly of the VisAbility Micro Insert follows, as the locking segment is positioned and snapped into place creating a single VisAbility Micro Insert. **Figure 4, Figure 5**, and **Figure 6** show how the VisAbility Micro Insert main body segment is used with the VisAbility Feeder Tube.

The VisAbility Feeder Tubes are provided sterile in a Tyvek peel pouch.

2.4 Docking Station

The Docking Station (see **Figure 7**) is a fixation device made of titanium and/or medical grade stainless steel that is used in conjunction with the VisAbility Micro Insert System. It is temporarily fixated on the eye, centered around the geometric corneal limbus for aligning and/or positioning the VisAbility Scleratome**.** The VisAbility Scleratome sits adjacent to the Docking Station to provide the location for the scleral tunnel incisions.

When the Docking Station is properly aligned, the four Micro Inserts are intended to be equally spaced between the rectus muscles to attempt to minimize the likelihood of pressure on the anterior ciliary arteries, which could result in reduced iris perfusion. The Docking Station is then temporarily fixated to the eye with 4 titanium double helix twist picks that gently engage the sclera near the limbus. The VisAbility Scleratome is then placed 1 quadrant at a time at the 1:30, 4:30, 7:30, and 10:30 clock positions of the Docking Station. The VisAbility Scleratome is positioned using the "locating ridge" on the blade guard of the Scleratome (see **Figure 8**).

The Docking Station is a re-usable instrument that can be sterilized by standard autoclave procedures. It is supplied by a surgical instrument provider, (b) (4).

2.5 Surgical Procedure

2.5.1 VisAbility Micro Insert Implantation

The following is a summary of the surgical procedure delineated in the protocol for the subjects in the pivotal clinical trial to support the PMA (discussed in **Section 7** and **Section 8** below):

Marking of Limbus

1. In the pre-operative area, the limbus was marked at the 12 and 6 o'clock positions with the subject upright to assist locating the rectus muscles during surgery and brimonidine was instilled in the operative eye.

2. The subject was transferred to the operating room (OR), prepped and draped in the usual sterile manner, and a locking eyelid speculum applied to the operative eye. Anesthesia was maintained throughout the procedure using topical anesthetic without epinephrine with or without conscious sedation.

3. The superior and inferior rectus muscles were identified and the location of the limbal marks confirmed by projecting along an axis from the midpoint of the insertions to the cornea. On a relatively dry limbus, the Positioning Barrel was aligned to the geometric limbus and rotated to align internal grooves with previously placed limbal marks. The VIS Barrel Marker was placed in its positioning slits and the eye marked.

Peritomy

4. Two conjunctival incisions, 3 mm in length or longer, were made starting approximately 0.5 mm posterior to the limbus at the 3 and 9 o'clock positions and blunt dissection was carried out posteriorly into sub-Tenon's space. Hydrodissection of Tenon's capsule was carried out in each of the four quadrants using anesthetic solution without epinephrine and a 360º peritomy was performed to allow exposure to bare sclera at the 3, 6, 9, and 12 o'clock positions. Cautery was not to be used.

Placement of Docking Station

5. The Docking Station was centered above the eye by aligning the 6 and 12 o'clock internal arrow points on the unit with the 6 and 12 o'clock limbal marks and the docking channels on the unit with the oblique line marks that had been made with the Barrel Marker on the surface of the eye. Once in proper position, the Docking Station was gently pressed to the sclera and fixated by rotating each of the four fixation points 180° clockwise to its stop using the Actuation Tool. Fixation and proper positioning of the docking station was verified.

Scleral Tunnel Creation & Implantation of the VisAbility Implant Segment

6. A scleral tunnel was created then immediately implanted with the Micro Insert in each quadrant in the following order: (1) inferonasal, (2) superonasal, (3) inferotemporal, (4) superotemporal (quadrant with the thinnest sclera). The eye was rotated and proptosed to provide adequate exposure of the sclera. Confirmation that the sclera near the Docking Station was bare of Tenon's capsular tissue was made. It was verified that the winding knob of the VisAbility (VIS) Scleratome had been fully actuated. The VIS Scleratome locating ridge was docked to the corresponding channel in the Docking Station with the VIS Scleratome blade guard flush with the surrounding edge of the Docking Station as shown in **Figure 8**. After the footplate was placed squarely on the sclera, the VIS Scleratome was activated by advancing the slide button toward the eye. The length of the scleral tunnel was confirmed using the spatula.

7. Per protocol, pre-operatively, the VIS Implant Main Body Segment (Implant Segment or Main Body Segment) was loaded into the VIS Feeder Tube (to form the VIS Feeder Tube assembly) enclosing the leading stabilization feet and facilitating their placement through the scleral tunnel using the Shuttle attached to the other end of the Feeder Tube (Shuttle-Implant Segment Assembly). While maintaining fixation of the eye with the Docking Station, the Shuttle Implant Segment assembly was grasped approximately 12 mm from its leading edge and the front end of the Shuttle was inserted into the tunnel to guide the VIS Feeder Tube into the scleral tunnel. The VIS Feeder Tube assembly was then advanced into the tunnel. After 3 mm or more of the VIS Feeder Tube has exited the tunnel, the exited VIS Feeder Tube was grasped, and the assembly pulled through the tunnel until the leading feet of the Implant Segment within the VIS Feeder Tube exited the tunnel. After the feet of the Main Body Segment had exited the tunnel, continued pulling on the VIS Feeder Tube disconnected it from the Main Body Segment exposing the feet. These steps of the procedure are shown in **Figure 6.** The VIS Center Insert (Locking) Segment was grasped by its top edges using the VIS Center Insert Implant Loading Forceps and guided into the receiving slot of the VIS Main Body Segment until it locked into place.

8. After implantation of the segments in all four quadrants, the VIS Docking Station was removed by using the Actuation Tool to rotate each of the four fixation points of the Docking Station counter-clockwise 180° to its stop to disengage the helical twist from the limbal sclera. Once free, the Docking Station was carefully lifted from the eye, and implant location was measured from the anterior center of the implant to the limbus. Adequate hemostasis was ensured prior to re-approximation and closure of the conjunctiva. At the completion of surgery, a removable punctal plug was placed in the inferior punctum, topical antibiotic and steroid drops were instilled in the eye, and a cold compress applied to the closed eye.

Prior to Postoperative Discharge

9. Immediately after surgery, pupil functionality was evaluated using a NeurOptics Pupillometer every 15 to 30 minutes until the percent pupil constriction was at least 25% at two time points at least 5 minutes apart. If this criterion was not met within 6 hours after the implantation surgery, the investigator was required to remove all four implant segments.

10. The following care guidelines were to be employed:

    - To help control pain postoperatively, an icepack was to be applied to the eye at intervals for approximately 30 minutes or longer as needed.
    - A topical non-steroidal anti-inflammatory drug (NSAID) immediately postoperatively was optional.
    - Chilled BSS instilled every 15 minutes and topical steroid drops every 15 to 30 minutes until the pupil reaction was greater than 25% were optional.

11. Prior to discharge the patient was given an oral carbonic anhydrase inhibitor.

Care after Postoperative Discharge

12. During the first week after surgery, the subjects were prescribed a topical antibiotic drop, topical steroid, and topical NSAID and/or oral medications (i.e., naproxen or acetaminophen with codeine) for pain as needed.

13. Absorbable and/or non-absorbable conjunctival sutures were able to be removed at one week postoperatively or later as needed.

2.5.2 VisAbility Micro Insert Removal

The VisAbility Micro Inserts may be removed, if indicated. The following is a summary of the procedure for removal of the Micro Insert Segments:

1. It was advised that removal be performed with magnification under a surgical microscope. Subject were prepped and draped in a sterile fashion. Topical anesthesia without epinephrine was applied.

2. Using a sterile sharp blade, such as, a 15-degree ophthalmic sharp, 18- to 21-gauge hollow injection needle, or equivalent, a small (2mm) scratch-down incision of the conjunctiva was made over both exposed ends of the VIS Implant segment and forceps were used to further expose the ends of the VIS Implant Segment from the overlying conjunctiva.

3. Once un-encapsulated, the solid end of the VIS Implant Main Body Segment was gripped with the jaws of the VIS Cutter (966-0030) with the tips perpendicular to

the length of the implant and one tip flat to the sclera and the VIS Cutter closed to sever the end of the VIS Main Body Segment, as shown in **Figure 9**. Once the locking barb was completely removed from the VIS Main Body Segment, the uncut end of the segment was grasped using the VIS Implant Loading Forceps, the distal end of the Shuttle Forceps, or other toothed forceps and pulled through the tunnel with a slight twisting motion to remove it from the eye. This step was repeated for each Implant Segment requiring removal.

4. The scleral and conjunctiva were assessed to determine whether suturing was required for closure. A topical antibiotic drop and steroid drop were instilled into the eye at the end of the case, and a light dressing applied to keep the eye closed overnight for patient comfort.

5. Topical antibiotic and steroid drops were prescribed for the first week after the surgery, as well as topical or oral medication for pain, as needed.

2.6 Proposed Mechanism

The applicant hypothesized and stated the following in the submission:

When implanted approximately 4.0 mm posterior to the limbus, the VisAbility Micro Inserts act as spacing elements within the sclera overlying the pars plana, and that there are three mechanisms by which the Micro Inserts act:

1) By producing an outward pull on the sclera overlying the ciliary muscle thus tightening the lax zonules.

2) By "reducing the tension on the posterior vitreous zonule (PVZ) by shortening the distance between the origin and insertion of the PVZ. This is achieved by an arc shortening effect resulting from separation of the scleral lamellae. This induces a shortening of the chord length and reduces the tension on the PVZ thus allowing freer movement of the ciliary muscle." Please see the following reference for a definition of the PVZ: Lütjen-Drecoll, Elke *et al*, Morphology and Accommodative Function of the Vitreous Zonule in Human and Monkey Eyes, Invest Ophthalmol Vis Sci. 2010;51:1554 –1564 (DOI: 10.1167/iovs.09-4008).

3) By "increasing local scleral rigidity, thereby reversing the aging effect of increased scleral elasticity."

FDA Commentary: The scleral expansion treatment is based on a theory of accommodation that is not well established.

3 Target Condition and Available Treatment Options

Presbyopia occurs naturally as you age (with the loss of accommodation) and results in the inability to focus up close.

Approved available treatment options for presbyopia include the following:

1) Glasses (Product Codes HOI, HQZ, HQG), including trifocals, bifocals, progressive lenses, and monovision lenses (prescription glasses and over-the-counter readers)

2) Contact lenses (CL) (Product Codes LPL, HQD, MUW, MWL), including multifocal contact lenses and CL monovision therapy (i.e., one eye corrected for far vision and the other corrected for near vision)

3) Corneal inlays (Product Code LQE)

4) Conductive keratoplasty (Product Code MWD)

4 Pre-Clinical Studies

4.1 Biocompatibility

Biocompatibility testing was performed on the VisAbility Micro Insert, VisAbility Scleratome, and VisAbility Feeder Tube. The biocompatibility assessment was performed in accordance with International Standard Organization (ISO) 10993-1: Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process, Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity, - Part 6: Tests for local effects after implantation, - Part 10: Test for irritation and skin sensitization, and – Part 11: Tests for systemic toxicity. All tests were performed in accordance with Good Laboratory Practices (GLP).

Table 1, **Table 2**, and **Table 3** summarizes the biocompatibility testing conducted on the VisAbility Micro Insert System and results.

FDA Commentary: The FDA reviewers found the biocompatibility information to be adequate.

4.2 Sterilization, Packaging, and Shelf-Life

The VisAbility Micro Insert, VisAbility Scleratome, and VisAbility Feeder Tube are sterilized using 100% ethylene oxide (EO). The sterilization validation was performed according to ISO 11135 (Sterilization of health care products – Ethylene oxide) using the overkill method. Sterilization validation parameters were designed to achieve a Sterility Assurance Level (SAL) of 10^{-6}.

The VisAbility Micro Insert main body segments are packaged in a small Tyvek peel pouch, the VisAbility Micro Insert locking segments are packaged in a small Tyvek peel pouch, and then the small pouches are then packaged in a large Tyvek peel pouch. The VisAbility Scleratome is supplied in a plastic blister tray and sealed with Tyvek lid stock. The VisAbility Feeder Tube is packaged in a small Tyvek peel pouch, which is then packaged in a large Tyvek peel pouch.

Packaging, shipping, and shelf life studies were conducted to verify that the packaging for the VisAbility Micro Insert System maintains a sterile barrier and that device performance meets product specifications through a 2-year shelf life.

FDA Commentary: The FDA reviewers found the sterilization, packaging, and shelf-life information to be adequate.

4.3 Bench Testing

Physico-chemical testing was conducted to physically characterize the material of VisAbility Micro Insert and to verify that the material remains stable throughout the implant life span. The physico-chemical testing included characterization exhaustive extraction testing, testing for leachables, hydrolytic stability testing, and testing for inorganic compounds.

Mechanical testing was performed on the VisAbility Micro Insert to assess the integrity under various load configurations. Functional testing in porcine eyes was performed to demonstrate that the VisAbility Micro Inserts are secured in scleral tunnels, that the VisAbility Scleratome could consistently create scleral tunnels, that the VisAbility Feeder Tube could hold the VisAbility Main Body segment, traverse the scleral tunnel, and be removed from the segment. **Table 4** and **Table 5** summarizes the bench testing conducted.

FDA Commentary: The FDA reviewers found the bench testing information to be adequate.

4.4 Manufacturing

Refocus Group, Inc. (Dallas, TX) is responsible for the overall manufacturing and release of the VisAbility Micro Insert System. The firm subcontracts all its manufacturing, production, assembly, cleaning, packaging, sterilization and verification or validation testing, including process validation for the VisAbility Micro Insert System. The inspections of the components are conducted by the contract manufacturers prior to sending them to the Refocus Group, Inc. All products received from the contract manufacturers by Refocus Group include documentation for acceptance including Certificates of Compliance. The final product labeling is applied by Refocus Group, Inc., prior to distribution of the VisAbility Micro Insert System. The in-process packaged components and the final VisAbility Micro Insert System remain secure until release by the Refocus Group, Inc., i.e., in-process components are released for sterilization by the contract manufacturer and final product, VisAbility Micro Insert System are released for distribution. All sub-contracted activities conducted by the contract manufacturers are

monitored and managed by the Refocus Group, Inc. per their procedure for the VisAbility Micro Insert System in the PMA.

FDA Commentary: FDA review of the manufacturing information is currently ongoing. The Panel will not be asked questions regarding the manufacturing.

4.5 Human Factors Testing

Human factors validation testing was performed to demonstrate that the user interface of the VisAbility Micro Insert System supports the intended uses, by the intended users (i.e., licensed physicians who have completed a residency in ophthalmology, completed a certification program, and have not previously performed this procedure), in the expected use environments without unacceptable use-related risks. Simulated-use human factors testing was performed using porcine eyes with eight test subjects, where each subject performed two procedures (i.e., two eyes). Each subject was provided with training followed by at least one-hour of decay before the subject could perform the simulated procedure. Critical tasks that were assessed were placement of the docking station, creation of the scleral tunnels, implantation of the VisAbility Micro Inserts, and removal of the docking station. Moderators were provided with test guidelines, and captured observations during the simulated procedures and subjective usability feedback regarding the device user interface and instructions for use. The testing did not identify or report any use-related issue for each critical task.

FDA Commentary: The FDA reviewer found the human factors testing information to be adequate.

5 Prior Clinical Experience

The version of the device (Model SGP-046) that is the subject of this PMA has received CE mark in 2005. However, per the applicant, Refocus Ocular Europe, B.V. had not actively pursued commercial sales in the EU, and no devices had been sold.

The applicant indicated that one commercial site had been established in Ireland. The site received 30 VisAbility™ Micro Inserts, 30 VisAbility™ Feeder Tubes, and 24 VisAbility™ Scleratomes and that 14 eyes of seven subjects were implanted with the device from August 2013 through August 2014.

The applicant had received one report of untoward event in one of the subjects implanted with the device in Ireland. In November 2015, the applicant was made aware of a patient who had been bilaterally implanted in January 2014 and subsequently underwent bilateral explantation of the superior temporal implants in January 2015 (12 months postoperatively). At 6 months postoperatively, this patient presented with persistent foreign body sensation and tearing in both eyes that was attributed to dry eye syndrome

caused by implants distorting the lid margin. Two months later (March 2015), the patient requested to have the implants removed and they were bilaterally explanted with no reported complications. The applicant stated that 12 months following bilateral explantation, the patient's uncorrected and best-corrected distance acuities were the same as at baseline in each eye, OD 20/16 and OS 20/16, and that the manifest refraction was unchanged from baseline following return of the ocular surface to baseline condition after bilateral removal of the device.

6 Regulatory History and Background Information

The current version of VisAbility Micro Insert System was studied under a pivotal clinical trial, IDE(b) (4). Prior iterations of the scleral implant (PresVIEW Scleral Implant Model PSI-001 and PSI Model SGP-046) and system components (e.g., two prior different versions of the Scleratome; initially scleral tunnels were created using diamond blades) were studied by the applicant in prior studies under (b) (4). A summary of these studies is provided below.

6.1 (b) (4) – Feasibility Clinical Trial of PSI-001

A feasibility clinical trial of the PresVIEW Scleral Implant Model PSI-001 was initiated in March 1999 following FDA approval of (b) (4). The feasibility trial enrolled 29 presbyopic subjects desiring improvement in near visual acuity at 6 clinical sites. Subjects were implanted in the primary eye only and followed for 24 months. Four PMMA segments were implanted in partial thickness scleral tunnels in the four oblique quadrants of the eye. The scleral tunnels were made using a diamond blade. Effectiveness results were mixed as a result of difficulty in creating the scleral tunnels, which led to development of an automated, electrically powered, re-usable incision device (the PresbyDrive System) that was used in (b) (4) pivotal trial as described below.

*FDA Commentary: As discussed above in **Section 2.1 VisAbility Micro Insert**, the PSI-001 scleral implants are the first version of the device and the trial did not include a locking segment (unlike the SGP-046). As discussed above in **Section 2.2 VisAbility Scleratome,** the electrically powered, reusable PresbyDrive System is the first version of the Scleratome that was used in(b) (4). This is not the same as the third and current version of the VisAbility Scleratome (REF 87562800) that is part of the subject device.*

6.2 (b) (4) – Pivotal Clinical Trial of PSI-001 (Protocol P-277-5)

A prospective, randomized controlled multicenter clinical trial of the PresVIEW Scleral Implant Model PSI-001 was approved by FDA in December 2003. Subjects were implanted with the PSI-001 and followed for 24 months. In the initial randomized controlled stage of this trial, 150 subjects were to be randomized in a 2:1 ratio either to a surgical cohort (N=100) or to a Deferred Treatment / Control cohort (N=50) with an interim report to be provided to FDA upon obtained preliminary data on 75 randomized

subjects. Subjects randomized to the deferred surgery/control cohort were eligible to receive the implant after completion of 6 months of follow-up in the trial.

In the initial stage of this trial, a total of 81 subjects were enrolled and randomized to either the PSI-001 Treatment Group (53) or the Deferred Treatment Control Group (28) at a ratio of 2:1 per the trial protocol. At the 3-month visit, 64% (23/36) of the eyes assigned to the PSI-001 Treatment Group had distance corrected near visual acuity 20/40 or better, as compared with 6% (1/18) of Deferred Treatment Control Group. At the 6-month postoperative exam 70% (30/43) of the eyes in the PSI-001 Treatment Group eyes had distance corrected near visual acuity 20/40 or better, as compared with 4% (1/23) of the Deferred Treatment Control eyes.

The applicant requested a trial expansion to the full trial cohort of 330 subjects and up to 660 eyes with bilateral implantation, which was approved by FDA in August 2005. However, only a total of 184 eyes of 135 subjects were implanted with the PSI-001 under this protocol prior to trial discontinuation by the applicant.

Initial effectiveness outcomes were consistent with the results of the initial subjects in the randomized substudy. However, the improvement in near visual acuity was not sustained over time in some subjects. During investigation of this finding, imaging of the PSI-001 segments revealed displacement of at least one of the implant segments in subjects who experienced an initial improvement in near vision followed by loss of this improvement. Subsequently, in a group of patients with displaced segments, repositioning and suturing of the segments were performed. Following these secondary surgical interventions (SSIs), many subjects showed improvements in near acuity. The results suggested that the stability of the PSI-001 segments in the scleral tunnel was related to clinical effectiveness.

The applicant had determined that suturing of the PSI-001 significantly increased procedure time and complexity. As a result, the applicant deferred further enrollment in the trial pending design changes to the scleral implant segment to resolve the displacement issue.

6.3 (b) (4) – Pivotal Clinical Trial of PSI Model SGP-046 (Protocol P-277-5)

To provide better fixation of the implant in the scleral tunnel, the applicant modified the device design. This design, known as the PSI Model SGP-046, incorporated a two-part implant segment; a main body with "feet" at both ends that protruded beyond the edges of the tunnel and a secondary locking insert. This version of the device was approved to be evaluated under IDE Supplement (b) (4) in June 2009. Enrollment was increased to 465 subjects to ensure an adequate sample size of 330 subjects would be enrolled and implanted with this new version of the device.

With the modified design of the PSI Model SGP-046 segment, another 48 patients were to be enrolled in a substudy and randomized (2:1 ratio) with 32 patients receiving the PSI

Model SGP-046 and 16 deferred surgery/control patients. As before, subjects randomized to the deferred surgery/control cohort were eligible to receive the PSI Model SGP-046 after completion of 6 months of follow-up in the trial. The results of patients who elected to have PSI Model SGP-046 surgery after completion of 6 months of follow-up in the deferred/control surgery group were included in the total patient cohort.

A smaller, lighter, disposable, and mechanically powered Scleratome was also introduced into the ongoing IDE clinical trial in April 2012. An exploratory analysis of 12-month clinical outcomes for 56 primary eyes (119 total eyes) implanted with the PSI Model SGP-046 using the disposable Scleratome showed greater improvements in near vision as compared to subjects implanted using the former version of this tool.

FDA Commentary: As discussed above in ***Section 2.2 VisAbility Scleratome,*** *this smaller, lighter, disposable, mechanically powered Scleratome is the second version of the device, which is not the same as the current, third version of the VisAbility Scleratome (REF 87562800).*

A total of 645 eyes of 330 subjects were enrolled and implanted with the PSI SGP-046 in this clinical trial. Subjects implanted with the PSI SGP-046 reported the following results:

- Distance Corrected Near Visual Acuity (DCNVA) at 40 cm of 20/40 or better was achieved by 80% (237/298) of subjects at 12 months, by 84% (210/249) of subjects at 18 months and by 91% (120/132) of subjects at 24 months.
- No persistent loss in Best Corrected Distance Visual Acuity (BCDVA) or Best Corrected Near Visual Acuity (BCNVA) was observed in any eye. BCDVA remained generally unchanged from baseline through the 24-month visit and all (100%) of the PSI treated eyes achieved BCNVA of 20/32 or better at all postoperative examinations.

Frequently reported ocular adverse events in this clinical trial were dry eye and improper conjunctival closure after the surgical procedure, the latter resulting in exposed implant segments. Exposed segments were treated with revised conjunctival closures. Other ocular adverse events included conjunctival tags, corneal abrasions, conjunctival injection, superficial punctuate keratitis (SPK), conjunctival thinning, and exposed suture. All of these were transient in nature and resolved without sequelae, generally with no or limited medical intervention. IOP increases secondary to postoperative administration of topical steroid drops were reported; in all cases, IOP returned to the baseline level after discontinuation of the steroid drops and/or short-term use of IOP lowering medications in a few cases. Three (3) cases of decreased iris vascular perfusion resulting in decreased pupil reactivity to light, and iris atrophy were reported in the complete cohort of 858 eyes of this IDE trial for an incidence of 0.35%.

FDA Commentary: Following the above trial, the applicant did not submit a PMA as they intended to make device design changes. They modified the second version of the Scleratome (i.e., the smaller, lighter, disposable, mechanically powered version) further and also introduced the Docking Station. Per the applicant, these modifications represented a "fundamental change in the surgical procedure," and thus, they believed that these "changes to the surgical instrumentation will yield clinical data that is not appropriate for pooling with the data collected" under (b) (4) *Consequently, the applicant proposed a new pivotal clinical trial that was submitted under* (b) (4)

6.4 (b) (4) – Pivotal Clinical Trial of VisAbility Micro Insert System (Protocol VIS-2014)

Clinical data to support this PMA for the VisAbility Micro Insert System was collected under the pivotal clinical trial IDE (b) (4) and approved on January 30, 2015. The protocol, VIS-2014, was designed to collect 24 months of follow-up. The VisAbility Micro Insert System utilized the same PSI SGP-046 used in (b) (4) trial discussed above and renamed it to the VisAbility Micro Insert (Model SGP-046). However, the applicant added a new surgical component, the Docking Station, and made significant modifications to the Scleratome, such as providing the device pre-assembled, integrating components, changing dimensions, and adding a ridge for placement into the new Docking Station. The applicant did not believe it would be appropriate to pool data generated using the modified surgical instrumentation with data collected under (b) (4) with prior versions of the surgical instrumentation or device. The design of this trial is discussed in **Section 7** below.

6.4.1 (b) (4) – Continued Follow-Up (Protocol VIS-2014-5YR)

The applicant submitted a second protocol, VIS-2014-5YR, under the IDE (b) (4) in order to obtain an additional 36 months of safety and effectiveness data from subjects who completed participation in the 24-month trial under VIS-2014. Subjects can be enrolled at any time through the 60-month visit window. The second protocol, VIS-2014-5YR, was approved on August 15, 2018 and this trial is still on-going.

6.4.2 (b) (4) – August 28, 2020 Annual Progress Report

On August 31, 2020, the applicant provided an interim report of the on-going continued follow-up study (Protocol VIS-2014-5YR) being conducted under IDE (b) (4) with a July 15, 2020 database lock. Of the 360 subjects (708 eyes) that were implanted during the 24-month VIS-2014 trial, 282 (78.3%) subjects (556 eyes) had been enrolled in the continued follow-up study by the time of the database lock. There were subjects from the pivotal trial that were still eligible to be enrolled into the continued follow-up study for

the 60-month visit at database lock. One hundred and eighty-six (186) subjects (368 eyes) were available for analysis at the 36-month visit, 263 subjects (519 eyes) were available at the 48-month visit, and 67 subjects (132 eyes) were available at the 60-month visit. This executive summary incorporates some of the safety events and information on hyperopic shifts from this recent report in **Section 8.4 Safety Outcomes** and **Section 8.5.2.6 Manifest Refractive Spherical Equivalent (MRSE) & MRSE and Cylinder Stability** below, respectively.

FDA Commentary: 114 eyes of 59 subjects are still eligible for enrollment into the VIS-2014-5YR trial.

6.5 P170040 – Premarket Approval Application of VisAbility Micro Insert System

The applicant submitted a modular PMA (b) (4). Preclinical testing was submitted under Modules 1 and 3 on October 11, 2016 and February 13, 2017, respectively. Manufacturing information was submitted under Module 2 on November 9, 2016. After submission of the final clinical module (Module 4) on December 15, 2017, a PMA number (P170040) was assigned.

6.5.1 P170040 – Submitted December 15, 2017

In P170040, the applicant provided data on 674 eyes (95.2%) in 340 subjects (94.4%) at **12 months of follow-up** consistent with the time of the primary endpoint to support the following indications for use (IFU):

> The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes, and require a minimum near correction of at least +1.25 D reading add.

FDA Commentary: In P170040, data from 44 eyes (6.2%) were available at 24 months of follow-up.

On March 15, 2018, FDA sent a Major Deficiencies letter requesting analyses that were pre-specified in the protocol, wavefront aberrometry information, and safety information. On June 18, 2018, the applicant submitted a Major Amendment, Amendment 3, (P170040/A003) in response to the Major Deficiencies letter with updated data on 688 eyes (97.2%) in 350 subjects (97.2%) at **12 months of follow-up**.

Through interactive review on July 30, 2018 and August 9, 2018, the applicant supplemented the data with additional adverse event data. After review of the information, FDA had significant safety concerns of scleral perforations and anterior segment ischemia, which can lead to potential loss of vision or the eye. Additional safety

concerns included the rate of secondary surgical interventions (SSI). The criteria for study success were not met (the first co-primary effectiveness endpoint was not met, but the second co-primary effectiveness endpoint was met). The wavefront aberrometry and defocus curve analyses (these analyses were specified as "exploratory" by the applicant) did not show clinically significant differences per FDA's assessment. Consequently, FDA believed that the benefits did not outweigh the risks and rendered a "Not Approvable" decision on September 12, 2018. FDA recommended that the applicant consider identifying a patient subpopulation within their IDE trial cohort where there may be reduced risk from use of the device.

6.5.2 P170040/A005 – Submitted April 26, 2019

On April 26, 2019, the applicant submitted a Major Amendment, Amendment 5, (P170040/A005). In this submission, following FDA's recommendation in the "Not Approvable" letter (see above), the applicant submitted analyses for a subpopulation for which they believed the benefits outweighed the risk.

Based on this sub-group, the applicant requested approval for the following IFU:

> The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years who meet the following criteria in both eyes: manifest spherical equivalent between -0.75D and +0.50D, refractive astigmatism less than or equal to 0.75 D, minimum near add at least +1.25D and scleral thickness between 530 and 680 microns.

FDA Commentary: The IFU above represents a subpopulation of the IDE trial cohort. This sub-group reflects two key changes from the patient population identified in the original PMA: (1) a reduction in refractive astigmatism from 1.00D to 0.75D (i.e., 0.25D difference) and (2) a limit on scleral thickness between 530 and 680 microns. This sub-group is hereinafter referred to as the ***Intended Use (IU) Cohort****.*

In P170040/A005, the applicant provided updated analyses on the original IFU cohort based on additional follow-up of subjects at 12 and 24 months: 687 eyes (97.0%) in 350 subjects (97.2%) at 12 months of follow-up and 668 eyes (94.4%) in 344 subjects (95.6%) at 24 months of follow-up. The applicant also provided analyses of the IU Cohort based on follow-up of subjects at 12 and 24 months: 638 eyes (97.6%) in 322 subjects (97.0%) at 12 months of follow-up and 624 eyes (95.4%) in 316 subjects (95.2%) at 24 months of follow-up.

*FDA Commentary: The effectiveness analyses provided in support of this IFU were based on **both 12 and 24 months of follow up.** The data were analyzed at both 12 and 24 months. However, the analyses of the IU Cohort are considered to be post-hoc. These analyses were performed in response to FDA's recommendation to identify a patient subpopulation within the IDE trial cohort where there could be reduced risk from use of the device.*

The applicant indicated that baseline characteristics were not associated with adverse events (i.e., no baseline characteristics were found to be predictors of better safety) and the identified sub-group would not further mitigate the risks. Proposed IFU modifications (a reduction in refractive astigmatism of 0.25D and limiting enrollment to eyes with thicker sclera *between 530 and 680 microns*) would not be expected to affect the rate of scleral perforations, anterior segment ischemia (ASI), explants, or conjunctival retraction. Therefore, FDA continued to have concerns regarding the safety. While the effectiveness of this cohort met the first co-primary effectiveness endpoint, it was based on a post-hoc analyses. Furthermore, it is unclear why reduction of astigmatism by 0.25D would lead to greater effectiveness, since the measurements were based upon distance corrected near visual acuities (meaning the astigmatism had already been corrected). Exploratory analyses (wavefront aberrometry and defocus curves) did not show clinically significant differences per FDA's assessment.

Because of continued concerns about the benefit-risk assessment, a second "Not Approvable" decision was rendered on October 22, 2019.

FDA Commentary: At the time of the first PMA "Not Approvable" decision for the originally proposed IFU, all safety analyses through 12 months and a preliminary update on AEs based on data collected after all subjects had passed the 24-month timepoint had been submitted. At the time of the second PMA "Not Approvable" decision for the modified IFU, all safety analyses through 24 months for the IU cohort had been submitted.

The applicant appealed the "Not Approvable" decision in a letter dated November 21, 2019 and requested supervisory review. The supervisory review by the Director of CDRH's Office of Product Evaluation and Quality concluded that CDRH would benefit from additional external scientific and clinical perspective on whether the data in the submission demonstrate that the probable benefits of the device outweigh the probable risks. The "Not Approvable" decision was set aside; the file was re-opened and the application was referred to the Ophthalmic Devices Advisory Panel to further discuss the evidence submitted before CDRH renders a final decision.

Following the supervisory review decision, the applicant informed FDA of their intent to pursue approval of their device for the IFU proposed in their original PMA, as stated below:

> The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes, and require a minimum near correction of at least +1.25 D reading add.

In support of this IFU, the applicant wants FDA and Panel to consider data based on **12-** and **24-months of follow-up** as presented in P170040/A005**.**

7 Clinical Trial Design

The VIS-2014 clinical trial, "A Prospective, Multicenter Clinical Trial of the VisAbility Implant System for Improvement of Near Visual Acuity in Presbyopic Patients," was a prospective, multicenter, non-masked, bilateral intervention trial conducted under IDE (b) (4) at 13 U.S. sites. As shown in **Figure 10** (FDA Generated Figure), 336 out of 396 subjects were enrolled without randomization. A subset of subjects (60/396) were randomized 1:1 at 3 of the 13 sites into one of two arms upon enrollment - the immediate treatment/surgery group or the untreated (deferred surgery) control group. This subset of subjects was designated by the applicant as the "randomized controlled substudy" or "randomized substudy". Non-randomized subjects were also enrolled at these three sites. Subjects randomized to the control group were followed for 6 months and were eligible to undergo VisAbility Implant surgery after completion of the six-month observation period, if they continued to meet the enrollment criteria. After surgery, all subjects in the non-randomized population and the randomized population were followed according to the same schedule through 24 months postoperatively.

A total of 360 subjects (306 from non-randomized and 54 randomized) underwent surgery in order to have 300 treated primary eyes available for analysis at 12 months postoperatively, the primary timepoint for one of the two co-primary effectiveness analyses.

For the List of Abbreviations and Definitions of Terms used throughout this document, please refer to **Appendix 1 – List of Abbreviations and Definitions of Terms**.

7.1 Enrollment Criteria

7.1.1 Inclusion Criteria

Patients who met the following criteria were considered for inclusion in this trial:

1. Subjects must be between ages of 45 to 60 at the time of enrollment.

2. Subjects must have best corrected distance visual acuity (BCDVA) of 20/20 in each eye.

3. Subjects must have distance corrected near visual acuity (DCNVA) @ 40 cm of 20/50, 20/63 or 20/80 in each eye.

4. Subjects must have uncorrected near visual acuity (UCNVA) @ 40 cm of 20/50, 20/63 or 20/80 in each eye.

5. Subjects must have preoperative manifest refraction spherical equivalent (MRSE) in each eye of -0.75 to +0.50 diopters with no more than 1.00 diopter of astigmatism. The difference between the MRSE and cycloplegic refraction spherical equivalent (CRSE) should be $\leq$ 0.50 diopter.

6. Subjects must require a minimum add of +1.25 or greater to read 20/20 at near (40 cm).

7. Subjects must be phakic in each eye.

8. Subjects must be alert, mentally competent, and able to understand and comply with the requirements of the clinical study, and be personally motivated to abide by the requirements and restrictions of the clinical study. Patients must be available for the follow-up period.

9. Subjects must be able to provide written informed consent.

7.1.2 Exclusion Criteria

Patients who met any one of the following criteria were excluded from this trial:

1. Subjects where either pupil has a baseline percent change from scotopic to photopic of less than 30% or an absolute difference of less than 1.00 mm between scotopic and photopic pupil size as measured by the NeurOptics Pupillometer.

2. Subjects with ocular inflammation, chronic uveitis, or other recurrent anterior or posterior segment inflammatory conditions in either eye; subjects with any ocular or systemic disease(s) posting a significant risk for ocular inflammation, including but not limited to autoimmune disorders (e.g., rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, ulcerative colitis, Crohn's disease, psoriasis, sarcoidosis, Behcet's disease), infections (toxoplasmosis, cat-scratch fever, West Nile virus, syphilis, tuberculosis, herpes zoster, herpes simplex, adenovirus), ocular trauma, or gout.

3. Subjects with scleral thickness of less than 530 microns as measured 3.5 to 4.0 mm posterior to the superior temporal quadrant limbus in either eye.

4. Subjects with a history of any prior intraocular procedure (e.g., corneal transplant, filtering procedures for glaucoma, vitrectomy, retinal detachment repair, cataract

surgery) or any prior refractive procedure (e.g. LASIK, surface excimer, or incisional surgery) in either eye.

5. Subjects with any history of prior extraocular muscle surgery or orbital surgery.

6. Subjects with chronic ocular disease, including but not limited to corneal pathology, primary or secondary glaucoma, iritis, herpes simplex, uveitis, trachoma, ocular pemphigoid, Sjogren's disease, uveal melanoma, Thyroid Related Immune Orbitopathy or clinically significant retinal pathology in either eye.

7. Subjects with any acute ocular disease that has not been completely treated and resolved for at least three months such as conjunctivitis, blepharitis, chalazion, corneal abrasion or keratitis in either eye.

8. Subjects with chronic systemic diseases which may affect the eye, including but not limited to diabetes, ulcerative colitis, systemic lupus erythematosus, Crohn's disease, collagen vascular disease, rheumatoid arthritis, any bleeding diathesis, or systemic manifestations of HIV/AIDS. Any other uncontrolled systemic disease (e.g., hypertension, cancer, etc.) that could compromise the patient's participation.

9. Use of any medication, such as coumadin, that could make the surgical procedure more difficult. Subjects using Coumadin, aspirin or NSAID medication under orders from a doctor must be able to provide written approval from the treating doctor for discontinuing this medication at least ten (10) days prior to surgery.

10. Subjects with chronic ocular surface disease, including but not limited to subjects with a prior diagnosis of chronic dry eye syndrome based on tests such as but not limited to, corneal or conjunctival staining, Ocular Surface Disease Index symptom score or Schirmer tear testing.

11. Subjects who are allergic to any medications used in the protocol.

12. Subjects who are pregnant, lactating, or of child-bearing age and not practicing a medically approved method of birth control

7.2 Clinical Assessments/Visit Schedule

Subjects were examined pre-operatively, immediately postoperatively on the day of surgery, and at one day, one week and at 1, 2, 3, 6, 12, 18 and 24 months post-operatively.

For the subjects included in the randomized substudy, subjects randomized to the deferred treatment/control group were examined at baseline and at 3 and 6 months during

the observation period. Subjects randomized to the immediate treatment group were examined according to the same schedule as the non-randomized cohort.

The schedule of visits and clinical evaluations performed at each visit are summarized in **Table 6** and include visual acuity, manifest refraction, minimum add requirement, pupillometry, slit lamp biomicroscopy, applanation tonometry, fundus examination, and patient-reported outcomes (PRO) questionnaire. Defocus curve measurements and wavefront measurements were performed in randomized substudy subjects only.

7.2.1 Anterior Segment Ischemia

Most of the blood supply to the anterior segment of the eye, including the iris and ciliary body, comes from the anterior ciliary arteries. Disruption of this blood supply, e.g., through surgery, may lead to anterior segment ischemia (ASI). The acute signs of ASI are pupil/iris changes, vessel leakage/uveitis, and corneal changes. According to an article that the applicant referenced [Olver JM, Lee JP. Recovery of anterior segment circulation after strabismus surgery in adult patients. Ophthalmology. 1992 Mar;99(3):305-15], acute ASI may be graded as follows:

Grade 1: Angiographic sector delay (delay in postoperative fluorescein filling of a sector of the iris when compared to the time the entire iris vasculature took to completely fill during preoperative iris angiography)
Grade 2: + pupil signs [i.e., decrease pupil reactivity, irregular pupil]
Grade 3: + vessel leakage/ "uveitis" [i.e., anterior chamber cell and flare]
Grade 4: + keratopathy [i.e., corneal edema with and without corneal folds (striae)].

Based on a survey article regarding ASI following strabismus surgery [Saunders et al, Surv Ophthalmol 38 (5) March-April 1994: 456-466], other signs of ASI include deposits on the anterior lens capsule and, in severe cases, fixed and dilated pupil, corneal ulceration, and hyphema. It may be difficult to differentiate the signs of acute ASI from postoperative inflammation not due to compromise of the anterior segment circulation. Patients with corneal involvement typically complain of pain and reduced visual acuity beginning one or two days after surgery followed by gradual improvement and return of preoperative acuity. There is no proven treatment for ASI. Late complications in patients with severe iris ischemia include iris atrophy, hyporeactive pupil, and permanent irregularity of the pupil. The following late complications of ASI have been reported that can result in vision loss or "loss" of the eye (in the case of phthisis bulbi): posterior synechiae (scarring inside the eye), rubeosis irides (abnormal blood vessel growth inside the eye), glaucoma, cataract (lens opacity), hypotony (extremely low intraocular pressure, common in severely affected eyes), phthisis bulbi (atrophied, shrunken, blind eye with hypotony; rare in severely affected eyes).

Also based on this article, the most important risk factor for ASI in patients undergoing strabismus surgery is age with ASI occurring almost exclusively in adults (older adults are especially at risk) and more frequently in patients with a history of circulatory disorders. Atherosclerosis, carotid artery disease and/or carotid-cavernous fistula, dysthyroid ophthalmopathy, and blood dyscrasias were identified as factors that

substantially increase the risk of ASI. Other risk factors include limbal conjunctival incision, hematologic disorders that increase blood viscosity, compromised long posterior ciliary circulation, and previous strabismus surgery.

Angiography of the anterior segment was not employed to evaluate anterior segment perfusion during the pivotal trial. Therefore, the presence of Grade 1 ASI could not be determined during this trial. Pupil reactivity was evaluated using the NeurOptics NPi-200 Pupillometer (NeurOptics, Inc., Irvine, CA). During the immediate postoperative period, measurements of the pupil diameter were obtained in both eyes every 15 to 30 minutes and the percent change calculated according the following formula:

> Percent Change (% CH) = {[dilated pupil diameter - constricted pupil diameter]/[dilated pupil diameter]} x 100.

A threshold of % CH $\geq$ 25% at two distinct time points at least 5 minutes apart was set. Subjects had to meet this threshold in the operative eye before the subject could be released from the surgical facility. If this threshold was not met within 6 hours postoperatively, immediate removal of all segments from the eye was required.

7.3 Primary Endpoints

7.3.1 Safety

There were no pre-specified primary safety endpoints. However, based on the protocol VIS-2014, descriptive statistics of the following safety parameters were provided for primary and all eyes:

- BCDVA
- Intraocular pressure (IOP)
- Slit Lamp findings
- Fundus exam findings
- Rate of adverse events

In addition, the applicant powered the trial in order to be able to detect adverse events (AEs) with a true rate of occurrence of at least 1% at 12 months postoperatively with 95% confidence.

The applicant provided the following specific examples of anticipated AEs in the protocol, although the applicant indicated that the anticipated AEs were not limited to these:

Intraoperative Events
- Scleral perforation
- Scleral perforation with vitreous prolapse

Lids and Lashes
- Ptosis
- Onset of or worsening to severe clinically significant lid margin disease (e.g., blepharoconjunctivitis, blepharitis, meibomitis, meibomian gland dysfunction, etc.) after 3 months postoperative

Cornea
- Corneal dellen after 1 week postoperative
- Corneal abrasion > 2mm after 1 week postoperative
- Dry eye signs (moderate or severe) of corneal and/or conjunctival staining, etc., requiring prescription medication after 6 months postoperative
- Corneal edema (moderate or severe) after 1 month postoperative
- Corneal infiltrate or ulcer

Conjunctiva/Sclera
- Conjunctival cyst
- Conjunctival thinning or erosion
- Moderate or severe conjunctival injection at 3 months postoperative or later
- Subconjunctival hemorrhage after 3 months postoperative

Anterior Segment, Iris, Lens
- Pupil abnormalities persisting after 3 months
- Grade 4 anterior segment ischemia (corneal edema, anterior chamber reaction, and decreased pupil reactivity)
- Anterior chamber cells or flare greater than mild at Day 1 through 1 Week
- Anterior chamber cells or flare after 1 week postoperative
- Intraocular Inflammation other than anterior chamber cells and flare (e.g., vitritis)
- Two grade change in lens opacity compared to baseline on two consecutive post-operative visits
- Displaced or missing implant segments

Intraocular Pressure
- Hypotony (IOP < 6 mmHg)
- Increase in IOP of > 10 mmHg over baseline or IOP > 30 mmHg at two consecutive visits at 1 week or later

BCDVA Loss
- Decrease in BCDVA of greater than or equal to 2 lines ($\geq$10 letters ETDRS [Early Treatment of Diabetic Retinopathy Study]) at 3 months or later

Fundus
- Choroidal effusion
- Retinal detachment
- Retinal or vitreous hemorrhage

Secondary Surgical Intervention

- Implant segment removal
- Exposed implant segments or conjunctival retraction requiring conjunctival re-approximation

Other
- Eye pain requiring oral prescription pain medication after 1 week postoperative
- Allergic reactions to medications, devices, sutures or anesthesia
- Other findings worsening two grades from baseline to a grade of +3 or +4

FDA Commentary: Please note that there were no pre-specified primary safety endpoints.

7.3.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint in the protocol was achievement of distance corrected near visual acuity (DCNVA) (at 40 cm) of Snellen equivalent 20/40 or better and at least 10 letters improvement in DCNVA on the Early Treatment of Diabetic Retinopathy Study (ETDRS) in the primary eye.

The primary eye was defined as the subject's dominant eye and was the eye to undergo surgery first.

This endpoint was to be evaluated with two objectives that needed to be met in order to consider the trial a success:

1. Achievement of DCNVA 20/40 or better and gain ≥10 letters DCNVA in 75% of the primary eyes of implanted subjects at 12-month. In order to meet this objective, the lower limit of the one-sided 97.5% confidence interval (CI) should be at least 75%.

2. Achievement of a statistically significant (one-sided $p<0.025$) difference in the proportion of primary eyes with DCNVA 20/40 or better and gain of ≥10 letters in subjects randomized to treatment versus deferred surgery as part of the randomized controlled substudy at 6-month.

7.4 Additional Sub-study Parameters

Defocus curve measurements and wavefront measurements were performed in randomized substudy subjects only. All statistical analyses of these measurements were considered exploratory by the applicant

7.5 Statistical Methods

7.5.1 Statistical Hypotheses and Targets

All subjects that underwent surgery from both the non-randomized and randomized populations were combined to analyze the first co-primary effectiveness endpoint for the first objective. The randomized population at the 6-month visit (6-months postoperatively for the surgery group and 6-months of observation for the control group) was used to analyze the second co-primary effectiveness endpoint for the second objective.

The null and alternative statistical hypotheses statements corresponding to the above objectives/endpoints were as follows:

1. First Co-Primary Effectiveness Endpoint for the First Objective:

   H_0 (null hypothesis): $p < 0.75$

   H_a (alternative hypothesis): $p \geq 0.75$

   Where, p is the probability that subjects achieve the effectiveness endpoint at 12 months postoperatively (12-month responder rate).

To evaluate the 1st objective, the lower one-sided 97.5% confidence interval (CI) 12-month responder rate was calculated considering the exact binomial distribution with a target rate of at least 75%.

2. Second Co-Primary Effectiveness Endpoint for the Second Objective:

   H_0 (null hypothesis): $p_1 \leq p_2$

   H_a (alternative hypothesis): $p_1 > p_2$

   Where:

   - p_1 is the percentage of primary eyes in the randomized surgery group who achieve the effectiveness endpoint at 6 months.
   - p_2 is the percentage of primary eyes in the randomized control group who achieve the effectiveness endpoint at 6 months (6-month "responder rate").

To evaluate the 2nd objective, the two-sided Fisher's exact test was used to compare the difference between 6-month responder rates of the randomized surgery group and

randomized control group. The p-value of the one-sided Fisher's exact test needed to be lower than the significant level of 0.025 to declare a success.

Based on protocol, VIS-2014, no statistical hypothesis was planned to access the safety of VisAbility Micro Insert System and no safety targets were set.

7.5.2 Missing Data

First Co-Primary Effectiveness Endpoint:

The applicant did not pre-specify any method for handling missing data for the primary analysis. However, the applicant specified in the protocol that explanted eyes would be counted as failures and included a plan for sensitivity analyses, as discussed in **Section 7.9** below.

Second Co-Primary Effectiveness Endpoint:

In Section 11.6, Analysis of Effectiveness Cohorts, of the protocol, the applicant stated:

> For the primary analysis of the second co-primary effectiveness endpoint, all reported 6-month data of the randomized primary eyes will be included in the analysis. Missing data will be imputed as follows:
>
> - Randomized Control Group: In the absence of 6 month visit data, the nearest available data recorded between and including the 3-month visit up to the 6-month visit will be utilized. Since this randomized control group does not receive the benefit of the surgery during this 6-month observation period, the lost to follow-up and missed visit rate could be higher and since no intervention occurs during the 6-month period, this imputation of missing data is warranted. In the absence of any observed data between the 3-month visit and 6-month visit, this missing data will not be imputed since failure to achieve the effectiveness endpoint is expected.
>
> - Randomized Surgery Group:
>
> - Explanted primary eyes will be imputed as failures.
> - In the absence of 6 month visit data, the nearest recorded data after 6 months up to and including 12-month visit data will be used. This imputation is warranted as the visit data between 6 and 12 months provides a predictive indicator of 6-month results. In the absence of any observed data between 6 and including 12 months, this other missing data will not be imputed.

7.6 Sample Size

The sample size was determined based on considerations of two co-primary effectiveness endpoints.

Full Trial Cohort Effectiveness Endpoint

The applicant stated that the sample size calculation for the statistical hypotheses described for Objective #1 in **Section 7.3.2** was based on the following criteria:

- The two-sided significance level = 0.05 (or one-sided significance level = 0.025).
- The statistical power = 90% at p = 0.825. The assumption of true responder rate of 0.825 is based on the simple average of success rate observed in previous Refocus clinical study data, as follows:
  - Disposable Scleratome group had an observed success rate of 88%.
  - Re-usable Scleratome group had an observed success rate of 77%.
  - Simple average of 88% and 77% is 82.5%.
- Binomial distribution was used for sample size calculation.

Based on the criteria above for Objective #1, a sample size of 360 was proposed to account for a 10 % drop-out rate by 12 months.

For safety analysis, in order to detect an Adverse Event (AE) with a true probability of occurrence among subjects of 1% with 95% probability, based on the binomial distribution, a sample of at least 299 eyes was required. A minimum sample size of 333 was proposed to account for 10% drop-out rate by 12 months.

The trial cohort was planned for 360 surgery subjects at up to 14 study sites. Also, no site enrolled and determined to be eligible more than 20% of the subject surgery cohort.

Randomized Sub-study

The applicant stated that the sample size for Objective #2 in **Section 7.3.2** was based on the following criteria:

- The two-sided significance level = 0.05 (or one-sided significance level = 0.025).
- Based on the randomized control group data collected in IDE (b) (4), the 6-month responder rate was estimated as 10% for the control group.
- Based on the surgery group data collected in IDE (b) (4), the 6-month responder rate was lower than the 12-month responder rate. Therefore, it is assumed that the 6-month responder rate of the randomized surgery group in this study will be approximately 0.75.
- The statistical power = 90%.
- Fisher's exact test was used for sample size calculation.

Based on the criteria above, a sample size of 30 randomized surgery group subjects and 30 randomized control group subjects were proposed to account for a 10% drop-out rate.

7.7 Definitions of Current Analysis Cohorts

The analysis cohorts to support the currently proposed IFU are defined below (Please see **Figure 10 (FDA Generated Figure))**

*FDA Commentary: As discussed above in **Section 6.5.2 P170040/A005 – Submitted April 26, 2019**, the IFU that was the subject of the second "Not Approvable" decision (P170040/A005) represented a subpopulation of the currently proposed IFU population and the full pivotal trial cohort. Following the appeal discussed above in **Section 6.5.2**, the applicant is currently proposing the following IFU (which is equivalent to the originally proposed IFU):*

The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes, and require a minimum near correction of at least +1.25 D reading add.

7.7.1 Safety

The applicant defined in the protocol the cohort for the analyses of safety as follows:

> **Safety Cohort**: All eyes (both primary and fellow eyes) that have undergone surgical preparation of the ocular surface.

This population includes eyes from both the randomized and non-randomized arms of the trial.

7.7.2 Effectiveness

The pre-specified analysis population for the first co-primary effectiveness in the protocol was as follows:

- Intent-to-Treat Population (ITT): The full analysis set consists of the primary eyes of all subjects that underwent surgical implantation. This includes subjects from both the randomized and non-randomized arms of the study.

FDA Commentary: Please note that the definition for the ITT population is not the commonly used definition. The ITT analysis population typically is used in the context of randomized trials, where all randomized patients are analyzed according to the treatment to which they were randomized, including patients who leave the trial prematurely [Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry, November 2016, p. 31]. Here, the applicant is referring to all subjects that underwent treatment (after they underwent treatment), including those treated after 6-months of observation in the randomized substudy.

In the initial original PMA submission (P170040), the applicant also introduced a post-hoc population of Bilateral Effectiveness Cohort (BEC):

- Bilateral Effectiveness Cohort (BEC): The full analysis set consists of the primary eyes of all subjects that underwent bilateral implantation (OD/OS), as indicated for this procedure. This includes subjects from both the randomized and non-randomized arms of the study.

FDA Commentary: The BEC population was not pre-specified as an analysis population in the protocol.

The analysis population for the second co-primary effectiveness endpoint was all primary eyes of subjects included in the randomized substudy.

7.8 Poolability Analysis

The pre-specified poolability analyses were conducted for both non-randomized and randomized populations. The 1st co-primary endpoint is based on a non-randomized population and the 2nd co-primary endpoint is based on a randomized population.

Poolability Analysis for First Co-Primary Effectiveness Endpoint

The applicant stated that the Fisher's exact test was used to compare the percentage of primary eyes achieving the 1st co-primary endpoint among the trial sites at 12-month. The p-value ≤ 0.15 indicates that the site effect was significant. The 12-month responder rates stratified by trial site was calculated for significant sites. Also, the 97.5% confidence interval for the average 12-month responder rate was calculated using normal distribution approximation.

Additionally, the Fisher's exact test was used to assess the effects of subject sex, race and age category at surgery on the 12-month responder rates for primary eyes using a significance level of 0.15. It should be noted that the age was categorized into 3 interval groups (i.e., 45-49, 50-54, and 55-60).

Poolability Analysis for Second Co-Primary Effectiveness Endpoint

The applicant stated that a logistic regression analysis was conducted to assess any potential differences of randomized group allocation and/or site by considering the treatment effect, trial site effect and site by treatment interaction and the p-values were compared with 0.15. It should be noted that the $p \leq 0.15$ indicates a significant difference.

If there was a significant difference ($p \leq 0.15$) in treatment effect, trial site effect, or a significant interaction effect between trial site effect and treatment effect ($p \leq 0.15$), then the 6-month responder rate for each trial group and the difference in the 6-month responder rate between the two randomized groups ($p_{treatment} - p_{deferred}$) were summarized by each trial site.

7.9 Sensitivity Analyses

The applicant stated in the protocol that sensitivity analyses for the 1st objective were to be performed using following imputation methods at 12 months:

- Best Case Analysis: All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes lost to follow-up or for primary eyes missing 12-month visit data, the best value from any protocol scheduled visit at 1 month or later (1-month, 3-month or 6-month visit) will be used. If such visit data does not exist for a primary eye, the effectiveness will be imputed as a success.

- Worst Case Analysis: All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes lost to follow-up or missing 12-month visit data, the worst value from any protocol scheduled visit at 1 month or later (1-month, 3-month or 6- month visit) will be used. If such visit data does not exist for a primary eye, the effectiveness will be imputed as a failure.

- Tipping Point Analysis: All discontinued primary eyes will be imputed as effectiveness failures. For primary eyes missing 12-month visit data for reasons other than discontinued, effectiveness will be initially be set to success. At this step, the lower limit of the one-sided 97.5% confidence intervals (CI) will be calculated. Serial calculations will then be performed using a decreasing number (i.e., n-1, n-2, …1) of successes to determine the maximum number of additional failures allowed for the lower bound one-sided 97.5% CI of the effectiveness endpoint percent estimate to achieve or exceed 75% success.

The applicant stated in the protocol that sensitivity analysis for the 2nd objective was to be performed using following imputation methods:

- Tipping Point Analysis: All discontinued primary eyes will be iteratively imputed as effectiveness success or failures. Let n_1 and n_2 be the number of discontinued primary eyes for the randomized surgery group and the randomized control group,

respectively. For the n_1 discontinued randomized surgery group primary eyes, they can be imputed as 0 failures, 1 failure, 2 failures, and up to n_1 failures, for a total of (n_1+1) possible imputations. For the n_2 discontinued randomized control group primary eyes, there are (n_2+1) possible imputations. Therefore, there are $(n_1+1) \times (n_2+1)$ possible combinations of success and failure imputations for these discontinued primary eyes. For each of these possible imputations, the lower limit of the one-sided 97.5% confidence intervals (CI) will be calculated. The imputations that have the lower one-sided 97.5% CI < 75% will be identified.

8 Clinical Trial Results

8.1 Accountability

Interested subjects were asked to sign a Screening Informed Consent document and were screened to determine initial eligibility. If preliminary eligibility was met, the subject was asked to sign a Trial Informed Consent Form (ICF). Once the ICF was signed, the subject was considered enrolled and underwent additional trial specific testing. If the subject satisfied all enrollment criteria, the full baseline examination data for that subject was provided to the Applicant for verification of eligibility. After approval by the applicant, the subject was either randomized to immediate surgery or deferred surgery (after 6 months of observation), if enrolled in the randomized substudy at one of the three of 13 participating sites, or scheduled for surgery, if enrolled in the non-randomized cohort.

As shown in **Figure 10 (FDA Generated Figure)**:

- 2586 subjects were screened
- 396 subjects were enrolled and their eligibility for surgery verified – 336 in the non-randomized cohort and 60 in the randomized substudy
- Of the 60 randomized subjects, 29 were randomized to immediate surgery and 31 were randomized to deferred surgery
- Of the 29 subjects randomized to immediate surgery, 28 were treated and 25 were available for analysis at 6 months postoperatively
- Of the 31 subjects randomized to deferred surgery, 29 were available for analysis after 6 months of observation
- 26 subjects in the deferred surgery group were treated after 6 months of observation
- 306 non-randomized subjects had surgery for a total of 360 treated subjects (28 + 26 + 306) or 360 treated primary eyes
- Of the 360 treated subjects, 348 were bilaterally treated and had implantation in the fellow eye for a total of 708 treated eyes.

Therefore, based on the analysis populations described in **Section 7.7**, the three analysis cohorts are as follows:

- Safety Cohort was compromised of 708 eyes of 360 subjects.
- Intent-to-Treat (ITT) Population was comprised of 360 primary eyes of 360 subjects.
- Bilateral Effectiveness Cohort (BEC) was comprised of 348 primary eyes of 348 bilaterally implanted subjects.

At 12 months postoperatively, the primary analysis timepoint for the first co-primary effectiveness endpoint, there were 346 primary eyes of 347 subjects available for analysis in the ITT cohort. Of these 346 primary eyes, 339 were included in the BEC population. By this timepoint, the Micro Inserts had been removed from four primary eyes, including 1 BEC eye. There were 341 fellow eyes available for analysis at the 12-month visit for a total of 687 eyes (346 primary + 341 fellow) with removal of the Micro Inserts (the device) from one fellow eye by this timepoint.

At 24 months postoperatively, the final timepoint, there were 337 primary eyes of 337 subjects available for analysis in the ITT cohort. Of these 337 primary eyes, 331 were included in the BEC population. By this timepoint, the device had been removed from eight primary eyes, including 5 BEC eyes. There were 311 fellow eyes available for analysis at the 24-month visit for a total of 668 (337 primary + 311 fellow) with removal of the device from 5 fellow eyes by this timepoint.

Please see **Table 7**, **Table 8**, and **Table 9** for greater detail regarding accountability of the Safety, ITT, and BEC populations at each of the trial timepoints.

Please see **Table 10** and **Table 11** for greater detail regarding accountability for the two arms of the substudy.

It should be noted that three subjects were enrolled into the randomized substudy at a fourth site (in addition to the three sites that conducted substudy). One subject was randomized into the immediate treatment group and two were randomized into the deferred treatment group. However, the site investigator requested withdrawal from participation in the randomized substudy due to inability to meet study requirements but continued with participation in the non-randomized study. The site treated an additional 8 subjects as part of the non-randomized study, for a total of 11 treated subjects (three randomized and 8 non-randomized). The three subjects that had been randomized at this site were re-categorized as being in the non-randomized cohort and were not included in the analyses of the randomized substudy (e.g., for the second co-primary effectiveness endpoint at 6 months postoperatively).

FDA Commentary: Removal of the 3 subjects from the randomized substudy and their conversion into "non-randomized" subjects may have introduced bias into the substudy, since these subjects were no longer included in the ITT analysis cohort for the substudy.

8.2 Demographics and Baseline Characteristics

Table 12 summarizes the demographic characteristics of all treated subjects stratified by trial population. Of the 360 treated subjects (total implanted), more than half were male (217, 60.3%). Subjects ranged in age from 45 to 60 years with an average age of 51.6 (SD 3.5) years. Most subjects reported their race as Caucasian (85.3%) with 5.0% reporting Asian, 4.2% black or African American, 1.1% native Hawaiian or other Pacific islander, and 4.4% other. Among all subjects, 10.6% identified as Hispanic or Latino, 88.6% as not Hispanic or Latino, and 0.8% did not respond. The dominant eye, which was designated as the primary eye, was the right eye for the majority of subjects (239, 66.4%). The same information is provided in this table for the treated randomized substudy subjects stratified by treatment arm (deferred treatment control group and immediate treatment group).

Table 13 also shows the demographic information for the 60 randomized substudy subjects (not just for those in the substudy who were implanted with the device as shown in **Table 12**) stratified by treatment arm.

*FDA Commentary: The demographic characteristics of the subjects in the two arms of the randomized substudy are similar, based on the stratified information in both **Table 12** and **Table 13**. Of note, the dominant eye (which was designated as the primary eye, treated first, and included in the hypothesis-tested effectiveness analyses) was the right eye in the majority of subjects in the immediate treatment group (79% and 76% in **Table 12** and **Table 13**, respectively) and the left eye in the majority of subjects in the control group (65% and 61% in **Table 12** and **Table 13**, respectively).*

As shown in **Table 14**, which summarizes the baseline characteristic of primary eyes of the 360 treated subjects, the baseline manifest refractive spherical equivalent (MRSE) ranged from -0.75 to +0.50 D with a mean of +0.12 D (SD 0.27) , baseline astigmatism ranged from -1.25 to 0.00 D with a mean of -0.28 D (SD 0.29), and the baseline cycloplegic refractive spherical equivalent (CRSE) ranged from -0.75 to +1.00 D with a mean of +0.22 D (SD 0.31). The average corneal keratometry measurements in the flat and steep meridians (K1 + K2/2) ranged from 39.50 to 48.43 D with a mean of 43.70 D (SD 1.40), and axial length measurements ranged from 21.6 to 25.7 mm with a mean of 23.6 mm (SD 0.74). Mean uncorrected distance visual acuity (UCDVA) was 20/20 (range 20/13 to 20/42), mean best corrected distance visual acuity (BCDVA) was 20/17 (range 20/13 to 20/24), mean uncorrected near visual acuity (UCNVA) was 20/68 (range 20/30 to 20/100), and mean distance corrected near visual acuity (DCNVA) was 20/63 (range 20/35 to 20/96) Snellen equivalent. The near add required at a testing distance of 40 cm ranged from +1.25 to +2.50 D with a mean of +1.62 D (SD 0.31). Mean minimum pupil size was 3.2 mm (SD 0.6; range 1.5 – 4.9) and mean maximum pupil size was 5.5 mm (SD 0.8; range 2.9 – 7.5). Scleral thickness (in the superior temporal quadrant) ranged from 530 to 800 µm with a mean of 572 µm (SD 43 µm). **Table 14** also shows the demographic information for the 60 randomized subjects stratified by treatment arm.

The baseline characteristics of the primary eyes of the 60 randomized subjects stratified by treatment group are summarized in **Table 15**.

*FDA Commentary: The baseline characteristics of the subjects in the two arms of the randomized substudy are similar, based on the stratified information in both **Table 14** and **Table 15**.*

8.3 Protocol Deviations

Protocol deviations are summarized in **Table 16**. There was a total of 236 protocol deviations - 47 were categorized as major and 189 were categorized as minor. Of note, two major protocol deviations listed as "Excluded concomitant medication" in the table refer to administration of topical lidocaine with epinephrine during the implantation surgery. Epinephrine was explicitly excluded from use during the surgery, because it could affect pupil function, which was used to monitor for anterior segment ischemia during the immediate postoperative period. In addition, one of the major deviations included in the category "Protocol assessment incomplete/not done" was failure to perform pupillometry in one subject at the Day 1 postoperative visit. Also, included in this category was failure to perform slit lamp biomicroscopy in one subject at the Month 1 postoperative visit.

8.4 Safety Outcomes

8.4.1 Adverse Events (AEs)

8.4.1.1 Systemic and Non-Ocular Adverse Events

There was a total of six systemic and non-ocular adverse events reported in 6 subjects (6/360, 1.7%) – Sjögren's Syndrome, trigeminal neuralgia, acute myopericarditis, arrhythmia, cholecystitis, and strep pneumonia with sepsis. The last four of these events were considered serious, because they required hospitalization.

FDA Commentary: The applicant did not explicitly state whether the systemic and non-ocular adverse events were related to the device or procedure. However, the applicant stated, "None of the ocular adverse events were determined to be SAEs [serious adverse events] and no unanticipated adverse device effects (UADEs) were reported over the course of the study. There were 6 reports of non-ocular adverse events and 4 of these were considered SAEs."

8.4.1.2 Surgical Complications

There was a total of 15 surgical complications that occurred in 13 (1.8%) eyes of 13 (3.6%) subjects out of the 708 eyes/360 subjects in the Safety Cohort. Ten of these

complications were reported as adverse events (AEs) – 8 **scleral perforations** and 2 "**pupil abnormalities**" resulting in **Micro Insert segment removal** due to failure to achieve adequate pupil response within the first 6 hours following surgery in the primary eye, as per the trial protocol, indicating anterior segment ischemia (ASI).

8.4.1.2.1 SCLERAL PERFORATIONS

The 8 scleral perforations that occurred in 8 eyes (1.1%) of 8 subjects (2.2%) included 5 cases with vitreous prolapse. Of the 8 subjects with scleral perforations, 3 subjects described below had notable sequelae.

One of these subjects had posterior vitreous detachment (**PVD**) with **retinal hemorrhage** noted at 1 week postoperatively on dilated fundus exam. This subject was one of the 5 with vitreous prolapse. The subject was not implanted in the quadrant of the perforation and the sides of the tunnel were sutured shut. On the first postoperative day, the subject had Grade 3+ cell and Grade 1+ flare (**Anterior Chamber Cells or Flare greater than mild at Day 1-1 Week**), **hypotony**, marked to severe corneal edema with Descemet's folds, marked to severe injection, subconjunctival hemorrhage in 3-4 quadrants, and marked to severe conjunctival edema, and the pupil was "round and constricted." These signs were improved at the 1-week postoperative visit, and one month later, retinal consult revealed a normal dilated fundus exam, with no evidence of retinal hemorrhage, tear, or detachment. BCDVA was 20/16 and there were no untoward findings in this eye through the 24 months.

Another of the 3 subjects with sequelae had 3 quadrants of posterior synechiae.

A third subject had chronic **conjunctival bleb** formation with significant decrease in IOP to 6 mmHg with cataract (**lens opacity**) development and **decrease** in vision [**Decrease in BCDVA of $\geq$ 2 lines ($\geq$ 10 letters) at 3 Months or Later**]. Scleral perforation was not "diagnosed" in this last subject until the 6-month postoperative visit. During the first week postoperatively, IOP was noted to be reduced from baseline with conjunctival edema noted at the 1-week visit, and, over the next few months of follow-up, the IOP was 6 mmHg in the operative eye with conjunctival edema and BCDVA of 20/25 or better. At the 6-month visit, the subject reported decreased vision. Pinhole vision was 20/70. On slit lamp examination, 3+ posterior subcapsular cataract, 3+ anterior subcapsular cataract, and 3-4+ nuclear sclerosis were noted. The assessment at this visit based on the constellation of exam findings was that the chronic conjunctival edema was due to the creation of an inadvertent bleb secondary to scleral perforation at the time of surgery.

FDA Commentary: Scleral perforations raise safety concerns, because they may cause untoward events. Untoward events that occurred during the trial included:

- *Hypotony*
- *Inadvertent bleb creation with chronically decreased IOP to 6 mmHg*
- *Posterior and anterior subcapsular cataract formation and nuclear sclerosis requiring cataract extraction*
- *Decrease in BCDVA from preoperative measurements of ≥2 lines*
- *Inflammatory reaction and Posterior synechiae formation*
- *Posterior vitreous detachment with retinal hemorrhage*

The case of scleral perforation resulting in bleb creation that went unrecognized for 6 months raises additional concerns regarding the effectiveness of the applicant's stated risk mitigation of the segments acting as scleral perforation tamponades.

8.4.1.2.2 OTHER SURGICAL COMPLICATIONS

Among the 5 cases of surgical complications that were not reported as separate AEs were 2 subjects noted to have "decreased IOP" intraoperatively which returned to normal by the Day 1 visit, 2 subjects with shallow tunnels in 1 quadrant that were recut with a new Scleratome and successfully implanted with the Insert Segments without further complications, and 1 subject with nausea and vomiting attributed to an administered medication (categorized as an "allergic reaction to medication") that resolved by day 1.

8.4.1.3 Postoperative Ocular Adverse Events

There was a total of 365 ocular AEs that occurred in 260 eyes (primary and/or fellow; 260/708, 36.7%) of 170 subjects (170/360, 47.2%) through the 24-month follow-up period of the trial. All ocular adverse events, including surgical and postoperative AEs, but excluding surgical complications not reported as AEs, are listed in **Table 17**. Please note that the events that appear in BOLD text in this section and the previous section (**Section 8.4.1.2**, **Surgical Complications**) are tabulated in **Table 17**.

8.4.1.3.1 ANTERIOR SEGMENT ISCHEMIA

Aside from the 2 subjects already discussed with "**pupil abnormalities**" resulting in implant segment removals on the day of surgery, at least 3 other subjects showed signs of ASI for a total of 5 subjects (5/360, 1.4%).

One subject was reported to have **ASI Grade 4** in the primary eye based on a slightly elliptical pupil with reduced function, "mild" corneal edema with striae, Grade 0.5+ anterior chamber cells and Grade 1+ (faint) flare. By 1 month postoperatively, UCDVA had returned to baseline and was 20/16 or better for all subsequent postoperative visits through 24 months, the pupil shape and function had returned to normal, and all other

examination findings were consistent with baseline findings. Due to the anterior segment response in the primary eye, the fellow eye was not implanted.
In a second subject, the pupil was peaked and there was an anterior chamber reaction on the first postoperative day (**Anterior Chamber Cells or Flare greater than mild at Day 1-1 Week**) consistent with Grade 3 ASI. In the days following surgery, UCDVA was 20/16 or better. The pupil shape returned to normal by postoperative day 4. However, anterior chamber reaction was present at postoperative visits until Month 3 (**Anterior Chamber Cells or Flare – any after 1 week**) and all clinical examination findings did not return to baseline until the 6-month postoperative visit.

The third subject with ASI complained of glare and reduced distance vision in the primary eye at the 1-month postoperative visit and was noted to have loss of the pupillary ruff from 6-8 o'clock and a slightly peaked pupil at 6 o'clock consistent with severe iris ischemia. However, UCDVA and BCDVA were slightly better than baseline. Over the next few months, BCDVA was 20/20 or better. Due to the persistent pupil abnormality in the primary eye, the fellow eye was not implanted. To reduce glare, pilocarpine was temporarily prescribed and, at the 18-month visit, safety glasses with AR coating were prescribed. At 24 months, BCDVA was 20/16 and the pupil was round with 1-2 clock hours of stable iris atrophy (**Pupil Abnormalities Persisting after 3 months**).

FDA Commentary: It should be noted that the applicant specified in the protocol that implant segments were to be removed from any eye with Grade 2 or 3 ASI "persisting 6 hours postoperative; therefore, the AE category 'Secondary Surgical Intervention: Implant segment removal' should be reported for these cases," and "at postoperative day one or later, the constellation of findings of Grade 4 ASI" should be reported in the anticipated AE category "Grade 4 anterior segment ischemia." Additionally, the applicant specified in the protocol that any persistent pupillary abnormalities due to reduced iris vascular perfusion should be reported in the anticipated AE category of "Pupil abnormalities persisting after 3 months." However, the constellation of findings for Grade 2 and those for Grade 3 ASI were not explicitly included in the list of anticipated AEs in the protocol, and the applicant did not specify that they should be reported as Grade 2 and Grade 3 ASI, respectively. Thus, the cases of Grade 2 and Grade 3 ASI reported in the PMA by the applicant are not listed in **Table 17** *(which was generated by the applicant). "Grade 1" ASI was not assessed. Some late signs of severe ASI, such as persistent pupil abnormality, lens opacity (a change of two grades from baseline on two consecutive postoperative visits), and hypotony (IOP < 6 mmHg), were specified as separate anticipated AEs in the protocol. Of the acute signs of ASI, only anterior chamber cell or flare "greater than mild at Day 1 through 1 Week" or "after 1 week postoperative" were specified as separate anticipated AEs.*

8.4.1.3.2 SECONDARY SURGICAL INTERVENTIONS

As shown on the second page of **Table 17**, there was a total of 28 **secondary surgical interventions** in 28 eyes (out of 708 operated or 4.0%) of 23 subjects (out of 360 operated or 6.4%). Aside from the 2 subjects already discussed with implant segment

removals on the day of surgery due to abnormal pupillary responses from ASI, there were an additional 11 eyes of 6 subjects that had all the **Micro Insert segments removed** for a total of 13 eyes (1.8%) of 8 subjects (2.2%). The reasons for the removals are summarized in **Table 18** and, besides abnormal pupil response, included foreign body sensation, ocular surface dryness, redness/poor cosmesis, residual refractive error, lack of perceptible effect, or a combination thereof. One of these subjects was noted to have scleral thinning in one quadrant in each eye following removal of the segments, but this thinning was deemed not to be clinically significant. Removals continued after subjects' completed participation in the 24-month pivotal trial as summarized in **Table 19**. Following completion of the pivotal trial, 7 subjects decided to have all the segments removed bilaterally (14 eyes). The reasons for removals in these subjects' eyes included foreign body sensation in 4 eyes, a combination of dry eye, redness, cosmesis and/or perceived lack of effect in 8 eyes, and the "patient's systemic health issues that could exacerbate ocular symptoms" in 2 eyes. Three (3) other subjects had one or two segments removed ("partial explants") from one eye each (3 eyes total). One subject had one segment removed due to dryness, another had a segment removed due to redness, and the third had two segments removed due to foreign body sensation. There were an additional 4 eyes of 2 subjects who were enrolled in the continued follow-up study (VIS-2014-5YR) reported to have removals of all segments after completing the trial (at 42-49 months postoperatively) due to ocular surface dryness and/or lid margin disease. It should be noted that not all subjects enrolled in the 24-month pivotal trial have been enrolled in the observational continued follow-up study.

FDA Commentary: In the annual report of the continued follow-up study (VIS-2014-5YR), the applicant reported that an additional subject had removal of a segment from the superior nasal quadrant of the left eye due to foreign body sensation after the subject exited the pivotal trial but prior to enrollment into VIS-2014-5YR. Another subject also had removal of an inferior temporal segment in the left eye with conjunctival transposition during continued follow-up study (VIS-2014-5YR) due to erosion through the conjunctiva after the subject complained of foreign body sensation at approximately 52 months postoperatively. One subject, who had two segments removed from one eye due to foreign body sensation following completion of the pivotal trial, had two segments removed from the other eye for the same reason during the VIS-2014-5YR study.

The most frequent secondary surgical intervention during the trial was **conjunctival re-approximation due to conjunctival retraction and/or exposed Micro Insert segments** [15/708 (2.1%) eyes of 15/360 (4.2%) subjects – 5 eyes had exposure of one segment and 10 eyes had no exposure of the segments. One eye required re-suturing of the conjunctiva a second time.

There were also two reports of **laser retinopexy**, which were not included in the counts of secondary surgical interventions in **Table 17** or the total rate above. One was for the management of a **retinal hole** with a fluid cuff and one was for the management of a **retinal tear** with **hemorrhage** attributed to being secondary to a **PVD**.

Other surgical procedures that occurred during the trial that were not tallied as AEs included, but were not necessarily limited to, at least 3 eyes of 2 subjects that had cataract extraction due to a 2-3 grade change in lens opacity (posterior subcapsular cataract, one due to inadvertent bleb creation already discussed above), 2 eyes of 2 subjects that had conjunctival cyst removal, and one eye that had LASIK.

FDA Commentary: In the annual report of the continued follow-up study (VIS-2014-5YR), the applicant reported that two other subjects had additional refractive surgery to address complaints with near vision during the observational continued follow-up study. One subject had clear lens extraction with multifocal intraocular lens implantation bilaterally after the 48-month follow-up visit. Another subject had monovision photorefractive keratectomy (PRK) in the left eye.

8.4.1.3.3 OTHER POSTOPERATIVE ADVERSE EVENTS

There were 159 "cornea/conjunctiva" AEs reported in 143 (20.2%) eyes of 89 (24.7%) subjects.

Dry eye signs (moderate or severe) of corneal and/or conjunctival staining, etc., requiring prescription medication after 6 months postoperative

The most common AE was **dry eye signs requiring prescription medication after 6 months** occurring in 87 eyes (out of 708, 12.3%) of 44 subjects (out of 360, 12.2%).

Conjunctival AEs

Conjunctival AEs were relatively common in comparison to other AEs, with 4.5% of eyes (32/708) and 5.6% (20/360) of subjects having **moderate or severe conjunctival injection at 3 months postoperatively or later**, 2.3% of eyes (16/708) of 4.2% of subjects (15/360) having **subconjunctival hemorrhage after 3 months postoperatively**, and 2.1% (15/708) of 4.2% of subjects having **conjunctival cyst**, as shown on pg. 1 of **Table 17**. An additional case of **conjunctival cyst** was not included in this tally but is noted on pg. 2 of **Table 17**, for a total of 16 events.

Corneal AEs

Corneal AEs included, but were not limited to, **abrasion > 2mm after 1 week** in 5 (0.7%) eyes of 5 (1.4%) subjects and 1 report each of **dellen after 1 week**, **infiltrate or ulcer**, neovascularization, and scar.

Increase in IOP of > 10 mmHg over baseline or IOP > 30 mmHg at two consecutive visits at 1 week or later

There was a total of 5 eyes (0.7%) of 5 subjects (1.4%) with increase in IOP of > 10mm Hg over baseline or IOP > 30mm Hg at two consecutive visits at 1 week or later. The

latter visit was no more than 1-month postoperatively and the IOP was controlled with a single glaucoma medication in all cases.

Decrease in BCDVA of ≥ 2 lines (≥ 10 letters) at 3 Months or later

Of all 708 treated eyes of 360 subjects, 10 eyes (1.4%) of 9 subjects (2.5%) cumulatively had a decrease in BCDVA from preoperative measurements of ≥ 2 lines (≥ 10 ETDRS letters) at the 3-month visit or later postoperatively.

The Panel will be asked to comment on their assessment of clinical significance of the adverse events given their nature, severity, and rate.

8.4.2 Pupillometry, Pupil Shape, and Iris Findings

The percent constriction of the pupil (or Percent Change as defined in **Section 7.2.1 Anterior Segment Ischemia** above) at each visit and the change in percent constriction is present in **Table 20**. The mean percent constriction preoperatively (preop) was 42.8% (SD 4.5%). The mean change from preop to each postoperative evaluation of the percent constriction of the pupil was the greatest on the operative day (-11%, SD 7.5%), but there continued to be a decrease in the mean change of the percent constriction from preop at each subsequent postoperative visit with a range of mean change from -0.7% to -2.4%.

As shown in **Table 21**, the mean maximum constriction velocity was 4.686 (SD 0.694) mm/sec preop. The mean change in maximum constriction velocity from preop initially increased slightly during the immediate postoperative period (0.077 mm/sec at Day 1 and 0.056 mm/sec at Week 1), but was decreased from preop at each subsequent visit with a range of mean change from -0.087 mm/sec to -0.183 mm/sec.

FDA Commentary: These results indicate that iris vascular perfusion might have been compromised during surgery with the resultant damage to the pupillary sphincter and a deficit in pupil function.

The applicant indicated that there was a total of 7 eyes with irregular or elliptical pupils at some point during the trial (A5, Vol. I, p. 299). Five of these cases were already discussed above in the AEs section (**Section 8.4.1**), including one eye with removal of the Micro Insert Segments on the day of surgery due to lack of sufficient recovery of the pupil response within the first 6 hours after surgery (indicative of ASI), one eye with Grade 4 ASI and another with findings consistent with Grade 3 ASI, one with a persistent pupil abnormality (consistent with a late sign of ASI), and one with scleral perforation with vitreous prolapse. The remaining 2 cases of abnormal pupil shape were in one eye in association with anterior chamber inflammation and in another eye with mild corneal edema at 1 day postoperatively. The applicant indicates that all pupils returned to their normal shape by 24 months postoperatively with all but one returning to normal shape by 6 months postoperatively.

The applicant also indicated that there was a total of 7 eyes with postoperative iris abnormalities reported during slit lamp examination (A5, Vol. I, p. 282-283 & Table 79, pp. 798-801 (not shown)). Five of these cases had abnormally shaped pupils and were discussed above; the eye with persistent pupil abnormality also had loss of pupillary ruff and iris atrophy. One subject had a constricted pupil on Day 1 followed by spontaneous resolution, which was not reported as an AE. Another subject (a white male who was 47 years old at the time of enrollment) had temporal iris atrophy attributed to normal aging, which was, therefore, not deemed an AE (Pupil Abnormalities Persisting after 3 months).

FDA Commentary: It is unclear why this case of temporal iris atrophy noted at 24 months postoperatively in a subject in his late 40's was attributed to normal aging rather than as a late sign of iris hypoperfusion from iris vasculature damage secondary to the surgery.

In the annual report of the continued follow-up study (VIS-2014-5YR), the applicant reported an additional subject with temporal segment iris atrophy first noted at the 36-month postoperative visit.

8.4.3 Conjunctival Findings

Conjunctival slit lamp examination (SLE) findings are summarized in **Table 22**. The majority of eyes had some degree of conjunctival injection through the Month 6 visit. Preoperatively, 81.2% of eyes (575/708) had no injection compared to 47.2% of eyes (324/686) having no injection at Month 6. Sixty-one eyes (8.8%) still had moderate to severe injection at the 2-month postoperative visit (60 moderate and 1 marked/severe out of 691 eyes at this visit).

All eyes had subconjunctival hemorrhages on the first postoperative day. Four eyes were still noted to have subconjunctival hemorrhages at the Month 3 visit. Two eyes at 12 months and 2 eyes at 24 months had subconjunctival hemorrhages.

All but 21.1% (85/705) of eyes evaluated for conjunctival edema had some degree of edema on the first postoperative day. There were 8 eyes (8/697, 1.1%) that still had moderate conjunctival edema at the 1-month postoperative visit. Twenty-seven out of 689 eyes (3.9%) had some degree of conjunctival edema at the 3-months postoperative visit (689 evaluated - 662 with "None" = 27). There were 8 eyes (8/685,1.2%) at 12 months and none at 24 months with conjunctival edema.

The "Other Conjunctival Findings" category in **Table 22** includes (but is not limited to) conjunctival cysts noted in 4 eyes (4/708, 0.6%) of 3 subjects (3/360, 0.8%) preoperatively and 26 eyes (26/708, 3.7%) of 24 subjects (24/360, 6.7%) postoperatively (A5, Vol. I, p. 278). Sixteen of these cases were reported as AEs, as discussed in **Section 8.4.1** above. The "Other Conjunctival Findings" category in **Table 22** also includes conjunctival retraction. In addition to the 15 cases of conjunctiva retraction requiring surgical intervention discussed above as AEs, there were another 28 eyes of 25 subjects

with conjunctival retraction for a total of 43 eyes (43/708, 6.1%) of 40 subjects (40/360, 11.1%)

*FDA Commentary: Please note that examination findings at interim visits are not reflected in the tables reporting the rates of those findings at each visit, e.g., **Table 22**.*

8.4.4 Corneal Findings

Corneal SLE findings are summarized in **Table 23**. Some degree of corneal edema was reported in 8.5% of eyes at Day 1 and in 2% at Week 1, with severe corneal edema reported in 1 eye at each of these visits. The case at Day 1 was in an eye with scleral perforation discussed above in the AE section. The case that presented at Week 1 resolved by the next visit. There were no cases of corneal edema that met the criteria for an AE, i.e., corneal edema (moderate or severe) after 1 month postoperatively.

The "Other Corneal Findings" category in **Table 23** includes (but is not limited to) corneal dellen in 2 eyes of 2 subjects (one of which was reported as an AE), corneal infiltrate in 1 eye associated with a corneal abrasion, and corneal epithelial defects in 3 eyes of 3 subjects treated as corneal ulcers. The infiltrate and epithelial defects resolved after 1-2 weeks of topical antibiotic therapy.

8.4.5 Anterior Chamber

Table 24 shows the results of the grading of anterior chamber (AC) cells during SLE. At the Day 1 postoperative visit, 4.4% of eyes had some degree of AC cells present. By Week 1, this percentage had decreased to 0.4%.

8.4.6 Position of Micro Insert Segments

Table 25 shows the results of the various subjective assessments of the Micro Insert Segments at each of the postoperative visits.

*FDA Commentary: **Table 25** shows the following:*

- At the 12-month visit, there were 0 segments missing and 156 segments in locations varying from intended (shallow segments, deep segments, segment non-tangential to the limbus, tilted segments, segment too close to the limbus, segment too far away from the limbus).

- At the 24-month visit, there were 3 segments missing and 137 segments in locations varying from intended (shallow segments, deep segments, segment non-tangential to the limbus, tilted segments, segment too close to the limbus, segment too far away from the limbus).

8.4.7 Intraocular Pressure

Intraocular pressure (IOP) at each visit and changes in IOP from baseline are summarized in **Table 26**. On average, the IOP increased during the early postoperative period from preoperatively (preop). The mean change in IOP was 2.9 (SD 4.0) mmHg at Day 1 and 3.0 (SD 4.1) mmHg at Week 1. In addition, 3.7% (26/706) of eyes at postoperative Day 1 and 4.1% (29/702) at Week 1 had IOP > 30 mmHg or an IOP increase > 10 mmHg from preop. A total of 60 eyes out of the 708 treated (8.5%) had an IOP > 30 mmHg or an IOP increase > 10 mmHg from preop at one or more postoperative visits (from Table 86, A5, Vol. I, p. 833 (not shown)). All these instances occurred earlier than at the 3-month visit, except for one at the 3-month visit.

There was a decrease in the mean change in IOP from preop at each postoperative visit starting at 3 months ranging from -0.3 to -0.8 mmHg. From the 6-month visit on, the percentage of subjects with a decrease in IOP from preop of > 5 mmHg was greater than the percentage with such an increase in IOP; the greatest difference between these percentages was at the 12-month visit at which 2.9% of eyes (20/687) had a decrease in IOP from preop of > 5 mmHg and 1.3% (9/687) had an increase.

FDA Commentary: It should be noted that within-eye changes in IOP of more than 5 mmHg are greater than the typical variability of the measurement in healthy eyes (i.e., eyes without glaucoma) [Pearce J and Maddess T. The Clinical Interpretation of Changes in Intraocular Pressure Measurements Using Goldmann Applanation Tonometry: A Review. J Glaucoma 2019; 28:302–306]. Therefore, the percentage of subjects with a decrease in IOP from preop of > 5 mmHg being greater than the percentage with such an increase in IOP from the 6-month visit on may indicate a true change in measurements rather than just measurement variability.

We can compare the changes in IOP from baseline between the deferred treatment (untreated control) group and the immediate treatment group of the randomized substudy. As shown in **Table 27**, the mean IOP of the control group increased slightly from baseline at the 3- and 6-month observation visits, with a mean change of 0.4 (SD 2.6) and 0.7 (SD 2.3) mmHg, respectively, while the mean IOP of the immediate treatment group decreased slightly, with a mean change of -1.0 mmHg (SD 2.6) at 3 months postoperatively and a mean change of -0.6 mmHg (SD 2.3) at 6 months postoperatively.

FDA Commentary: The reason for the decrease in IOP measurements postoperatively is unclear. The segments may lower measurements of intraocular pressure by changing the mechanical properties of the eye, by decreasing aqueous production, by increasing aqueous outflow, or there may be some other reason for the change in measurements not directly related to the device.

8.4.8 Best Corrected Distance Visual Acuity

As shown in **Table 28**, while all eyes had BCDVA of 20/20 or better vision preoperatively, 4 eyes did not have this level of vision at the 12-month postoperative visit

and 3 eyes did not have this level of vision at the 24-month postoperative visit. **Table 29** shows that the mean change in the number of lines of BCDVA from baseline was 0.43 (SD 0.70) at 12 months and 0.46 (SD 0.71) at 24 months postoperatively with 2 (0.3%) eyes having 2 lines or more of loss of BCDVA from baseline at 12 months and no eyes having this degree of change from baseline in BCDVA at 24 months.

8.4.9 Summary of Safety Outcomes

8.4.9.1 Surgical Complications

Out of the 708 eyes of 360 subjects included in the Safety Cohort, there was a total of 15 surgical complications related to the Micro Insert implantation procedures of 13 (1.8%) eyes of 13 (3.6%) subjects. These included 8 scleral perforations that occurred in 8 eyes (1.1%) of 8 subjects (2.2%), 2 eyes of 2 subjects with decreased IOP, 2 eyes of 2 subjects with shallow tunnels in 1 quadrant, 1 subject with nausea and vomiting, and 2 eyes of 2 subjects with inadequate pupillary response within the first 6 hours following surgery, an indication of ASI that resulted in Micro Insert segment removal.

8.4.9.1.1 SCLERAL PERFORATIONS

Vitreous prolapse was seen with 5 of the 8 reported cases of scleral perforation. Sequelae of the scleral perforations included PVD with retinal hemorrhage, inflammatory reaction with grade 3+ AC cells, marked to severe conjunctival injection and edema, hypotony, and marked to severe corneal edema with Descemet's folds, the formation of posterior synechiae in 3 quadrants, and inadvertent bleb creation (unrecognized for approximately 6 months) with a significant decrease in IOP to 6 mmHg, which resulted in a decrease in BCDVA from preoperative measurements of $\geq$ 2 lines with nuclear sclerosis and posterior and anterior subcapsular cataract formation that required cataract extraction.

8.4.9.1.2 ANTERIOR SEGMENT ISCHEMIA (ASI)

There was a total of 5 eyes (5/708, 0.7%) of 5 subjects (5/360, 1.4%) with ASI – 2 subjects with abnormal pupil response without adequate recovery in their primary eyes following surgery on the operative day, 1 with Grade 4 ASI, 1 with Grade 3 ASI, and 1 with a chronically abnormal pupil and iris atrophy. There was a total of 7 (1.0%) eyes with irregular or elliptical pupils at some point during the trial and a total of 7 eyes with postoperative iris abnormalities on slit lamp examination. In addition, analyses of the pupillometry results revealed that there was a decrease in the percent constriction of the pupil at each postoperative evaluation from preoperatively, which was greatest on the operative day (mean -11%, SD 7.5%), but which continued to be present at each subsequent postoperative visit (mean change from -0.7% to -2.4%). The mean change in maximum constriction velocity from preop initially increased slightly during the early postoperative period (0.077 mm/sec at Day 1 and 0.056 mm/sec at Week 1), but was decreased from preop at each subsequent visit with a range of mean change from -0.087 mm/sec to -0.183 mm/sec. These changes, while small, raise the possibility that iris vascular perfusion compromise during surgery may have resulted in damage to the pupillary sphincter and a persistent deficit in pupil function on average.

8.4.9.2 Secondary Surgical Interventions

Secondary surgical interventions during the trial included, but may not have been limited to, Micro Insert segment removals in 13 eyes (1.8%) of 8 subjects (2.2%), conjunctival re-approximation due to conjunctival retraction and/or exposed Micro Insert segments in 15 (2.1%) eyes of 15 (4.2%) subjects, laser retinopexy in 2 eyes of 2 subjects, cataract extraction in 3 eyes of 2 subjects, conjunctival cyst removal in 2 eyes of 2 subjects, and LASIK in 1 eye, for a total of 36 secondary surgical interventions, a rate of 5.1% (36 events/708 eyes). It should be noted that a total of 43 eyes (6.1%) of 40 subjects (11.1%) had conjunctival retraction. Following the trial, all segments were removed from 18 eyes of 9 subjects, 2 segments (of 4) were removed from 2 eyes of 1 subject, and 4 subjects each had 1 segment removed from 1 eye, as compared to the 13 eyes (1.8%) of 8 subjects (2.2%) with all segments removed during the trial. Also, 2 subjects had refractive surgery for near vision complaints.

8.4.9.3 Other Adverse Events (AEs) and Abnormal Findings

8.4.9.3.1 OCULAR SURFACE

Commonly reported AEs included dry eye signs requiring prescription medication after 6 months (12.3% of eyes, 12.2% of subjects) and conjunctival AEs, such as, moderate or severe conjunctival injection at 3 months postoperatively or later (4.5% of eyes, 5.6% of subjects), subconjunctival hemorrhage after 3 months postoperatively (2.3% of eyes, 4.2% of subjects, and conjunctival cyst (just over 2% of eyes and 4% of subjects). It should be noted, however, that while 0.6% of eyes of 0.8% of subjects (3/360,) had conjunctival cysts preoperatively, a total of 3.7% of eyes of 6.7% of subjects had conjunctival cysts postoperatively. Conjunctival abnormalities noted on SLE that were not considered AEs were also common. While 18.8% of eyes had some degree of conjunctival injection preoperatively, the majority of eyes had some degree of conjunctival injection postoperatively through the Month 6 visit (52.8% of eyes at 6-months postoperatively). Sixty-one eyes (8.8%) still had moderate to severe injection at the 2-month postoperative visit (60 moderate and 1 marked/severe out of 691 eyes at this visit). All eyes had subconjunctival hemorrhages on the first postoperative day. Four eyes were still noted to have subconjunctival hemorrhages at the Month 3 visit. Two eyes at 12 months and 2 eyes at 24 months had subconjunctival hemorrhages. All but 21.1% (85/705) of eyes evaluated for conjunctival edema had some degree of edema on the first postoperative day. There were 8 eyes (8/697, 1.1%) that still had moderate conjunctival edema at the 1-month postoperative visit. Twenty-seven out of 689 eyes (3.9%) had some degree of conjunctival edema at the 3-months postoperative visit (689 evaluated - 662 with "None" = 27). There were 8 eyes (8/685,1.2%) at 12 months and none at 24 months with conjunctival edema.

Corneal AEs included, but were not limited to, abrasion > 2mm after 1 week in 5 (0.7%) eyes of 5 (1.4%) subjects and 1 report each of dellen after 1 week, infiltrate or ulcer, neovascularization, and scar. However, there was a total of 2 eyes of 2 subjects with corneal dellen and 3 eyes of 3 subjects with corneal epithelial defects treated as corneal ulcers (in addition to an eye with corneal infiltrate associated with a corneal abrasion).

Some degree of corneal edema was reported in 8.5% of eyes at Day 1 and in 2% at Week 1, with severe corneal edema reported in 1 eye at each of these visits.

8.4.9.3.2 ANTERIOR CHAMBER (AC)

At the Day 1 postoperative visit, 4.4% of eyes had some degree of AC cells present. By Week 1, this percentage had decreased to 0.4%.

8.4.9.3.3 INTRAOCULAR PRESSURE (IOP)

There were 5 eyes (0.7%) of 5 subjects (1.4%) with increase in IOP of > 10mm Hg over baseline or IOP > 30mm Hg at two consecutive visits at 1 week or later, which were reported as AEs. However, a total of 8.5% of treated eyes had an IOP > 30 mmHg or an IOP increase > 10 mmHg from preop at one or more postoperative visits at or before the 3-month visit. In addition, 3.7% of eyes at postoperative Day 1 and 4.1% at Week 1 had IOP > 30 mmHg or an IOP increase > 10 mmHg from preop. On average, the IOP increased during the early postoperative period from preop (mean 2.9 mmHg at Day 1 and 3.0 mmHg at Week 1). By 3 months and at each subsequent visit, there was a decrease in the mean change in IOP from preop (-0.3 to -0.8 mmHg), and, from the 6-month visit on, the percentage of subjects with a decrease in IOP from preop of > 5 mmHg was greater than the percentage with such an increase in IOP, with the biggest difference in these percentages seen at the 12-month visit (2.9% of eyes with a decrease vs. 1.3% with an increase. These results of a decrease in IOP measurements following surgery for the overall Safety Cohort are supported by the results of the randomized substudy. When comparing changes in IOP from baseline between the two arms of the randomized substudy, the IOP of the control group increased slightly from baseline at the 3- and 6-month observation visits (mean change of 0.4 and 0.7 mmHg, respectively), while the IOP of the immediate treatment group decreased slightly (mean change of -1.0 mmHg at 3 months postoperatively and a mean change of -0.6 mmHg at 6 months postoperatively).

8.4.9.3.4 BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)

A total of 10 eyes (1.4%) of 9 subjects (2.5%) cumulatively had a decrease in BCDVA from preoperative measurements of $\geq$ 2 lines ($\geq$ 10 ETDRS letters) at the 3-month visit or later postoperatively reported as AEs. When only considering those eyes available for analysis at the applicable visits and BCDVA loss of > 2 lines (rather than $\geq$ 2 lines), 2 (0.3%) eyes fit the category of BCDVA loss at the 12-month visit and no eyes fit this category at the 24-month visit. The mean change in the number of lines of BCDVA from preop was 0.43 (SD 0.70) at 12 months and 0.46 (SD 0.71) at 24 months postoperatively. While all eyes had BCDVA of 20/20 or better vision preoperatively, only 4 eyes did not have this level of vision at the 12-month postoperative visit and only 3 did not have this level of vision at the 24-month postoperative visit.

The Panel will be asked to comment on whether the data submitted provide reasonable assurance of safety of the device for the proposed indication for use.

8.5 Effectiveness Results

8.5.1 Primary Effectiveness Endpoint

First Co-Primary Effectiveness Endpoint:

Although the applicant pre-specified in the protocol that the 12-month timepoint was the primary timepoint for the analysis, in Amendment 5 (P170040/A005), upon FDA's recommendation in the first "not approvable" decision, the applicant presented a post-hoc analysis of the data at the 24-month visit in addition to the 12-month analysis.

The effectiveness results at both 12 and 24 months are presented below for both the ITT and the post-hoc BEC populations.

In addition, during review of the PMA, FDA requested that the applicant present analyses of monocular DCNVA like those for the ITT population for the treated fellow eyes and all primary and fellow eyes together to ensure that the results were similar.

FDA Commentary: It should be noted that post-hoc analyses introduce uncertainty into the findings; statistical inferences should be drawn with caution.

12-month Results:

As shown in **Table 30**, for the ITT population, 277 of 350 (79.1%) primary eyes had DCNVA 20/40 or better and at least 10 letters of improvement on the ETDRS chart from baseline (responder). For this analysis, four eyes that had had removals prior to the 12-month timepoint were counted as failures and 346 were available for analysis at the 12-month visit for a total of 350 primary eyes of 350 subjects included in the analysis. The lower bound of the 95% CI for this 12-month responder rate considering the exact binomial distribution was 74.5%, which is lower than target value of 75%.

FDA Commentary: Please note that the lower bound of the two-sided 95% CI is equivalent to the pre-specified one-sided 97.5% lower CI. Therefore, the 1st co-primary effectiveness endpoint was not achieved.

As shown in **Table 31**, 266 of 342 (77.8%) fellow eyes were responders. The lower bound of the 95% CI for this 12-month responder rate was 73.0%. Also as shown in **Table 31**, when primary and fellow eyes were combined the responder rate was 78.5% (543/692) with a lower 95% CI of 74.2%. Both of these CIs are below the 75% target.

As shown in **Table 30**, for the post-hoc BEC population, 275 of 340 (80.9%) primary eyes were responders. The lower bound of the 95% CI for rate was 76.3%. This is higher than the target value of 75%.

As indicated in **Table 8**, there were six subjects who missed the 12-month visit and four who were lost to follow-up in the ITT population. The primary eyes of these missing

subjects were not included in the primary analysis of the 1st co-primary effectiveness endpoint. As indicated in **Table 9**, there were six subjects who missed the 12-month visit and two who were lost to follow-up in the BEC population. The primary eyes of these missing subjects were not included in the post-hoc analysis of the 1st co-primary effectiveness endpoint using the BEC population. Sensitivity analyses were conducted to examine the effect of the missing data on the 1st co-primary endpoint. The results for each method of imputation, as defined in **Section 7.9** above, are as follows:

- Best case method: As shown in **Table 30**, for the ITT population, 285 of 360 (79.2%) primary eyes were considered responders at 12-months. The lower bound of the 95% CI was 74.6%, which was lower than the target value of 75%. For the BEC population, 282 of 348 (81.0%) primary eyes were considered responders. The lower bound of the 95% CI was 76.5%, which was higher than the target value of 75%.

FDA Commentary: By the best case sensitivity analysis, the 1st co-primary effectiveness endpoint (12 months) was not met for the pre-specified ITT population and was met for the post-hoc BEC population. It should be noted that the definition of "best case" analysis in Section 7.9 is different from the commonly understood definition of "best case" analysis, which all missing data is imputed as a success.

- Worst case method: As shown in **Table 30**, for the ITT population, 279 of 360 (77.5%) primary eyes were considered responders at 12 months. The lower bound of the 95% CI was 72.8%, which was lower than target value of 75%. For the BEC population, 277 of 348 (79.6%) primary eyes were considered responders. The lower bound of the 95% CI was 75.0%, which was the minimum target value.

FDA Commentary: By the worst case sensitivity analysis, the 1st co-primary effectiveness endpoint was not met for the pre-specified ITT population and was met for the post-hoc BEC population. It should be noted that the definition of "worst case" analysis in Section 7.9 is different from the commonly understood definition of "worst case" analysis, which is all missing data is imputed as a failure.

- Tipping point method: As shown in **Figure 11,** for the ITT population at 12-months, the target of the lower 95% CI for the responder rate of 75% or more could be achieved only if all 10 missing subjects were counted as a successes. As shown in **Figure 12**, for the BEC population at 12-months, the target of the lower 95% CI for the responder rate of 75% or more could be achieved when two or more of the 10 missing subjects were counted as successes.

Post-hoc **24-month** Results:

As shown in **Table 32**, for the ITT population, 289 of 344 (84.1%) primary eyes had DCNVA 20/40 or better and at least 10 letters of improvement on the ETDRS chart from baseline (responder). For this analysis, eight eyes that had removals prior to the 24-month timepoint were counted as failures, 337 were available for analysis at the 24-month visit,

but one eye was excluded that had intraocular lens (IOL) implantation, for a total of 344 primary eyes of 344 subjects included in the analysis. The lower bound of the 95% CI for this 24-month responder rate considering the exact binomial distribution was 79.7%, which is higher than the target value of 75%.

As shown in **Table 33**, 275 of 334 (82.3%) fellow eyes were responders. The lower bound of the 95% CI for this 24-month responder rate was 77.8%. Also as shown in **Table 33**, when primary and fellow eyes were combined the responder rate was 79.2% (564/678) with a lower 95% CI of 79.2%. Both of these CIs are above the 75% target.

FDA Commentary:
It should be noted when considering the analysis of all treated eyes together that the correlation between the eyes of subjects was not taken into account and is unknown.

As shown in **Table 32**, for the BEC population, 278 of 335 (85.7%) primary eyes were responders. The lower bound of the 95% CI for this rate was 81.5%. This is higher than the target value of 75%.

The results for each method of imputation, as defined in **Section 7.9** above, are as follows:

- Best case method: As shown in **Table 32,** ITT population, 301 of 360 (83.6%) primary eyes were considered responders at 24-months. The lower bound of the 95% CI was 79.4%, which was higher than the target value of 75%. For the BEC population, 297 of 348 (85.3%) primary eyes were considered responders. The lower bound of the 95% CI was 81.2%, which was higher than the target value of 75%.

- Worst case method: As shown in **Table 32**, for the ITT population, 291 of 360 (80.8%) primary eyes were considered responders at 24 months. The lower bound of the 95% CI was 76.4%, which was higher than target value of 75%. For the BEC population, 289 of 348 (78.7%) primary eyes were considered responders. The lower bound of the 95% CI was 78.7%, which was higher than the target value.

Second Co-Primary Effectiveness Endpoint:

In response to the submission of Supplement 2 of IDE (b) (4), FDA relayed a Study Design Consideration to indicate that we disagreed with the method for handling missing data for the primary effectiveness analysis of the randomized substudy results that was specified in the protocol, because it did not include imputation of missing data in every case. However, the applicant did not revise the protocol to address this concern. During review of the PMA, FDA requested that the applicant provide the analysis using the following revised imputation method:

- For the Randomized Control Group: In the absence of 6-month visit data, utilize the nearest available data recorded between and including the 3-month visit up to the 6-month visit, as described in the protocol. In the absence of any observed data between the 3-month visit and 6-month visit, rather than not imputing the missing data, the applicant was asked to impute the missing data using the last observation carried forward (including data at baseline)

- For the Randomized Surgery Group: As described in the protocol, impute explanted primary eyes as failures and, in the absence of 6-month visit data, use the nearest recorded data after 6 months up to and including the 12-month visit. In the absence of any observed data between 6 and including 12 months, rather than not imputing the missing data, impute the missing data using data recorded between and including the 3-month visit up to the 6-month visit. If this data is also missing, the applicant was asked to impute the data from the last observation carried backward, and if still not available, the last observation carried forward (including data at baseline).

By this revised method, for the two subjects randomized to the deferred treatment group with missing data at the 6-month observation timepoint, the missing DCNVA data was imputed by data available at baseline. For the four subjects randomized to the immediate treatment group, the missing 6-month data was imputed by available 12-month data for three subjects and by the baseline data for one subject. For further details regarding how missing data was imputed by both imputation methods, please see **Table 34**.

As shown in **Table 35**, there was a statistically significant difference ($p < 0.001$) in the percentage of substudy subjects with DCNVA of 20/40 or better and a gain of at least 10 letters on the ETDRS chart in the primary eye regardless of imputation method - 2/31 (6.5%) in the deferred treatment (untreated control) group vs. 18/29 (62.1%) in the immediate treatment group by the revised imputation method and 2/29 (6.9%) in the deferred treatment group vs. 18/28 (64.3%) in the immediate treatment group by the protocol-defined imputation method.

FDA Commentary: The responder rate for the randomized immediate treatment group was statistically significantly greater than for the randomized control group ($p<0.001$). Therefore, the 2nd co-primary endpoint was met.

The following tipping point sensitivity analysis was provided:

- Tipping point method: The applicant stated, "Based on 2 deferred treatment eyes and 4 control subjects with missing 6-month DCNVA, there are 15 combinations of success/failure assumptions (ranging from 0 success for both groups to 2 control/4 immediate-treatment success) for the tipping point analysis." As shown in **Table 36**, the Fisher's exact tests p-values were less than 0.05 for all combinations of success and failure.

8.5.2 Additional Effectiveness Analyses

A full list of the effectiveness analyses tables and figures submitted by the applicant can be found in **Appendix 2 – List of PMA Effectiveness Tables and Figures.**

This section summarizes the non-hypothesis-driven analyses that FDA believed were the most pertinent for supporting the reasonable assurance of effectiveness for the proposed indications for use.

8.5.2.1 Distance Corrected Near Visual Acuity (DCNVA)

Table 37 shows that for the ITT primary eyes 2/360 (0.6%) pre-operatively, 289/347 (83.5%) at 6 months postoperatively, 313/346 (90.5%) at 12 months postoperatively, and 314/337 (93.5%) at 24 months postoperatively had DCNVA of 20/40 or better. No eyes in this cohort had DCNVA of 20/25 or better at baseline. However, 183/346 (52.9%) primary eyes at 12 months and 188/336 (56.0%) at 24 months had this level of vision. The number of ITT primary eyes with DCNVA of 20/20 or better was 84/346 (24.3%) at 12 months and 86/336 (25.6%) at 24 months. See **Table 38** for the same information for the primary eyes of subjects in the randomized substudy at baseline and the 3- and 6-month visits stratified by treatment group.

Table 39 shows that the mean change in the number of lines of DCNVA from baseline for the ITT primary eyes was 2.80 (SD 1.52), which is equivalent to 14 letters (2.8 lines x 5 letters/line), at 6 months, 3.15 (SD 1.44) at 12 months and 3.35 (SD 1.33) at 24 months. This table also stratifies the percentage of subjects at each postoperative timepoint by the number of lines gained or lost in DCNVA from baseline. **Table 40** contains similar information to **Table 39**, except for the randomized substudy population. The mean change in the number of lines of DCNVA from baseline for the primary eyes in the control group was 0.28 (SD 1.27) and in the immediate treatment group was 2.68 (SD 1.42).

FDA Commentary: The mean change in the number of lines of DCNVA from baseline were similar for the ITT population and the immediate treatment group (treatment group) of the randomized substudy at 6 months. The difference in the mean change of DCNVA between the two arms of the randomized substudy at 6 months was 2.40 lines (2.68 – 0.28) in favor of the treatment group.

8.5.2.2 Uncorrected Visual Acuity (UCVA)

The device is intended for bilateral implantation to "improve unaided near vision" in patients with low refractive error based upon the proposed indications for use (IFU). Because the intended patient population has good uncorrected distance vision, FDA anticipated that patients will expect to achieve good unaided near vision while maintaining good unaided distance vision with the device. However, the hypothesis-tested primary effectiveness endpoint parameter was unilateral DCNVA, which does not

directly support the unaided bilateral visual acuity claims in the IFU. Therefore, the additional analyses below were performed that more directly reflect the proposed IFU.

Binocular Uncorrected Near Visual Acuity (UCNVA)

Table 41 shows that all subjects in the ITT population at each visit including preoperatively had binocular UCNVA of 20/80 or better. Preoperatively, 100/360 (27.8%) subjects had 20/40 or better binocular UCNVA. At 12 months postoperatively, 328/341 (96.2%) ITT subjects had this level of binocular UCNVA, and at 24 months, the number was 316/329 (96.0%). The binocular UCNVA was 20/25 or better, in 8/360 (2.2%) ITT subjects preoperatively, 235/341 (68.9%) at 12 months postoperatively, and 239/329 (72.6%) at 24 months. The binocular UCNVA was 20/20 or better, in 2/360 (0.6%) ITT subjects preoperatively, 107/341 (31.4%) at 12 months postoperatively, and 126/329 (38.3%) at 24 months.

As shown in **Table 42**, the mean change in the number of lines of binocular UCNVA from baseline for the ITT subjects was 2.85 (SD 1.40) at 12 months and 3.02 (SD 1.35) at 24 months. This table also stratifies the percentage of subjects at each postoperative timepoint by the number of lines gained or lost in binocular UCNVA from baseline.

Summary statistics for binocular UCNVA are represented as box plots in **Figure 13** at the preoperative and 6-, 12-, 18-, and 24-month postoperative visits for only those subjects that had responded to question #11 on the NAVQ and had binocular UCNVA available at that visit. Data for 359 subjects are represented in the box plot for the preoperative visit and for 337, 341, 326, and 330 subjects for the 6-, 12-, 18-, and 24-month postoperative visits, respectively.

Binocular uncorrected distance visual acuity (UCDVA) was not measured during the trial.

Within-Subject Changes from Baseline in UCNVA vs. UCDVA

Figure 14 and Figure 15 are scatter plots in which each dot represents the primary eye of an individual subject in the ITT population. The x-axis represents the change in UCNVA from baseline and the y-axis represents the change in UCDVA from baseline. The vertical reference line is drawn at a gain of 10 letters from baseline of UCNVA and the horizontal reference line is drawn at a loss of 5 letters from baseline of UCDVA. These reference lines divide the plot into four quadrants.

FDA Commentary: A change of ≤1 line (5 letters) on the ETDRS chart is typically considered to be within the measurement error. A change of ≥2-lines (10 letters) is typically considered to be clinically significant (e.g., FDA-recognized standard ISO 11979-7).

The upper right quadrant (Quadrant 1) contains all eyes with a gain of at least 10 letters in UCNVA and no more than a 5-letter loss (or a gain) in UCDVA. The upper left quadrant (Quadrant 2) contains all eyes with a gain of less than 10 letters or a loss of

UCNVA and no more than a 5-letter loss in UCDVA. The lower left quadrant (Quadrant 3) contains all eyes with gain of UCNVA of less than 10 letters or a loss of UCNVA and a loss of UCDVA of more than 5 letters. The lower right quadrant (Quadrant 4) contains all eyes with gain of UCNVA of 10 letters or more in UCNVA, but a loss of more than 5 letters of UCDVA.

FDA Commentary: Quadrant 1 represents the most favorable outcomes in terms of UCVA and Quadrant 3 represents the least favorable.

Figure 14 shows that of the 346 primary eyes in the ITT cohort with UCNVA and UCDVA data available at both baseline and 12 months postoperatively, 260 (75.1%) were in Quadrant 1, 77 (22.3%) were in Quadrant 2, 6 (1.7%) were in Quadrant 3, and 3 (0.9%) were in Quadrant 4. **Figure 15** shows that of the 335 primary eyes in the ITT cohort with UCNVA and UCDVA data available at both baseline and 24 months postoperatively, 262 (78.2%) were in Quadrant 1, 55 (16.4%) were in Quadrant 2, 8 (2.4%) were in Quadrant 3, and 10 (3.0%) were in Quadrant 4.

8.5.2.3 Near Add Power Required

All visual acuities were measured using the OPTEC 6500 view-in system (Stereo Optical). The add power was determined by adding plus lenses using this system at a simulated distance of 40 cm.

FDA Commentary: Please note that, during testing in OPTEC 6500's view-in system, the subject cannot be monitored for squinting, which improves visual acuity by increasing the depth of focus.

As shown in **Table 43**, for the primary eyes of the ITT population, the near add power required preoperatively ranged from +1.25 to +2.50 D with a mean of the +1.62 D (SD 0.31). At 6 months postoperatively, the add ranged from 0.00 to +2.00 D with a mean of +0.79 D (SD 0.43) and a mean change from baseline of -0.86 (SD 0.52). At 12 months postoperatively, the add ranged from 0.00 to +2.00 D with a mean of +0.68 D (SD 0.45) and a mean change from baseline of -0.99 (SD 0.56). At 24 months postoperatively, the add ranged from 0.00 to +1.75 D with a mean of +0.58 D (SD 0.45) and a mean change from baseline of -1.07 (SD 0.58).

Similar information is shown in **Table 44** for the randomized substudy population. At baseline, the near add power required ranged from +1.25 to +2.25 D with a mean of the +1.82 D (SD 0.31) for the primary eyes of the deferred treatment (control) group, and from +1.25 to +2.50 D with a mean of the +1.77 D (SD 0.39) for the primary eyes of the immediate treatment (treatment) group. At the 6-month visit, the add ranged from +1.25 to +2.50 D with a mean of +1.82 D (SD 0.35) and a mean change from baseline of -0.02 (SD 0.21) in the control group, and ranged from 0.00 to +1.50 D with a mean of +0.84 D (SD 0.37) and a mean change from baseline of -0.92 (SD 0.50) D in the treatment group.

FDA Commentary: The difference in the mean change from baseline of the near add power required between the treatment group and control group of the randomized substudy at 6 months was 0.90 D [-0.92 – (-0.02)].

8.5.2.4 Defocus

Defocus curve testing was limited to subjects in the randomized substudy. It was performed monocularly behind a phoropter with the subjects' best distance correction dialed in and using a computer-controlled LCD distance chart with ETDRS letters at 6 m with subjects viewing the smallest letters corresponding to their BCDVAs. Starting with -4.00 D added to the distance correction, the lens power in the phoropter was progressively reduced then increased in +0.50-D increments through the addition +2.00 D to the distance correction with the visual acuity being recorded at each step.

The defocus curves are presented in **Figure 16** for the primary eyes of the deferred treatment (control) group with available data at baseline (N=30) and observation at 6 months (N=28) and in **Figure 17** for the primary eyes of the immediate treatment (treatment) group with available data at baseline (N=29) and at 6 months postoperatively (N=24). The mean change in logMAR visual acuity (VA) from baseline to the 6-month visit for the primary eyes in each group is presented for each step in lens power in **Table 45**. As shown in **Table 45**, at a lens power of -2.50 D, which corresponds to a near testing distance of 40 cm, the mean change in VA was -0.070 logMAR for the control group and -0.169 logMAR for the treatment group.

FDA Commentary: Based on the defocus curve testing, the difference in the mean change in logMAR VA from baseline to the 6-month visit between the primary eyes of the treatment group and the control group is -0.099 logMAR [-0.169 – (-0.070)], which is equivalent to 1 line or 5 letters on the ETDRS chart in favor of the treatment group.

Given the lack of masking of the subjects and testers, it is possible the placebo effect contributed some degree of improvement in these subjective outcomes.

*Please note that these results are not consistent with the change in DCNVA outcomes discussed in **Section 8.5.2.1** (The difference in the mean change of DCNVA between the two arms of the randomized substudy at 6 months was 2.40 lines (2.68 – 0.28 lines) in favor of the treatment group.)*

8.5.2.5 at Wavefront

Wavefront aberrometry was performed only on subjects in the randomized substudy using the using the iTrace Wavefront Aberrometer (Tracey Technologies Corp.) to determine whether there was a difference between the deferred treatment (control) group and the immediate treatment (treatment) group in the "static" measurements in each Zernike wavefront term at the 6-month visit compared to baseline, and in the "dynamic"

change in any of the Zernike wavefront terms as subjects fixated at various test distances at the 6-month visit. All eyes were tested using a distance target at 6 m and near targets at five different testing distances. During each examination, measurements were repeated three times at each distance.

The "iTrace Aberrometer Accommodation Testing Protocol" (provided in Amendment 3) described the testing procedures and analyses to be performed. In Amendment 3, comparisons between baseline and 6-month values for each arm of the substudy were tested for significance using paired Student's t-test, and group differences were compared using Student's t-test, using Analyse-It, Version 4.80 (Analyse-It, Leeds, UK). The applicant indicated that all statistical analyses for this substudy were all considered "exploratory." Note that the IDE protocol for the clinical study did not include any pre-specified hypothesis tests related to the substudy, except for the 2nd co-primary effectiveness endpoint regarding DCNVA 20/40 or better and gain of ≥10 letters. (All the wavefront analyses presented in the Amendment 3 report, were analyzed over a pupil diameter of 2 mm (zone 1 (Z1)).).

Data were analyzed for the primary eye at baseline and the 6-month visit for both the Immediate Treatment and Deferred Treatment groups. The following wavefront Zernike descriptors were analyzed:

- Spherical Equivalent (Defocus) – C04
- Oblique Astigmatism – C03
- Vertical Astigmatism – C05
- Vertical Coma – C07
- Horizontal Coma – C08
- Secondary astigmatism – C11
- Spherical aberration – C12
- Vertical Secondary astigmatism – C13

Wavefront aberrometry was performed on substudy subjects out to 2-years postoperatively, but there was no control group after 6-months. This section of the summary summarizes the wavefront results from the first 6 months of the trial, allowing comparison to the randomized control group.

Note that the protocol for this testing (provided in Amendment 3 of the PMA) states that the iTrace measurement methodology would, "follow the general methods described in the following published studies:

- *Win-Hall DM, Glasser A. Objective accommodation measurements in pseudophakic subjects using an autorefractor and an aberrometer. J Cataract Refract Surg. 2009 Feb;35(2):282-90.*
- *Win-Hall DM, Glasser A. Objective accommodation measurements in prepresbyopic eyes using an autorefractor and an aberrometer. J Cataract Refract Surg. 2008 May;34(5):774-84."*

FDA Commentary: The second reference above, which reports a study of subjects 38 – 49 years old, states, "This study shows the viability of using the iTrace aberrometer … for clinical objective accommodation measurements." The study reported that even on a 49-year-old subject (who had the lowest accommodative amplitude of the subjects), the iTrace device was able to measure an objective amplitude of 0.7 diopters. Thus, it appears that the methodology used was adequate to measure small, but clinically meaningful levels of accommodation.

FDA Commentary: Because the wavefront aberrometry statistical analyses from this substudy were considered "exploratory" by the applicant, all p-values presented here should be considered "nominal p-values." We note that only the analyses provided in Amendment 3 were based upon the statistical testing described in the "iTrace Aberrometer Accommodation Testing Protocol." In Amendment 5, the applicant included additional wavefront analyses in addition to the analyses provided in Amendment 3. However, these analyses and the associated statistical hypothesis test results were not specified in the original wavefront aberrometry protocol and thus, were post-hoc. We also note that no statistical hypothesis testing for this substudy (in either Amendments 3 or 5) accounted for multiplicity of testing.

Amendment 3 Analyses per iTrace Protocol

Static Testing

To determine whether the treatment may alter the aberrations of the eye to improve near vision, testing was performed monocularly on the eye without refractive correction in place while viewing the 6-m distance target.

There were no statistically significant differences in the Zernike wavefront parameters with static testing except for oblique astigmatism and horizontal coma, as shown in **Table 46**. For oblique astigmatism, the difference between baseline (-0.01) and 6-month (-0.02) values in the treatment group was statistically significant ($p = 0.02$). The applicant remarked that this, "does not represent a clinically significant change." The difference between arms was statistically significant (0.01 in the control vs. -0.02 in the treatment arm) ($p = 0.007$). For horizontal coma, the difference between baseline (0.003) and 6-month (0.002) values in the control group was statistically significant ($p = 0.0001$), but the treatment group did not show a statistically significant change from baseline.

FDA Commentary: While the differences in static oblique astigmatism measurements within the treatment group between baseline and 6 months postoperatively and between arms at 6 months were statistically significant, they were not clinically significant (per the applicant's evaluation). In addition, the differences in the measurements between baseline and 6 months for each arm and the differences in the measurements between arms were not clinically significant for any of the other wavefront parameters analyzed (per the applicant's evaluation).

Dynamic Change

To determine whether the treatment may improve accommodation, testing was performed with eye corrected for distance using a soft contact lens. The change from the distance (6m) to each consecutive near target stimulus (1 m, 66 cm, 50 cm, 40 cm, and 33 cm) at 6 months for each of the wavefront parameters, were compared between the treatment arm and the control arm. Significance was tested with Student's t-test. (Forty centimeters is the distance of particular interest to support the IFU, because it is the standard testing distance used in the trial for assessing the primary effectiveness endpoint of distance-corrected near visual acuity.)

There were no statistically significant differences between substudy arms in "dynamic" changes from distance to any near point for any of the Zernike wavefront parameters except for vertical coma measured at 1 m ($p = 0.03$), as shown in **Table 47**. The change was 0.0006 in the control group and -0.0005 in the treatment group. To see the dynamic change results for each wavefront parameter at each "near" target distance, please refer to **Table 54**, **Table 55**, **Table 56**, **Table 57**, **Table 58**, and **Table 59** in **Appendix 3 - Dynamic Wavefront Tables**.

FDA Commentary: The applicant's report indicated there were no clinically significant dynamic changes from distance to near in either arm or differences between arms for any wavefront parameters using the near target at any distance tested.

Amendment 5 Analyses

In Amendment 5, the applicant presented new analyses of the Zernike coefficients. (As noted above, none of these analyses were specified in the "iTrace Aberrometer Accommodation Testing Protocol.") These analyses primarily looked at changes from baseline in the "dynamic" measurements, analyzed over pupil diameters of 3 mm (zone 2, or Z2) and 5 mm (zone 3, or Z3). For the changes from baseline for the randomized subjects at 6 months, they compared the two arms ("immediate treatment" and "deferred treatment"). They combined the primary eyes from the "immediate treatment" arm and the "deferred treatment" arm into a single cohort (without a control group) looking only at changes from baseline at 6 months, 12 months, and 24 months. In addition, the statistical analyses included both parametric and non-parametric methods, and additional Zernike coefficients were used from C0 to C40. These additional analyses found a number of new, statistically significant changes from baseline in some Zernike coefficients. However, the applicant indicated that the changes did not reach levels of clinical significance. They wrote in their conclusion regarding the wavefront results:

> The only dynamic finding related to the change induced by viewing of a near target was a small but statistically significant change in C04 Defocus Zernike. This result was consistent in both the full cohort analysis and the Intended Use analysis. Although the change in the CO4 Defocus term was statistically significant over zones 2 and 3, the magnitude of the average change was small and most likely not clinically significant.

…

There are several possible reasons why this study failed to show significant changes in either the lower or the higher order aberrations that would correlate with the significant improvement in near vision seen in this VisAbility clinical trial. At the outset of the study, the applicant had concerns about the ability of the iTrace Wavefront Aberrometer to capture the dynamic response to a near target since the technology provides a snapshot of what is happening at a time often several seconds after a near target is presented. At the time of the study initiation, however, the iTrace Wavefront Aberrometer was the only aberrometer available…

FDA Commentary: In comparing test and control arms at 6 months, the Amendment 5 report states that although statistically significant changes were found, "no clinically significant changes were found" (A005, V1, p364). For example, the differences between arms for C03 (oblique astigmatism) were all less than 0.1 D.

We note that changes due to accommodation would be reflected in changes in the C04 Defocus term. The statistically significant changes related to the C04 Defocus term at 12 and 24 months, correspond to mean changes in spherical equivalent ranging from 0.071 D to 0.165 D.

The applicant has noted that none of the aberrometry data is indicative of a clinically significant change, and they suggest that this iTrace aberrometer is not sufficiently sensitive to detect clinically significant dynamic changes (that correspond to the improvements seen in subjective acuity measurements). Based on FDA's assessment, while it is possible that there is some unusual minor change in the wavefront that is not apparent from the analyses of the Zernike components, the iTrace appears to be capable of measuring most clinically significant dynamic optical changes, as noted in Win-Hall DM and Glasser A (2008), mentioned above.

8.5.2.6 Manifest Refractive Spherical Equivalent (MRSE) & MRSE and Cylinder Stability

Manifest refractive spherical equivalent (MRSE) and stability were analyzed for all treated eyes (Safety Cohort). MRSE and change in MRSE from baseline to each postoperative time point are shown in **Table 48**. Analyses of stability of MRSE is shown in **Table 49**.

As shown in **Table 48**, the mean pre-operative MRSE was +0.126 (SD 0.265) D. After surgery, there was a myopic shift in MRSE from pre-operative measurements that peaked at the 2-month postoperative visit (mean MRSE -0.047 D, SD 0.331, **Table 48**). A shift back toward the hyperopic direction occurred between 2 and 3 months, as shown in **Table 49** (mean change 0.084 D, SD 0.266), with the mean MRSE returning close to the pre-operative value at 6 months, as shown in **Table 48** (mean +0.144, SD 0.327). The

mean MRSE continued to become more hyperopic through the end of the trial, but the refractive error remained low, with a mean MRSE at 24 months of +0.252 D (+0.385). No subject had a change in MRSE from baseline of > 2.00 D at any time point.

The criteria that FDA typically use to define the time point of refractive stability for the population are as follows:

- At least 95% of subjects have a change in manifest refractive spherical equivalent (MRSE) $\leq$ 1.00 D between 2 consecutive visits.
- The mean rate of change in MRSE as determined by paired analysis is less than or equal to 0.50 D per year (or 0.04 D/month) between 2 refractions performed at least 3 months apart.
- The 95% confidence interval for the mean rate of change includes zero or a rate of change attributable to normal aging.
- The mean rate of change of MRSE decreases monotonically over time with a projected asymptote of zero or a rate of change attributable to normal aging.
- Stability is confirmed at the subsequent time point following the point of stability

Most of the same stability criteria are often applied to cylinder.

Table 49 shows that, for each time interval, more than 99% of treated eyes (of those eyes with data at each visit of the interval) had a mean change in MRSE of no more than 1.00 D. The mean monthly rate of change in MRSE was less than 0.04 D/month at each time interval starting at 1-to-3 Months. The 95% confidence interval (CI) for the mean change included zero only at the 1-to-2 Month interval. However, the mean change was small and the 95% CI for the mean rate of change was close to zero, especially starting at the 6-to-12 Month interval (mean change no more than 0.057 D with 95% CI of 0.037, 0.077). After the myopic changes seen through the first two months, the mean rate of hyperopic change showed a slight increase in the 3-to-6 Month interval (0.084 D/month), compared to the prior 2-to-3 Month interval (0.036 D/month). All intervals afterward showed mean rates of hyperopic change <0.010 D/month.

The applicant performed vector analyses to assess the stability of manifest refractive cylinder. **Table 50** shows that the mean change in vector cylinder magnitude from pre-operatively to the 1-month postoperative visit was 0.347 D (SD 0.344). For each time interval, more than 99% of treated eyes had a mean change in vector cylinder magnitude of no more than 1.00 D. The mean monthly rate of change in vector cylinder magnitude was less than 0.04 D/month at each time interval starting at 6-to-12 Months, and the mean magnitude of vector change did not exceed 0.25 D during any interval starting at 3-to-6 Months. (Note that magnitude of vector change for any eye is always positive, so mean magnitude of vector change generally does not asymptote to zero due to measurement variability.)

FDA Commentary: There was an initial myopic shift in mean MRSE postoperatively with a subsequent hyperopic shift. The greatest mean MRSE was +0.252 (SD 0.385) at the final 24-month visit with the greatest mean change in MRSE at this visit (+0.118, SD 0.330). Stability of MRSE was reached by 6 months postoperatively.

During the annual report of the continued follow-up study (VIS-2014-5YR), the applicant reported 23 eyes of 18 subjects with hyperopic shifts of greater than 1 D from baseline with both eyes of one subject having greater than 2 D of hyperopic shift from baseline. Regarding these results, the applicant cited the Beaver Dam Eye Study of adults over 40 years old and stated that these analyses "may represent general population trends and not be specifically related to the VisAbility device or procedure." However, FDA notes that this is not completely supported by the article as the authors state, "Individuals with mild and moderate nuclear sclerosis showed varying degrees of hyperopic shifts over five years (0.22 D: 95% CI: 0.20 D–0.25 D; 0.23 D: 95% CI: 0.20 D–0.27 D, respectively)." [Invest Ophthalmol Vis Sci. 2018 Sep; 59(11): 4518–4524].

8.5.2.7 Patient-Reported Outcomes

A questionnaire was administered to subjects that included an 11-item version of the Near Activity Visual Questionnaire (NAVQ) and supplemental questions (two items) as an additional evaluation of effectiveness. Additional information was requested from the applicant to evaluate whether the questionnaire provided valid and reliable measurements. However, the applicant did not provide the additional information needed to support the use of the questionnaire and interpretation of the questionnaire data for the clinical trial.

FDA Commentary: FDA relayed concerns during the IDE and PMA review to the applicant regarding the evidence needed to verify the validity and reliability of the NAVQ in the clinical study. Further evidence on the development work, including literature review design, focus group and cognitive interview scripts and transcripts, Rasch Analysis results, etc., was requested to verify the revised NAVQ has been evaluated and is a valid assessment of the concept of interest. Without the additional information requested, the questionnaire results were challenging to interpret and therefore did not meaningfully contribute to the FDA review of the PMA.

8.5.3 Poolability Analyses

The poolability analyses for the 1st and 2nd co-primary endpoints are presented below.

First Co-Primary Effectiveness Endpoint:

The methodology of poolability analyses was described in **Section 7.8**. As shown in **Table 51** and **Table 52**, the responder rates for the 1st co-primary endpoint by site, at 12 and 24-month for the ITT population, are not poolable. **Table 51** for ITT population at

12-month, indicates that the 1st co-primary endpoint was achieved only at sites 003 (N=31, CI=(78.6%, 99.2%)), 006 (N=36, CI=(81.3%, 99.3%)), and 009 (N=36, CI=(85.5%, 99.9%)). So, it appears that the trial success is mostly driven by these three sites.

Table 52, for ITT population at 24-month, indicates that the 1st co-primary endpoint was achieved only at sites 003 (N=29, CI=(82.2%, 99.9%)), 008 (N=67, CI=(77.8%, 94.7%)), and 009 (N=36, CI=(90.3%, 100%)). So, it appears that the trial success is mostly driven by these three sites.

Second Co-Primary Effectiveness Endpoint:

The methodology of poolability analyses was described in **Section 7.8**. **Table 53** shows that there was a significant interaction effect between trial site effect and treatment effect ($p \leq 0.15$). Therefore, the data were not poolable.

The applicant conducted extra analyses to address the poolability issues and was not able to explain the site-to-site variations, for the 1st coprimary endpoint, and the interaction effect between site and treatment effect, for the 2nd co-primary endpoint.

FDA Commentary: For the 1st co-primary endpoint, there was variability in effectiveness outcomes across sites and the data may not be generalizable. The results were mostly driven by sites by 003, 006 and 009 at 12-month and by sites by sites 003, 008 and 009 at 24-month. For the 2nd co-primary endpoint, there was a significant interaction effect between trial site and treatment (p-value = 0.084).

The applicant was not able to explain the variability in effectiveness outcomes for the 1st and 2nd co-primary endpoints.

8.5.4 Covariate Analyses

As discussed in the Regulatory History section (**Section 6.5.2**) above, the applicant conducted additional exploratory analyses to determine whether a subgroup of subjects could be identified with a better benefit-risk profile (the new "Intended Use" or "IU" Cohort).

The following baseline characteristics (covariates) were examined for ITT population, in order to identify a potential subpopulation with an improved risk-benefit ratio:

- Anterior Chamber Depth (ACD)
- Astigmatism axis (manifest refractive cylinder)
- Astigmatism magnitude (by manifest refraction)
- Axial Length
- Distance Corrected Near Visual Acuity (DCNVA)
- Inter Ocular Pressure (IOP)
- Keratometry

- Maximum/Minimum Pupil Size
- Manifest Refraction Spherical Equivalent (MRSE)
- Near Add
- Scleral Thickness

Please see **Table 60 – Table 95** in **Appendix 4 – Covariate Analyses – Effectiveness Tables** for the analyses of these factors. Based on these analyses, the applicant identified manifest refractive cylinder magnitude and scleral thickness as factors which positively influenced effectiveness outcomes and were the basis for the proposal of a new intended use population, the IU Cohort, and revision of the IFU.

*FDA Commentary: As discussed in **Section 6.5.2** above, the applicant had requested (Amendment 5, P170040/A005) approval for a revised IFU (IU Cohort) based on these analyses. FDA has questions regarding the benefit-risk assessment for the revised IFU.*

For a list of the analyses performed by the applicant for covariate analyses for safety, please see **Appendix 5 – Covariate Analyses – Safety Tables List**.

FDA Commentary: No baseline characteristics were found to be predictors of better safety outcomes.

8.5.5 Summary of Effectiveness Outcomes

The pre-specified protocol analyses were based on the ITT population results at 12 months for the first co-primary effectiveness endpoint and 6 months for the second co-primary effectiveness endpoint. The hypothesis-tested primary effectiveness endpoint was DCNVA 20/40 or better and at least 10 letters of improvement on the ETDRS chart from baseline.

For the 1st co-primary endpoint, the responder rate for the primary eyes was 79.1% with a lower 95% limit of 74.5%. The target value of 75% for the lower bound of the 95% CI of the percentage of responders in the ITT population at the 12-month visit **was not met**.

The applicant provided additional post-hoc (not pre-specified) analyses for the Bilateral Effectiveness Cohort (BEC) at 12 and 24 months and 24 months ITT analyses. Statistical inferences from these analyses should be drawn with caution.

For the 2nd co-primary endpoint, the target was met, because there was a statistically significant difference ($p < 0.001$) in the percentage of responders in the two arms of the randomized substudy at 6 months, regardless of imputation method. The responder rate was almost 7% in the primary eyes of the deferred treatment (untreated control) group by both imputation methods and 62.1% or 64.3% in the immediate treatment group, depending on imputation method.

The protocol required both primary and secondary endpoints to be met in order for it to be considered success. Although the 2nd co-primary endpoint was met, the trial was not a success, because both endpoints needed to be met.

Based on the poolability analyses, there was significant variability in the effectiveness outcomes by site, indicating that the outcomes may not be generalizable to the broader US intended user and patient population, and the applicant could not identify factors to provide a plausible explanation for these site differences. In addition, analyses of various factors effects on the outcomes did not support a clinically plausible subgroup of the intended use population with better outcomes.

The 2nd co-primary endpoint randomized substudy analysis showing a statistically significant difference between the two arms (based on a subjective test that is prone to potential bias) and the difference between the two arms in the change in DCNVA of 2.40 lines (2.68 – 0.28 lines) in favor of the treatment group, were not consistent with the results of the defocus curve testing and wavefront measurements (objective measurements). For defocus curve testing, the difference in the mean change in logMAR visual acuity from baseline to the 6-month visit between the primary eyes of the control group and the treatment group, using the 2.50 D lens power equivalent to a near testing distance of 40 cm, was 1 line on the ETDRS chart. Per the applicant, there were no clinically significant differences within or between arms in wavefront measurements with static testing and no clinically significant changes from distance to near in either arm or differences between arms on dynamic testing.

The mean change in the number of lines of DCNVA from baseline for the ITT primary eyes was 2.80 (SD 1.52) at 6 months, 3.15 (SD 1.44) at 12 months, and 3.35 (SD 1.33) at 24 months.

The mean change in the number of lines of binocular UCNVA from baseline for the ITT subjects was 2.85 (SD 1.40) at 12 months and 3.02 (SD 1.35) at 24 months.

At the 6-month visit, the decrease mean change from baseline from baseline of the near add power required was 0.90 D greater in the treatment group than in the control group of the randomized substudy (-0.02 (SD 0.21) in the control group; -0.92 (SD 0.50) D in the treatment group). The mean changes from baseline of the near add power required for the primary eyes of the ITT group at 6, 12, and 24 months postoperatively [-0.86 (SD 0.52), -0.99 (SD 0.56), and -1.07 (SD 0.58), respectively] were somewhat similar to the mean change in add from baseline for the primary eyes of the treatment group of the randomized substudy at 6 months.

For the analysis of the within-subject changes from baseline of UCNVA vs. UCDVA in the primary eyes of the ITT cohort with this data available at both baseline and the postoperative visit (without removal), 75.1% of subjects had a gain of at least 10 letters in UCNVA and no more than a 5-letter loss (or a gain) in UCDVA and 1.7% had a gain of UCNVA of less than 10 letters (or a loss of UCNVA) and a loss of UCDVA of more than

5 letters at 12 months postoperatively. At 24 months postoperatively, these percentages were 78.2% and 2.4%, respectively.

The Panel will be asked whether the results provide reasonable assurance of effectiveness of the device for the proposed indication for use.

9 Benefit-Risk Analysis

The applicant is proposing this device for the following indications:

> The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes, and require a minimum near correction of at least +1.25 D reading add.

Approved available treatment options for presbyopia include glasses, contact lenses, corneal inlays, and conductive keratoplasty.

The risks of the device, based on the adverse events that occurred during the pivotal clinical trial, include, but are not limited to:

- scleral perforation with sequelae, such as, hypotony,
- anterior segment ischemia (ASI), and
- secondary surgical interventions, such as, removal of segments due to conjunctival erosion with segment exposure and other ocular surface problems.

The applicant was unable to identify a sub-population for which the risks were reduced. In addition, the applicant was unable to demonstrate that further modifications to the surgical technique and/or training could mitigate these risks. Furthermore, there is uncertainty about the risks with respect to scleral perforations and ASI. The creation of the scleral tunnel during the surgical procedure did not allow visualization of the tunnel floor. Therefore, some scleral perforations may have gone unrecognized. Uncertainty regarding the rate of ASI was introduced by the protocol definition of ASI as an AE being limited to Grade 4.

Regarding the benefits, 79.1% (277 of 350) of primary eyes of the ITT population achieved the pre-specified primary effectiveness endpoint of DCNVA 20/40 or better and at least 10 letters of improvement on the ETDRS chart from baseline at 12 months. At the post-hoc effectiveness analysis timepoint of **24 months**, 84.1% (289 of 344) primary eyes of the ITT population achieved this endpoint.

However, the pivotal trial did not meet the pre-specified trial success criteria, which were based on meeting both co-primary effectiveness endpoints. The first co-primary effectiveness endpoint, based on subjective DCNVA testing at 12 months without comparison to a control, was not met. The second co-primary effectiveness endpoint (at 6 months) was met, but this analysis was performed on a small subpopulation, and although

this substudy had a control arm and was randomized, it was unmasked. The results across sites for each of the co-primary effectiveness endpoints varied and may not be generalizable. The defocus curve exploratory analysis showed a 1-line difference in the mean change in visual acuity between the primary eyes of the control group and the treatment group at a near testing distance equivalent of 40 cm (2.50 D lens power). The exploratory analysis of the wavefront testing showed no clinically significant change per the applicant's assessment. During the annual report of the continued follow-up study (VIS-2014-5YR), the applicant reported 23 eyes of 18 subjects with hyperopic shifts of greater than 1 D from baseline with both eyes of one subject having greater than 2 D of hyperopic shift from baseline.

The Panel will be asked whether the benefits for the proposed indicated population outweigh the risks.

10 Post-Market Plan

Note: The inclusion of a Post-Market Plan section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-market plan, including post-approval study plans or commitments, does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-market plan or post-approval study could be considered. The issues noted below are FDA's comments regarding the applicant's Post-Market Plan and potential post-approval studies for the Panel to include in the deliberations should FDA find the device approvable based upon the clinical premarket data.

An overview of the post-market plan proposed by the applicant is provided below and panel input on these are requested.

FDA Commentary: The post-market plan described below was provided by the applicant in P170040/A005, which was submitted in response to the first "Not Approvable" decision.

10.1 Overview of Proposed Post-Market Plan

The applicant proposed a post-market plan to continue monitoring and reporting on the device performance. There are three components: (1) the continued follow-up of the premarket cohort, (2) a new enrollment study, and (3) a controlled post-market device roll-out. A summary of the main elements for each component, is presented below.

10.1.1 Study 1: Continued Follow-up of Premarket Cohort, VIS-2014-5YR (protocol approved under IDE)

The VIS-2014-5YR is a continuation of the premarket study cohort, designed to assess the long-term safety and effectiveness of the VisAbility Micro Insert in presbyopic subjects.

Study Element	Description of the Current Plan
Study Objective	Extend the follow-up of VIS-2014 participants and obtain long-term (5-year) safety and effectiveness data
Basic Study Design	A long-term, multi-center, prospective, single-arm study through extending the follow-up of the premarket cohort with no additional intervention. The results will be mostly descriptive in nature. Endpoints including rate of SAEs and reasons of explantation will be evaluated for safety assessment; change in uncorrected and distance corrected near visual acuity and letters correct in the primary eye of bilaterally implanted subjects, as compared to baseline (VIS-2014), will be evaluated for effectiveness assessment. The study proposal does not include one or more hypotheses, success criteria, or a statistical analysis plan.
Study Population	Subjects will be drawn from the 360 subjects who were implanted or explanted with the VisAbility™ Micro Insert as part of the VIS-2014 clinical trial who consent to participate in the extended follow-up.
Endpoints	Descriptive statistics and summaries will be provided for the following endpoints: Primary safety endpoints: • Explant rate and reason(s) • Rate of Anterior Segment Ischemia (Grades 2 – 4) • Rate of segment exposure due to conjunctival and/or scleral erosion • Rate of serious adverse events (SAEs) Secondary safety endpoints: • Best Corrected Distance Visual Acuity (BCDVA) • IOP increase > 10 mm Hg over baseline or IOP > 30 mm Hg • Slit Lamp findings • Fundus exam findings • Rate of adverse events (AE's) Secondary effectiveness outcome:

	• Change in uncorrected and distance corrected near visual acuity and letters correct in the primary eye of bilaterally implanted subjects (with all eight implants in place), as compared to baseline (VIS-2014).
Sample Size	No sample size calculation is provided.
Length of follow-up and follow-up frequency	Two additional years for those with implants (from 36-month to 60-month). More specifically, subjects who provide consent to participate in the extended follow-up will be examined at 36-, 48-, and 60-months post-operatively, with no planned interventions. Those who decline participation will be documented accordingly and will not be considered for longer term follow-up.

FDA Commentary: In (b) (4) *, FDA approved the applicant's protocol of VIS-2014-5YR, which is to collect data out to 60 months. This study is currently ongoing. The applicant is now proposing to use data from protocol of VIS-2014-5YR for this 1st PAS.*

10.1.2 Study 2: New Enrollment Post-Approval Study: VIS-2014-PAS

In Amendment 5 (P170040/A005), the applicant proposed a new enrollment PAS, Study 2 (VIS-2014-PAS) to "provide additional data on the intended device population."

Study Element	Description of the Current Plan
Study Objectives	To provide additional, prospective, descriptive data on the intended population; to evaluate device performance stratified by surgeon experience.
Basic Study Design	This PAS will be a multicenter, prospective, and single-arm study. Patients who meet the inclusion/exclusion criteria and provide consent will be enrolled and followed for 1-year. Patients will be enrolled from up to 15 sites. "Informal comparisons to the pre-approval data without formal statistical hypothesis tests" is proposed.
Study Population	Inclusion Criteria 1. Subjects must be between the ages of 45 and 60. 2. Subjects must have a manifest spherical equivalent between -0.75D and +0.50D with refractive astigmatism less than or equal to 0.75 D. 3. Subjects must have a minimum near add requirement of at least +1.25D.

Study Element	Description of the Current Plan
	4. Subjects must be phakic in each eye. 5. Subjects must be alert, mentally competent, and able to understand and comply with the requirements of the clinical study. 6. Subjects must be able to provide written informed consent. Exclusion Criteria 1. Subjects who do not meet the indications for use for this device; 2. Subjects who have any of the following conditions described in the labeling contraindications of this device: a. Either pupil has a baseline percent change from scotopic to photopic of less than 30%, or an absolute difference of less than 1.00 mm between scotopic and photopic pupil size as measured by the NeurOptics Pupillometer. b. Ocular inflammation, chronic uveitis, or other recurrent anterior or posterior segment inflammatory conditions in either eye; any ocular or systemic disease(s) posting a significant risk for ocular inflammation, including but not limited to autoimmune disorders (e.g., rheumatoid arthritis, ankylosing spondylitis, Reiter's syndrome, ulcerative colitis, Crohn's disease, psoriasis, sarcoidosis, Behcet's disease), infections (toxoplasmosis, cat-scratch fever, West Nile virus, syphilis, tuberculosis, herpes zoster, herpes simplex, adenovirus), ocular trauma, or gout. c. Scleral thickness of less than 530 microns or greater than 680 microns as measured 3.5 to 4.0 mm posterior to the superior temporal quadrant limbus in either eye. d. Any acute ocular disease that has not been completely treated and resolved for at least three months such as conjunctivitis, blepharitis, chalazion, corneal abrasion or keratitis in either eye. e. Use of any medication, such as coumadin, that could lead to excessive bleeding and make the surgical procedure more difficult. Patients using Coumadin, aspirin or NSAID medication should discontinue the medication 10 days prior to surgery. It is recommended that written approval to discontinue these medications is obtained from the treating doctor prior to discontinuing this medication. f. Chronic ocular surface disease, including but not limited to patients with a prior diagnosis of chronic dry eye syndrome based on tests such as but not limited to, corneal or conjunctival staining, Ocular Surface Disease Index symptom score or Schirmer tear testing. g. Allergies to any of the medications used in the surgical procedure.

Study Element	Description of the Current Plan
	3. Any condition, which, in the judgment of the Investigator, would preclude adequate evaluation of the device's safety and performance (e.g. pregnancy).
Endpoints	Descriptive and summary of the following endpoints will be provided: Means, standard deviations, and ranges (min/max) will be derived from the continuous measurements. Frequencies, rates (cumulative incidence), and proportions will be used for summarizing the categorical and ordinal outcomes. Primary safety outcomes: • Rate of occurrence of Anterior Segment Ischemia (Grades 2-4) • Rate of scleral perforations Secondary safety outcomes: • Rate of secondary surgical interventions • Conjunctival retraction • Explant (full or partial) Primary effectiveness outcomes: • Change in DCNVA from baseline
Sample Size	150 subjects is proposed, not calculated based on a hypothesis test.
Length of follow-up and follow-up frequency	1-year Subjects will be examined at one day, one week and at 1, 6, & 12 months, post-operatively

FDA Commentary: The criteria proposed for enrollment are based on the IU Cohort IFU (Amendment 5, P170040/A005), not the original IFU as currently proposed.

The new enrollment PAS proposal does not include one or more hypotheses, success criteria, or a statistical test analysis plan. The applicant does not delineate what "additional data" is the focus of the first objective. Furthermore, there are no specifics in the plan for how the second objective of evaluating device performance by surgeon experience will be addressed. The evaluation of the proposed PAS has not yet been discussed with the study sponsor.

The Panel will be asked to comment on this PAS.

10.1.3 Proposed Post-Approval Controlled Access

If the VisAbility™ Micro Insert System were to be approved, the applicant proposed controlled access consisting of: (1) controlled market rollout, (2) appropriate training, and (3) certification of surgeons. The goal of the controlled rollout and surgeon training is to focus on maximizing surgical outcomes for the VisAbility™ Micro Insert System procedure.

FDA Commentary: FDA could restrict the sale, distribution or use of the device.

Controlled Rollout

The initial roll out for the first three to six months will be limited to those surgeons that were involved in the clinical study. The applicant will conduct wet lab and staff training for each of the physician practices to ensure that they are adequately prepared to offer the VisAbility™ Micro Insert Procedure to the appropriate patients, and to perform the surgery following the approved surgical protocol.

Following the initial three- to six-month roll out period, the applicant would launch the device in six to nine months in three select targeted cities. Approximately 35-45 trained surgeons will be offered the VisAbility™ Micro Insert Procedure by the end of the first year. Surgeons will continue to have all patients enrolled in a third-party data registry, monitoring surgical outcomes, and responding appropriately with additional training as required. Surgeons will also have support and access to a team of personnel, including experienced clinical application experts, a patient-focused practice management team, and highly trained regional sales professionals.

Surgeon Training

Qualified surgeons are to be trained and certified in the selection of appropriate patients, performance of successful surgery, and management of potential complications. In the event of product and instrumentation update, the applicant will provide continuing education to previously certified VisAbility™ Micro Insert System surgeons regarding these updates through seminars and direct visits from qualified Refocus representatives or their designees.

Surgeon Certification

Once verified by the applicant, the surgeon name will be added to the list of those certified to be able to receive VisAbility™ Micro Insert System products and perform the VisAbility™ Micro Insert procedure. Additionally, a Refocus surgeon proctor will be available to the certified surgeon, and a regional specialist will also be available to both surgeon and staff of certified sites.

In the event of product and instrumentation updates, the applicant will provide continuing education to previously certified surgeons regarding updates through seminars and direct visits by the applicant's representatives. To maintain certification status, the previously certified VisAbility™ Micro Insert System surgeons will be retrained by the Refocus representatives, with all training documented.

FDA Commentary: The applicant has not provided details to all the elements of the controlled access plan as proposed above. Therefore, it is unclear how this training, post-operative support and monitoring plans differ from what was implemented during the IDE trial. A summary of the training and post-operative support and monitoring activities conducted under the IDE trial are provided below:

IDE Investigator Training
• Per the study monitoring plan in the protocol, the applicant or CRO (contract or clinical research organization) personnel were to meet with investigators and clinical staff prior to initiation of the trial in order to "familiarize" them with the protocol, which included the enrollment criteria and postoperative care.
• Per the applicant (P170040/A005), investigators were trained on surgical best practices.
• Wet Lab Training - Demonstration of proficiency
• Minimum 5 eyes for proctoring
Post-Operative Support and Monitoring
• Clinical monitoring by medical monitor and data safety monitoring board
• Clinical trial investigators had to adhere to IDE reporting requirements per 21 CFR 812.
• Collection of safety and effectiveness data (i.e., adverse events) on subjects under IDE (pivotal trial and continued follow-up study).

During review of Amendment 5 (P170040/A005), FDA requested greater detail regarding potential mitigations of risks based on lessons learned during the pivotal trial to which the applicant responded via e-mail "…adherence to the original techniques and procedures taught to investigators at the outset of the study continue to represent the best mitigations for these events."

The applicant has not performed or provided data (e.g., a learning curve assessment) to demonstrate that intraoperative adverse events (e.g., scleral perforation and ASI) were limited to early cases, and that training will further mitigate these risks.

10.2 Summary of Proposed Post-Market Plan

There are three parts to the proposed Post-Market Plan:

- Utilizing ongoing 5-year follow-up study (protocol VIS-2014-5YR under IDE G140025) as the 1st PAS.

- New-enrollment study, 2nd PAS (VIS-2014-PAS), based on proposed study objectives (1) to provide additional, prospective, descriptive data on intended population, and (2) to evaluate device performance stratified by surgeon experience, but without enrollment criteria consistent with the current IFU, any proposed hypothesis, success criteria, goal, or statistical test plan, or specificity with regard to what "additional data" is the focus of the first objective or how the second objective will be addressed.

- Controlled access consisting of (1) controlled market rollout, (2) appropriate training, and (3) certification of surgeons.

The Panel will be asked if a post-approval study is needed (in the event that the PMA were to be approved), and if so, whether the proposed post-approval study plan is sufficient to address remaining concerns.

11 Tables

Table 1 Summary of VisAbility Micro Insert Biocompatibility Tests

Test Category	Animal or Species	Test Substance	Test Result
Cytotoxicity: Agarose Diffusion Assay	L-929 Mouse Fibroblast Cells	VisAbility Micro Insert Implant	Negative for Cytotoxicity
Cytotoxicity: Elution Assay	L-929 Mouse Fibroblast Cells	Minimum Essential Media (MEM) Extract	Negative for Cytotoxicity
Cytotoxicity: Neutral Red Uptake Assay	L-929 Mouse Fibroblast Cells	MEM Extract	Negative for Cytotoxicity
Sensitization: Maximization Assay	Guinea Pig	Saline and Cottonseed Oil Extracts	Negative for Sensitization
Irritation: Ocular Irritation	Rabbit	Saline and Cottonseed Oil Extracts	Negative for Irritation
Genotoxicity: Bacterial Reverse Mutation Assay	E. coli and Salmonella typhimurium	Cottonseed Oil Extract	Non-Mutagenic
Genotoxicity: Mouse Lymphoma Assay	L5178Y/TK+/- Mouse Lymphoma Cells	Saline and PEG Extract	Non-Mutagenic and non-Clastogenic
Genotoxicity: Bone Marrow Micronucleus Assay	Mouse	Saline and Cotton Seed Oil Extract	Non-Clastogenic and non-Aneugenic
Genotoxicity: Chromosome Aberration Assay	Hamster Ovary Cells	PEG and Ham's F-12 Extract	Non-Clastogenic
Hemolysis: Assay (Direct and Indirect Contact)	Human and Rabbit Blood	Saline Extract	Non-Hemolytic
Acute Systemic Toxicity	Mouse	Saline and Cottonseed Oil Extract	Negative for Systemic Toxicity
Sub-Acute Systemic Toxicity	Mouse	Saline Extract	Negative for Systemic Toxicity
Material-Mediated Pyrogen Test	Rabbit	Saline Extract	Non-Pyrogenic
Implantation: Six-Month Ocular Implantation	Rabbit	VisAbility Micro Insert	No significant biological local response

Implantation: One-Week Muscle Implantation	Rabbit	VisAbility Micro Insert	No significant biological response

Table 2 Summary of VisAbility Scleratome Biocompatibility Tests

Test Category	Animal or Species	Test Substance	Test Result
Cytotoxicity: Elution Assay	L-929 Mouse Fibroblast Cells	MEM Extract	Negative for Cytotoxicity
Sensitization: Maximization Assay	Guinea Pig	Saline and Cottonseed Oil Extracts	Negative for Sensitization
Intracutaneous Reactivity	Rabbit	Saline and Cottonseed Oil Extracts	Negative for Irritation

Table 3 Summary of VisAbility Feeder Tube Biocompatibility Tests

Test Category	Animal or Species	Test Substance	Test Result
Cytotoxicity: Elution Assay	L-929 Mouse Fibroblast Cells	MEM Extract	Negative for Cytotoxicity
Sensitization: Maximization Assay	Guinea Pig	Saline and Cottonseed Oil Extracts	Negative for Sensitization
Intracutaneous Reactivity	Rabbit	Saline and Cottonseed Oil Extracts	Negative for Irritation

Table 4 Summary of Material/Chemical Characterization Tests

Test	Results
Exhaustive Extraction	Passed
Leachability	Passed
Hydrolytic Stability	Passed
Inorganic Compounds	Passed

Table 5 Summary of Mechanical Tests

Test	Purpose	Results
VisAbility Micro Insert – Perpendicular Loading	Integrity of Assembled VisAbility Micro Insert	Passed
VisAbility Micro Insert – 3-point bending	Integrity of Assembled VisAbility Micro Insert	Passed
VisAbility Micro Insert – Compression	Integrity of Assembled VisAbility Micro Insert	Passed
VisAbility Micro Insert – Break Strength	Integrity of Assembled VisAbility Micro Insert	Passed
Length, Width, and Depth of Tunnel Creation –	VisAbility Scleratome Function	Passed

Simulated Use in Porcine Eyes		
Docking Station Interfacing and Placement – Simulated Use in Porcine Eyes	VisAbility Scleratome Function	Passed
Scleratome Actuation/Retraction	VisAbility Scleratome Function	Passed
VisAbility Micro Insert Segment and Shuttle Loading in Feeder Tube – Simulated Use in Porcine Eyes	Feeder Tube Function	Passed
VisAbility Micro Insert Segment Placement and Removal from Feeder Tube – Simulated Use in Porcine Eyes	Feeder Tube Function	Passed

Table 6 Schedule of Visits and Measurements

		Initial								Follow-up	
	Pre-Op	0 Day	1 Day	1 Week	1 Month	2 Months	3 Months	6 Months	12 Months	18 Months	24 Months
Slit Lamp Biomicroscopy OD, OS	✓[2]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Applanation Tonometry OD, OS	✓[2]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Gonioscopy OD, OS	✓								✓		
Scleral Thickness Measurement OD, OS	✓										
Implant Assessment OD, OS			✓	✓	✓	✓	✓	✓	✓	✓	✓
Axial Length / ACD OD, OS	✓								✓		✓
Corneal Topography / Keratometry OD, OS	✓										
Pupillometry OD, OS	✓[2]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Posterior Pole exam with 78 /90D lens OD, OS	✓[2]		✓		✓	✓	✓	✓		✓	
Dilated Indirect Ophthalmoscopy 20/30D lens OD, OS	✓			✓					✓		✓
Visual Fields OD, OS	✓										
Cup/Disk Ratio OD, OS	✓								✓		✓
Cycloplegic Refraction w/ VA OD, OS	✓								✓		✓
Manifest Refraction OD, OS	✓			✓[4]	✓	✓	✓	✓	✓	✓	✓
BCDVA OD, OS	✓[2]			✓	✓	✓	✓	✓	✓	✓	✓
UCDVA OD, OS	✓		✓[1]	✓	✓	✓	✓	✓	✓	✓	✓
UCNVA @ 40 cm OD, OS, OU	✓						✓	✓	✓	✓	✓
UCIVA @ 66 cm OU	✓						✓	✓	✓	✓	✓
DCNVA @ 40 cm OD, OS, OU	✓				✓	✓	✓	✓	✓	✓	✓
Patient Preferred Distance DCN - OD, OS, OU UCN - OU	✓						✓	✓	✓	✓	✓
Minimum add to achieve 20/20	✓						✓[3]	✓[3]	✓[3]	✓[3]	✓[3]
NAVQ (Validated PRO) & Patient Questionnaire	✓							✓	✓	✓	✓
Sub-Study Only Wavefront measurements[3]	✓						✓	✓	✓	✓	✓
Sub-Study Only Defocus Curve[3]	✓						✓	✓	✓	✓	✓

[1]Visual acuity will be measured using pinhole on day 1
[2]Fellow Eye Safety Exam (when fellow eye surgery is 61-180 days after primary eye surgery)
[3]Randomized Sub-study subjects only – control group subjects are examined through 6 months and the surgery group through 24 months.
[4]Measure BCDVA using baseline refraction

Table 7 Accountability - All Eyes*

708 Eyes	Preop	1 Day	1 Week	1 Month	2 Months	3 Months	6 Months	12 Months	18 Months	24 Months
Available for Analysis	708 (100.0%)	706 (99.7%)	702 (99.2%)	698 (98.6%)	691 (97.6%)	689 (97.3%)	686 (96.9%)	687 (97.0%)	652 (92.1%)	668 (94.4%)
Discontinued	0 (0.0%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	5 (0.7%)	13 (1.8%)	13 (1.8%)
Explant	0 (0.0%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	5 (0.7%)	13 (1.8%)	13 (1.8%)
Deceased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Active[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up[2]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.3%)	5 (0.7%)	7 (1.0%)	19 (2.7%)	27 (3.8%)
Missed Visit[3]	0 (0.0%)	0 (0.0%)	4 (0.6%)	8 (1.1%)	14 (2.0%)	15 (2.1%)	15 (2.1%)	9 (1.3%)	24 (3.4%)	0 (0.0%)
% Accountability[4]	708 (100.0%)	706 (100.0%)	702 (99.4%)	698 (98.9%)	691 (97.9%)	689 (97.6%)	686 (97.2%)	687 (97.7%)	652 (93.8%)	668 (96.1%)

* All eyes (both primary and fellow eyes) that have undergone surgical preparation of the ocular surface.
1 Active eyes: eyes not yet seen or not yet eligible for the interval.
2 Lost to follow-up: eyes that would not be examined at the scheduled visit and are not considered active or discontinued.
3 Missed visit: eyes not examined at the scheduled visit, but may be seen at a subsequent visit.
4 % Accountability=[available for analysis / (enrolled-discontinued-active)] x 100

Table 8 Accountability - Intent-to-Treat Population*

360 Eyes	Preop	1 Day	1 Week	1 Month	2 Months	3 Months	6 Months	12 Months	18 Months	24 Months
Available for Analysis	360 (100.0%)	358 (99.4%)	357 (99.2%)	357 (99.2%)	350 (97.2%)	352 (97.8%)	347 (96.4%)	346 (96.1%)	326 (90.6%)	337 (93.6%)
Discontinued	0 (0.0%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (1.1%)	8 (2.2%)	8 (2.2%)
Explant	0 (0.0%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	4 (1.1%)	8 (2.2%)	8 (2.2%)
Deceased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Active[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up[2]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	3 (0.8%)	4 (1.1%)	11 (3.1%)	15 (4.2%)
Missed Visit[3]	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	8 (2.2%)	5 (1.4%)	8 (2.2%)	6 (1.7%)	15 (4.2%)	0 (0.0%)
% Accountability[4]	360 (100.0%)	358 (100.0%)	357 (99.7%)	357 (99.7%)	350 (97.8%)	352 (98.3%)	347 (96.9%)	346 (97.2%)	326 (92.6%)	337 (95.7%)

* All primary eyes that have been implanted with at least one Micro Insert segment.
1 Active eyes: eyes not yet seen or not yet eligible for the interval.
2 Lost to follow-up: eyes that would not be examined at the scheduled visit and are not considered active or discontinued.
3 Missed visit: eyes not examined at the scheduled visit, but may be seen at a subsequent visit.
4 % Accountability=[available for analysis / (enrolled-discontinued-active)] x 100

Table 9 Accountability - Bilateral Effectiveness Cohort*

348 Eyes	Preop	1 Day	1 Week	1 Month	2 Months	3 Months	6 Months	12 Months	18 Months	24 Months
Available for Analysis	348 (100.0%)	348 (100.0%)	347 (99.7%)	347 (99.7%)	340 (97.7%)	342 (98.3%)	339 (97.4%)	339 (97.4%)	321 (92.2%)	331 (95.1%)
Discontinued	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	5 (1.4%)	5 (1.4%)
Explant	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	5 (1.4%)	5 (1.4%)
Deceased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Active[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up[2]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	2 (0.6%)	2 (0.6%)	8 (2.3%)	12 (3.4%)
Missed Visit[3]	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	8 (2.3%)	5 (1.4%)	7 (2.0%)	6 (1.7%)	14 (4.0%)	0 (0.0%)
% Accountability[4]	348 (100.0%)	348 (100.0%)	347 (99.7%)	347 (99.7%)	340 (97.7%)	342 (98.3%)	339 (97.4%)	339 (97.7%)	321 (93.6%)	331 (96.5%)

* All primary eyes that have been implanted with at least one Micro Insert segment.
1 Active eyes: eyes not yet seen or not yet eligible for the interval.
2 Lost to follow-up: eyes that would not be examined at the scheduled visit and are not considered active or discontinued.
3 Missed visit: eyes not examined at the scheduled visit, but may be seen at a subsequent visit.
4 % Accountability=[available for analysis / (enrolled-discontinued-active)] x 100

Table 10 Accountability - Primary Eyes Randomized Substudy

	Baseline	3 Months	6 Months
Deferred Treatment Group*, 31 Eyes			
Available for Analysis	31 (100.0%)	29 (93.5%)	29 (93.5%)
Discontinued	0 (0.0%)	2 (6.5%)	2 (6.5%)
Explant	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deceased	0 (0.0%)	0 (0.0%)	0 (0.0%)
Active[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up[2]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missed Visit[3]	0 (0.0%)	0 (0.0%)	0 (0.0%)
% Accountability[4]	31 (100.0%)	29 (100.0%)	29 (100.0%)
	Preop	**3 Months**	**6 Months**
Immediate Treatment Group*, 29 Eyes			
Available for Analysis	29 (100.0%)	28 (96.6%)	25 (86.2%)
Discontinued	0 (0.0%)	1 (3.4%)	1 (3.4%)
Explant	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deceased	0 (0.0%)	0 (0.0%)	0 (0.0%)
Active[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up[2]	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missed Visit[3]	0 (0.0%)	0 (0.0%)	3 (10.3%)
% Accountability[4]	29 (100.0%)	28 (100.0%)	25 (89.3%)

* 5 primary eyes in the Deferred Treatment Group and 1 primary eye in the Immediate Treatment Group withdrew consent before implantation.
1 Active eyes: eyes not yet seen or not yet eligible for the interval.
2 Lost to follow-up: eyes that would not be examined at the scheduled visit and are not considered active or discontinued.
3 Missed visit: eyes not examined at the scheduled visit, but may be seen at a subsequent visit.
4 % Accountability=[available for analysis / (enrolled-discontinued-active)] x 100

Table 11 Accountability - Primary Eyes of Immediate Treatment Group in the Randomized Substudy

29 Eyes	Preop	1 Day	1 Week	1 Month	2 Months	3 Months	6 Months	12 Months	18 Months	24 Months
Available for Analysis	29 (100.0%)	28 (96.6%)	28 (96.6%)	28 (96.6%)	28 (96.6%)	28 (96.6%)	25 (86.2%)	28 (96.6%)	25 (86.2%)	27 (93.1%)
Discontinued	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)
Explant	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Deceased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrew Consent Prior to Surgery	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)
Active[1]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to Follow-up[2]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
Missed Visit[3]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.3%)	0 (0.0%)	3 (10.3%)	0 (0.0%)
% Accountability[4]	29 (100.0%)	28 (100.0%)	28 (100.0%)	28 (100.0%)	28 (100.0%)	28 (100.0%)	25 (89.3%)	28 (100.0%)	25 (89.3%)	27 (96.4%)

1 Active eyes: eyes not yet seen or not yet eligible for the interval.
2 Lost to follow-up: eyes that would not be examined at the scheduled visit and are not considered active or discontinued.
3 Missed visit: eyes not examined at the scheduled visit, but may be seen at a subsequent visit.
4 % Accountability=[available for analysis / (enrolled-discontinued-active)] x 100

Table 12 Demographics and Eye Status - Safety Cohort (Intent-to-Treat Population)

	Randomized			
	Deferred Treatment Group N = 26	Immediate Treatment Group N = 28	Non-randomized N = 306	Total Implanted N = 360
Age at Consent (years)				
n	26	28	306	360
Mean (SD)	51.0 (3.2)	50.1 (3.3)	51.8 (3.5)	51.6 (3.5)
Median	51	50	52	51
Min	45, 58	45, 58	45, 60	45, 60
Sex				
Female	9 (34.6%)	10 (35.7%)	124 (40.5%)	143 (39.7%)
Male	17 (65.4%)	18 (64.3%)	182 (59.5%)	217 (60.3%)
Race				
Asian	0 (0.0%)	1 (3.6%)	17 (5.6%)	18 (5.0%)
Black or African American	1 (3.8%)	0 (0.0%)	14 (4.6%)	15 (4.2%)
Caucasian	22 (84.6%)	23 (82.1%)	262 (85.6%)	307 (85.3%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	4 (1.3%)	4 (1.1%)
Other	3 (11.5%)	4 (14.3%)	9 (2.9%)	16 (4.4%)
Ethnicity				
Hispanic or Latino	9 (34.6%)	9 (32.1%)	20 (6.5%)	38 (10.6%)
Not Hispanic or Latino	17 (65.4%)	19 (67.9%)	283 (92.5%)	319 (88.6%)
Not Reported	0 (0.0%)	0 (0.0%)	3 (1.0%)	3 (0.8%)
Dominant Eye*				
OD	9 (34.6%)	22 (78.6%)	208 (68.0%)	239 (66.4%)
OS	17 (65.4%)	6 (21.4%)	98 (32.0%)	121 (33.6%)
Implanted Status				
Bilateral	23 (88.5%)	27 (96.4%)	298 (97.4%)	348 (96.7%)
Unilateral	3 (11.5%)	1 (3.6%)	8 (2.6%)	12 (3.3%)

* As per protocol, the primary eye is the dominant eye.

Table 13 Demographics and Eye Status - Randomized Substudy Subjects

	Randomized**	
	Deferred Treatment Group N = 31	**Immediate Treatment Group N = 29**
Age at Consent (years)		
n	31	29
Mean (SD)	51.6 (3.4)	50.2 (3.3)
Median	52	50
Min	45, 59	45, 58
Sex		
Female	14 (45.2%)	11 (37.9%)
Male	17 (54.8%)	18 (62.1%)
Race		
Asian	0 (0.0%)	1 (3.4%)
Black or African American	1 (3.2%)	0 (0.0%)
Caucasian	27 (87.1%)	24 (82.8%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)
Other	3 (9.7%)	4 (13.8%)
Ethnicity		
Hispanic or Latino	10 (32.3%)	9 (31.0%)
Not Hispanic or Latino	21 (67.7%)	20 (69.0%)
Not Reported	0 (0.0%)	0 (0.0%)
Dominant Eye*		
OD	12 (38.7%)	22 (75.9%)
OS	19 (61.3%)	7 (24.1%)
Implanted Status		
Bilateral	23 (74.2%)	27 (93.1%)
Unilateral	3 (9.7%)	1 (3.4%)
Not implanted	5 (16.1%)	1 (3.4%)

* As per protocol, the primary eye is the dominant eye.

** Includes all randomly assigned subjects

Table 14 Baseline Characteristics - Randomized Substudy and Non-Randomized Primary Eyes - Intent-to-Treat Population

	Randomized			
	Deferred Treatment Group[3] N = 26	Immediate Treatment Group N = 28	Non-randomized N = 306	Total Implanted N = 360
DCNVA (Snellen)[1]				
n (Reported)	26	28	306	360
Mean (SD) - LogMAR	0.516 (0.104)	0.519 (0.080)	0.498 (0.080)	0.501 (0.082)
Mean - Snellen	20/66	20/66	20/63	20/63
Median - LogMAR (Snellen)	0.53 (20/68)	0.52 (20/66)	0.50 (20/63)	0.50 (20/63)
Min - LogMAR (Snellen)	0.24 (20/35)	0.36 (20/46)	0.36 (20/46)	0.24 (20/35)
Max - LogMAR (Snellen)	0.64 (20/87)	0.64 (20/87)	0.68 (20/96)	0.68 (20/96)
UCNVA (Snellen)[1]				
n (Reported)	26	28	306	360
Mean (SD) - LogMAR	0.502 (0.105)	0.511 (0.087)	0.534 (0.082)	0.530 (0.085)
Mean - Snellen	20/63	20/65	20/68	20/68
Median - LogMAR (Snellen)	0.51 (20/65)	0.50 (20/63)	0.54 (20/69)	0.52 (20/66)
Min - LogMAR (Snellen)	0.18 (20/30)	0.40 (20/50)	0.36 (20/46)	0.18 (20/30)
Max - LogMAR (Snellen)	0.64 (20/87)	0.66 (20/91)	0.70 (20/100)	0.70 (20/100)
Bilateral UCIVA (Snellen)[1]				
n (Reported)	26	28	306	360
Mean (SD) - LogMAR	0.362 (0.116)	0.367 (0.160)	0.322 (0.152)	0.328 (0.151)
Mean - Snellen	20/46	20/47	20/42	20/43
Median - LogMAR (Snellen)	0.38 (20/48)	0.40 (20/50)	0.34 (20/44)	0.34 (20/44)
Min - LogMAR (Snellen)	0.12 (20/26)	0.02 (20/21)	-0.16 (20/14)	-0.16 (20/14)
Max - LogMAR (Snellen)	0.52 (20/66)	0.62 (20/83)	0.72 (20/105)	0.72 (20/105)
UCDVA (Snellen)[1]				
n (Reported)	26	28	306	360
Mean (SD) - LogMAR	-0.005 (0.066)	0.006 (0.060)	-0.012 (0.092)	-0.010 (0.088)
Mean - Snellen	20/20	20/20	20/19	20/20
Median - LogMAR (Snellen)	0.00 (20/20)	0.00 (20/20)	-0.02 (20/19)	0.00 (20/20)
Min - LogMAR (Snellen)	-0.10 (20/16)	-0.08 (20/17)	-0.20 (20/13)	-0.20 (20/13)
Max - LogMAR (Snellen)	0.14 (20/28)	0.12 (20/26)	0.32 (20/42)	0.32 (20/42)
BCDVA (Snellen)[1]				
n (Reported)	26	28	306	360
Mean (SD) - LogMAR	-0.060 (0.067)	-0.041 (0.062)	-0.072 (0.064)	-0.068 (0.065)
Mean - Snellen	20/17	20/18	20/17	20/17
Median - LogMAR (Snellen)	-0.04 (20/18)	0.00 (20/20)	-0.08 (20/17)	-0.08 (20/17)
Min - LogMAR (Snellen)	-0.18 (20/13)	-0.18 (20/13)	-0.20 (20/13)	-0.20 (20/13)
Max - LogMAR (Snellen)	0.00 (20/20)	0.06 (20/23)	0.08 (20/24)	0.08 (20/24)

1 Summary statistics of the number of letters were converted to Snellen.

2 Near add was only collected from Substudy.

3 All Deferred surgery group subjects met initial eligibility (inclusion/exclusion) criteria. Baseline characteristics for analyses (as reported here) were taken at the 6-month observation visit.

	Randomized			
	Deferred Treatment Group[3] N = 26	Immediate Treatment Group N = 28	Non-randomized N = 306	Total Implanted N = 360
MRSE (D)				
n (Reported)	26	28	306	360
Mean (SD)	0.034 (0.241)	0.036 (0.274)	0.137 (0.268)	0.122 (0.268)
Median	0.000	0.000	0.250	0.125
Min, Max	-0.500, 0.500	-0.500, 0.500	-0.750, 0.500	-0.750, 0.500
Near Add (D)[2]				
n (Reported)	26	28	306	360
Mean (SD)	1.798 (0.354)	1.768 (0.396)	1.588 (0.291)	1.617 (0.312)
Median	1.75	1.75	1.50	1.50
Min, Max	1.25, 2.50	1.25, 2.50	1.25, 2.50	1.25, 2.50
Axial Length (mm)				
n (Reported)	26	28	306	360
Mean (SD)	23.615 (0.810)	23.588 (0.823)	23.549 (0.724)	23.557 (0.736)
Median	23.62	23.62	23.55	23.56
Min, Max	22.08, 25.55	22.19, 24.71	21.60, 25.69	21.60, 25.69
IOP (mmHg)				
n (Reported)	26	28	306	360
Mean (SD)	15.0 (2.7)	14.0 (1.6)	14.8 (2.5)	14.7 (2.5)
Median	15	14	15	14
Min, Max	9, 19	10, 17	9, 22	9, 22
Pupil Size - Maximum (mm)				
n (Reported)	26	28	306	360
Mean (SD)	5.22 (1.00)	5.45 (0.81)	5.52 (0.74)	5.49 (0.77)
Median	5.4	5.5	5.6	5.6
Min, Max	2.9, 6.8	3.9, 7.2	2.9, 7.5	2.9, 7.5

[1] Summary statistics of the number of letters were converted to Snellen.

[2] Near add was only collected from Substudy.

[3] All Deferred surgery group subjects met initial eligibility (inclusion/exclusion) criteria. Baseline characteristics for analyses (as reported here) were taken at the 6-month observation visit.

	Randomized			
	Deferred Treatment Group[3] N = 26	Immediate Treatment Group N = 28	Non-randomized N = 306	Total Implanted N = 360
Pupil Size - Minimum (mm)				
n (Reported)	26	28	306	360
Mean (SD)	2.93 (0.67)	3.05 (0.58)	3.18 (0.54)	3.16 (0.56)
Median	2.9	3.0	3.2	3.1
Min, Max	1.5, 4.3	2.1, 4.7	1.6, 4.9	1.5, 4.9
Astigmatism (D)				
n (Reported)	26	28	306	360
Mean (SD)	-0.375 (0.302)	-0.286 (0.270)	-0.276 (0.288)	-0.284 (0.288)
Median	-0.50	-0.25	-0.25	-0.25
Min, Max	-1.25, 0.00	-1.00, 0.00	-1.00, 0.00	-1.25, 0.00
Cycloplegic Spherical Equivalent (D)				
n (Reported)	26	28	306	360
Mean (SD)	0.178 (0.285)	0.121 (0.377)	0.232 (0.301)	0.219 (0.307)
Median	0.250	0.063	0.250	0.250
Min, Max	-0.500, 0.750	-0.625, 0.875	-0.750, 1.000	-0.750, 1.000
Corneal Keratometry, (K1+K2)/2				
n (Reported)	26	28	306	360
Mean (SD)	43.451 (1.407)	43.579 (1.642)	43.736 (1.382)	43.703 (1.403)
Median	43.55	43.31	43.83	43.75
Min, Max	39.69, 46.50	39.81, 46.60	39.50, 48.43	39.50, 48.43
Scleral Thickness (um)				
n (Reported)	26	28	306	360
Mean (SD)	565.8 (30.2)	567.1 (34.9)	573.2 (45.0)	572.2 (43.4)
Median	560	560	560	560
Min, Max	530, 630	530, 660	530, 800	530, 800

[1] Summary statistics of the number of letters were converted to Snellen.

[2] Near add was only collected from Substudy.

[3] All Deferred surgery group subjects met initial eligibility (inclusion/exclusion) criteria. Baseline characteristics for analyses (as reported here) were taken at the 6-month observation visit.

Table 15 Baseline Characteristics - Randomized Substudy Subjects

	Randomized**	
	Deferred Treatment Group[3] N = 31	**Immediate Treatment Group N = 29**
DCNVA (Snellen)[1]		
n (Reported)	31	29
Mean (SD) - LogMAR	0.508 (0.103)	0.519 (0.079)
Mean - Snellen	20/64	20/66
Median - LogMAR (Snellen)	0.52 (20/66)	0.52 (20/66)
Min - LogMAR (Snellen)	0.24 (20/35)	0.36 (20/46)
Max - LogMAR (Snellen)	0.64 (20/87)	0.64 (20/87)
UCNVA (Snellen)[1]		
n (Reported)	31	29
Mean (SD) - LogMAR	0.497 (0.106)	0.512 (0.085)
Mean - Snellen	20/63	20/65
Median - LogMAR (Snellen)	0.50 (20/63)	0.50 (20/63)
Min - LogMAR (Snellen)	0.18 (20/30)	0.40 (20/50)
Max - LogMAR (Snellen)	0.64 (20/87)	0.66 (20/91)
Bilateral UCIVA (Snellen)[1]		
n (Reported)	31	29
Mean (SD) - LogMAR	0.348 (0.119)	0.366 (0.157)
Mean - Snellen	20/45	20/46
Median - LogMAR (Snellen)	0.38 (20/48)	0.40 (20/50)
Min - LogMAR (Snellen)	0.12 (20/26)	0.02 (20/21)
Max - LogMAR (Snellen)	0.52 (20/66)	0.62 (20/83)
UCDVA (Snellen)[1]		
n (Reported)	31	29
Mean (SD) - LogMAR	0.010 (0.083)	0.006 (0.059)
Mean - Snellen	20/20	20/20
Median - LogMAR (Snellen)	0.00 (20/20)	0.00 (20/20)
Min - LogMAR (Snellen)	-0.10 (20/16)	-0.08 (20/17)
Max - LogMAR (Snellen)	0.26 (20/36)	0.12 (20/26)
BCDVA (Snellen)[1]		
n (Reported)	31	29
Mean (SD) - LogMAR	-0.054 (0.066)	-0.043 (0.062)
Mean - Snellen	20/18	20/18
Median - LogMAR (Snellen)	-0.02 (20/19)	0.00 (20/20)
Min - LogMAR (Snellen)	-0.18 (20/13)	-0.18 (20/13)
Max - LogMAR (Snellen)	0.04 (20/22)	0.06 (20/23)

[1] Summary statistics of the number of letters were converted to Snellen.

[2] Near add was only collected from Substudy.

[3] All Deferred surgery group subjects met initial eligibility (inclusion/exclusion) criteria. Baseline characteristics for analyses (as reported here) were taken at the 6-month observation visit.

** Includes all randomly assigned subjects

	Randomized**	
	Deferred Treatment Group[3] N = 31	**Immediate Treatment Group N = 29**
MRSE (D)		
n (Reported)	31	29
Mean (SD)	0.073 (0.247)	0.047 (0.276)
Median	0.125	0.000
Min, Max	-0.500, 0.500	-0.500, 0.500
Near Add (D)[2]		
n (Reported)	31	29
Mean (SD)	1.798 (0.344)	1.767 (0.389)
Median	1.75	1.75
Min, Max	1.25, 2.50	1.25, 2.50
Axial Length (mm)		
n (Reported)	31	29
Mean (SD)	23.523 (0.795)	23.574 (0.811)
Median	23.59	23.57
Min, Max	22.08, 25.55	22.19, 24.71
IOP (mmHg)		
n (Reported)	31	29
Mean (SD)	15.2 (2.6)	14.1 (1.6)
Median	16	14
Min, Max	9, 19	10, 17
Pupil Size - Maximum (mm)		
n (Reported)	31	29
Mean (SD)	5.23 (0.96)	5.49 (0.82)
Median	5.3	5.5
Min, Max	2.9, 6.8	3.9, 7.2

[1] Summary statistics of the number of letters were converted to Snellen.

[2] Near add was only collected from Substudy.

[3] All Deferred surgery group subjects met initial eligibility (inclusion/exclusion) criteria. Baseline characteristics for analyses (as reported here) were taken at the 6-month observation visit.

** Includes all randomly assigned subjects

	Randomized**	
	Deferred Treatment Group[3] N = 31	**Immediate Treatment Group N = 29**
Pupil Size - Minimum (mm)		
n (Reported)	31	29
Mean (SD)	2.94 (0.64)	3.07 (0.58)
Median	2.9	3.0
Min, Max	1.5, 4.3	2.1, 4.7
Astigmatism (D)		
n (Reported)	31	29
Mean (SD)	-0.355 (0.308)	-0.284 (0.265)
Median	-0.50	-0.25
Min, Max	-1.25, 0.00	-1.00, 0.00
Cycloplegic Spherical Equivalent (D)		
n (Reported)	31	29
Mean (SD)	0.190 (0.285)	0.138 (0.381)
Median	0.250	0.125
Min, Max	-0.500, 0.750	-0.625, 0.875
Corneal Keratometry, (K1+K2)/2		
n (Reported)	31	29
Mean (SD)	43.664 (1.446)	43.623 (1.630)
Median	43.65	43.38
Min, Max	39.69, 46.50	39.81, 46.60
Scleral Thickness (um)		
n (Reported)	31	29
Mean (SD)	563.5 (29.4)	567.6 (34.4)
Median	560	560
Min, Max	530, 630	530, 660

[1] Summary statistics of the number of letters were converted to Snellen.

[2] Near add was only collected from Substudy.

[3] All Deferred surgery group subjects met initial eligibility (inclusion/exclusion) criteria. Baseline characteristics for analyses (as reported here) were taken at the 6-month observation visit.

** Includes all randomly assigned subjects

Table 16 Protocol Deviations

Type of Deviation	Total Events	Percent of Total Possible
MAJOR		
Excluded concomitant medication[1]	2	0.282%
Fellow eye supplemental baseline testing incomplete[3]	18	5.028%
Missed Endpoint Visit[2]	12	1.563%
6 Months (Randomized Substudy)	3	5.000%
12 Months	9	1.271%
Protocol assessment incomplete/not done[2]	12	1.563%
Dilated assessments	2	0.260%
Implant assessment	1	0.130%
Non-dilated assessments	4	0.521%
Pupillometry	1	0.130%
Slit biomicroscopy	1	0.130%
Visual acuity	3	0.391%
Surgery more than 60 days after baseline examination[1]	3	0.424%
MINOR		
Fellow eye surgery not performed[3]	7	1.955%
Missed visit[4]	77	2.213%
1 Week	4	0.565%
1 Month	8	1.130%
2 Months	14	1.977%
3 Months	15	2.119%
6 Months[5]	12	1.767%
18 Months	24	3.390%
Protocol assessment incomplete/not done[6]	101	1.819%
Dilated assessments[2]	5	0.651%
Non-dilated assessments[7]	7	0.169%
PRO[8]	3	0.145%
Pupillometry[6]	41	0.738%
Sub-study assessment[8]	2	0.096%
Visual acuity[9]	43	0.766%
Protocol procedure/assessment done incorrectly[9]	4	0.071%
Light meter equipment failure	1	0.018%
Pupillometry	3	0.053%
Total protocol deviations	**236**	

1 The percent was calculated based on total number of treated eyes, 708.

2 Percentages were calculated based on the total number subject visits for the randomized substudy (60) and the 12 month examination interval (708), while the percentage of total missed visits was based on the sum of all possible individual examination intervals (768).

3 The percent was calculated based on total number of subjects with treated primary eyes that were eligible for fellow eye implantation, 358.

4 Percentages were calculated based on the total number subject visits for each individual examination interval (708), while the percentage of total missed visits was based on the sum of all possible individual examination intervals (3,480).

5 Percentages were calculated based on the total number subject visits for the 6 month examination interval (708), minus the Randomized Substudy Immediate Treatment Group subjects (31), 679.

6 The percent was calculated based on total number of subject visits per protocol for all the treated eyes, 5,554.

7 The percent was calculated based on the total number of subject visits that measured this assessment, 4,152.

8 The percent was calculated based on the total number of subject visits that measured this assessment, 2,074.

9 The percent was calculated based on the total number of subject visits that measured this assessment, 5,614.

Table 17 Ocular Adverse Events - Safety Cohort

Events	Number (%) of Subjects N = 360	Number (%) of Eyes N = 708	Number of Events
Any Ocular Adverse Events	**170 (47.2%)**	**260 (36.7%)**	**365**
Visual Acuity	**9 (2.5%)**	**10 (1.4%)**	**10**
Decrease in BCDVA of ≥ 2 lines (≥ 10 letters) at 3 Months or Later	9 (2.5%)	10 (1.4%)	10
Lid	**33 (9.2%)**	**64 (9.0%)**	**64**
Ptosis	0 (0.0%)	0 (0.0%)	0
Onset of or worsening to severe clinically significant lid margin disease after 3 months	33 (9.2%)	64 (9.0%)	64
Cornea/Conjunctiva	**89 (24.7%)**	**143 (20.2%)**	**159**
Corneal dellen after 1 week	1 (0.3%)	1 (0.1%)	1
Corneal abrasion > 2mm after 1 week	5 (1.4%)	5 (0.7%)	5
Corneal edema (moderate or severe) after 1 month	0 (0.0%)	0 (0.0%)	0
Corneal infiltrate or ulcer	1 (0.3%)	1 (0.1%)	1
Dry eye signs requiring prescription medication after 6 months	44 (12.2%)	87 (12.3%)	87
Conjunctival Cyst	15 (4.2%)	15 (2.1%)	15
Conjunctival thinning or erosion	0 (0.0%)	0 (0.0%)	0
Conjunctival Injection-moderate or severe @ 3 months or more	20 (5.6%)	32 (4.5%)	32
Subconjunctival hemorrhage after 3 months	15 (4.2%)	16 (2.3%)	18
Iris/Pupil	**1 (0.3%)**	**1 (0.1%)**	**1**
Pupil Abnormalities persisting after 3 months	1 (0.3%)	1 (0.1%)	1
Anterior Chamber	**8 (2.2%)**	**8 (1.1%)**	**9**
Anterior Segment Ischemia Grade 4	1 (0.3%)	1 (0.1%)	1
Anterior Chamber Cells or Flare greater than mild at Day 1 - 1 Week	2 (0.6%)	2 (0.3%)	2
Anterior Chamber Cells or Flare-any after 1 week	6 (1.7%)	6 (0.8%)	6
Lens	**2 (0.6%)**	**3 (0.4%)**	**3**
Lens Opacity-a worsening of two grades as compared to baseline noted on two consecutive visits	2 (0.6%)	3 (0.4%)	3
Sclera (Intraoperative Events)	**8 (2.2%)**	**8 (1.1%)**	**8**
Scleral perforation alone	3 (0.8%)	3 (0.4%)	3
Scleral perforation with vitreous prolapse	5 (1.4%)	5 (0.7%)	5
Intraocular Pressure	**6 (1.7%)**	**6 (0.8%)**	**6**
Hypotony (IOP < 6mmHg)	1 (0.3%)	1 (0.1%)	1
Increase in IOP of > 10mm Hg over baseline or IOP > 30mm Hg at two consecutive visits at 1 week or later	5 (1.4%)	5 (0.7%)	5
Fundus/Posterior Pole	**3 (0.8%)**	**3 (0.4%)**	**3**
Choroidal effusion	0 (0.0%)	0 (0.0%)	0
Retinal detachment	0 (0.0%)	0 (0.0%)	0
Retinal hemorrhage	3 (0.8%)	3 (0.4%)	3

Percentage is based on the number of implanted eyes.
An eye could be reported with the same events multiple times. Also, an eye could be reported with multiple adverse events.

Events	Number (%) of Subjects N = 360	Number (%) of Eyes N = 708	Number of Events
Vitreous hemorrhage	0 (0.0%)	0 (0.0%)	0
Secondary Surgical Intervention	**23 (6.4%)**	**28 (4.0%)**	**28**
Micro Insert segment removal	8 (2.2%)	13 (1.8%)	13
Exposed Micro Insert segment or conjunctival retraction requiring conjunctival reapproximation	15 (4.2%)	15 (2.1%)	15
Symptoms	**0 (0.0%)**	**0 (0.0%)**	**0**
Eye pain requiring oral prescription pain medication after 1 week	0 (0.0%)	0 (0.0%)	0
Allergic Reactions	**2 (0.6%)**	**4 (0.6%)**	**4**
To Medications	2 (0.6%)	4 (0.6%)	4
To Sutures	0 (0.0%)	0 (0.0%)	0
To Anesthesia	0 (0.0%)	0 (0.0%)	0
To Other	0 (0.0%)	0 (0.0%)	0
Other	**50 (13.9%)**	**63 (8.9%)**	**70**
Other	0 (0.0%)	0 (0.0%)	0
Bacterial Conjunctivis	4 (1.1%)	5 (0.7%)	5
Bee Sting on Eyelid	1 (0.3%)	1 (0.1%)	1
Bells Palsy	1 (0.3%)	1 (0.1%)	1
Branch Retinal Vein Occlusion	1 (0.3%)	1 (0.1%)	1
Central Serous Retinopathy	1 (0.3%)	1 (0.1%)	1
Chalazion	5 (1.4%)	5 (0.7%)	6
Choroidal Nevus	1 (0.3%)	1 (0.1%)	1
Conjunctival Bleb	1 (0.3%)	1 (0.1%)	1
Conjunctival Cyst	1 (0.3%)	1 (0.1%)	1
Conjunctival Foreign Body	2 (0.6%)	2 (0.3%)	2
Corneal Abrasion	1 (0.3%)	2 (0.3%)	2
Corneal Foreign Body	1 (0.3%)	1 (0.1%)	2
Corneal Neovascularization	1 (0.3%)	1 (0.1%)	1
Corneal Scar	1 (0.3%)	1 (0.1%)	1
Dry Aged Related Macular Degeneration	1 (0.3%)	1 (0.1%)	1
Environmental Allergic Conjunctivis	2 (0.6%)	3 (0.4%)	3
Epi Retinal Membrane or Macular Pucker	1 (0.3%)	1 (0.1%)	1
Foreign Body Sensation	2 (0.6%)	4 (0.6%)	4
Herpes Zoster Ophthalmicus	1 (0.3%)	1 (0.1%)	1
Hordeolum	5 (1.4%)	5 (0.7%)	5
Hypertensive Optic Neuropathy	1 (0.3%)	2 (0.3%)	2
Infectious Neuroretinitis	1 (0.3%)	1 (0.1%)	1
Internal Hordeolum	2 (0.6%)	2 (0.3%)	2
Intraocular Inflammation Other Than AC Cell Flare	1 (0.3%)	1 (0.1%)	1
Laser Retinopexy or Repair of Retinal Hole	1 (0.3%)	1 (0.1%)	1

Percentage is based on the number of implanted eyes.
An eye could be reported with the same events multiple times. Also, an eye could be reported with multiple adverse events.

Events	Number (%) of Subjects N = 360	Number (%) of Eyes N = 708	Number of Events
Nodular Episcleritis	1 (0.3%)	1 (0.1%)	1
Non-Arteritic Anterior Ischemic Optic Neuropathy	1 (0.3%)	1 (0.1%)	1
Pigment Epithelial Detachment	1 (0.3%)	1 (0.1%)	1
Posterior Scleritits	1 (0.3%)	1 (0.1%)	1
Posterior Vitreous Detachment	2 (0.6%)	2 (0.3%)	2
Pterygium	1 (0.3%)	1 (0.1%)	1
Retinal Hemorrhage	1 (0.3%)	1 (0.1%)	1
Retinal Hole	1 (0.3%)	1 (0.1%)	1
Retinal Tear	1 (0.3%)	1 (0.1%)	1
Suspected Herpes Zoster	1 (0.3%)	1 (0.1%)	1
Trochlear Palsy	1 (0.3%)	1 (0.1%)	1
Viral Conjunctivitis	3 (0.8%)	6 (0.8%)	6
Vogt-Koyanagi-Harada (VKH) Syndrome	1 (0.3%)	2 (0.3%)	2
Vortex Keratopathy	1 (0.3%)	2 (0.3%)	2

Percentage is based on the number of implanted eyes.
An eye could be reported with the same events multiple times. Also, an eye could be reported with multiple adverse events.

Table 18 Removal Reasons

Subject	Eye	Primary or Fellow	Removals by Reason: Foreign Body Sensation	Ocular Surface Dryness	Perceived Lack of Effect	Pupil Response	Redness/ Cosmesis	Residual Refractive Error
(b) (6)	OD	Primary*			1		1	
	OS	Fellow*			1		1	
	OD	Primary*		1	1			
	OS	Fellow*		1	1			
	OD	Primary				1		
	OD	Primary				1		
	OD	Primary					1	
	OD	Fellow*			1			1
	OS	Primary*			1			1
	OD	Primary*	1				1	
	OS	Fellow*	1				1	
	OD	Primary*	1	1				
	OS	Fellow*	1	1				
		TOTAL	4	4	6	2	5	2

Note: Removals (eyes) n=13
* Indicates multiple reasons for removal were given.

Table 19 Long Term Explants in the ITT Safety Cohort

	Off-study/interim				5 Year Follow-Up			
	% of Patients (N=360)		% of Eyes (N=708)		% of Patients (N=248)		% of Eyes (N=492)	
Primary Reasons	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Post 24 month full explants	7	1.9%	14	2.0%	2	0.8%	4	0.8%
Perceived lack of effect	2	0.6%	4	0.6%	-	-	-	-
Foreign body sensation	2	0.6%	4	0.6%	-	-	-	-
Cosmesis	1	0.3%	2	0.3%	-	-	-	-
Systemic AE	1	0.3%	2	0.3%	-	-	-	-
Dryness	1	0.3%	2	0.3%	1	0.4%	2	0.4%
Lid Margin Disease	0	0.0%	0	0.0%	1	0.4%	2	0.4%
Post 24 month partial explants	3	0.8%	3	0.4%	-	-	-	-
Redness	1	0.3%	1	0.1%	-	-	-	-
Foreign body sensation	1	0.3%	1	0.1%	-	-	-	-
Dryness	1	0.3%	1	0.1%	-	-	-	-

Table 20 Pupillometry - Percent Constriction - Safety Cohort

	Preop N = 708	Op N = 708	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
Pupil Percent Constriction (%)											
n (Reported)	708	706	704	697	695	686	686	680	683	651	664
Mean (SD)	42.8 (4.5)	32.1 (6.6)	41.2 (5.5)	41.0 (5.1)	40.3 (5.1)	41.2 (5.0)	41.4 (5.0)	41.7 (4.9)	42.0 (4.8)	41.5 (4.7)	41.7 (4.8)
Median	43	30	42	41	41	42	42	42	42	42	42
Min, Max	31 54	2 63	20 56	11 56	15 56	19 56	20 56	26 53	28 57	24 57	22 53
Not Reported	0	2	2	5	3	5	3	6	4	1	4
Change in Pupil Percent Constriction (%)											
n (Reported)		706	704	697	695	686	686	680	683	651	664
Mean (SD)		-11 (7.5)	-1.6 (5.4)	-1.8 (4.4)	-2.4 (4.3)	-1.6 (4.1)	-1.4 (4.1)	-1.1 (4.2)	-0.7 (4.0)	-1.3 (4.0)	-1.0 (4.1)
95% CI[1]		(-11, -10)	(-2.0, -1.2)	(-2.1, -1.4)	(-2.7, -2.1)	(-1.9, -1.3)	(-1.7, -1.1)	(-1.4, -0.8)	(-1.0, -0.5)	(-1.6, -1.0)	(-1.3, -0.7)
Median		-12	-1	-2	-2	-1	-2	-1	-1	-1	-1
Min, Max		-41 21	-25 14	-38 11	-29 9	-25 10	-29 12	-16 15	-16 15	-23 12	-22 13
Not Reported		2	2	5	3	5	3	6	4	1	4

[1] 95% confidence interval was based on t-distribution.

Table 21 Pupillometry - Pupil Reaction - Maximum Constriction Velocity - Safety Cohort

	Preop N = 708	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
Pupil Reaction - Maximum Constriction Velocity (mm/sec)										
n (Reported)	708	703	697	695	686	686	680	683	651	664
Mean (SD)	4.686 (0.694)	4.766 (0.930)	4.746 (0.854)	4.543 (0.755)	4.587 (0.795)	4.585 (0.760)	4.575 (0.753)	4.597 (0.769)	4.500 (0.762)	4.557 (0.762)
Median	4.71	4.82	4.75	4.53	4.62	4.59	4.57	4.60	4.49	4.59
Min, Max	2.41 6.64	2.05 7.64	1.09 8.03	1.87 6.94	1.89 7.64	1.95 6.95	2.26 7.15	2.25 7.32	1.80 7.28	2.19 7.19
Not Reported	0	3	5	3	5	3	6	4	1	4
Change in Pupil Reaction - Maximum Constriction Velocity (mm/sec)										
n (Reported)		703	697	695	686	686	680	683	651	664
Mean (SD)		0.077 (0.849)	0.056 (0.737)	-0.144 (0.667)	-0.107 (0.673)	-0.112 (0.648)	-0.118 (0.654)	-0.087 (0.661)	-0.183 (0.652)	-0.118 (0.672)
95% CI[1]		(0.015, 0.140)	(0.001, 0.111)	(-0.194, -0.094)	(-0.157, -0.056)	(-0.160, -0.063)	(-0.168, -0.069)	(-0.136, -0.037)	(-0.233, -0.132)	(-0.169, -0.067)
Median		0.13	0.05	-0.13	-0.11	-0.11	-0.11	-0.07	-0.15	-0.13
Min, Max		-2.62 3.31	-3.23 2.93	-2.94 2.20	-2.92 2.85	-2.65 2.75	-2.55 2.89	-2.45 2.55	-2.46 2.29	-3.01 3.25
Not Reported		3	5	3	5	3	6	4	1	4

[1] 95% confidence interval was based on t-distribution.

Table 22 Slit Lamp - Conjunctiva - Safety Cohort

	Preop N = 708	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
Conjunctival Injection										
n (Reported)	708	706	702	697	691	689	686	687	652	668
None	575 (81.2%)	10 (1.4%)	2 (0.3%)	61 (8.8%)	94 (13.6%)	191 (27.7%)	324 (47.2%)	393 (57.2%)	403 (61.8%)	470 (70.4%)
Trace	120 (16.9%)	15 (2.1%)	60 (8.5%)	159 (22.8%)	238 (34.4%)	259 (37.6%)	253 (36.9%)	228 (33.2%)	200 (30.7%)	161 (24.1%)
Mild	13 (1.8%)	130 (18.4%)	195 (27.8%)	350 (50.2%)	298 (43.1%)	218 (31.6%)	102 (14.9%)	64 (9.3%)	41 (6.3%)	37 (5.5%)
Moderate	0 (0.0%)	338 (47.9%)	308 (43.9%)	104 (14.9%)	60 (8.7%)	21 (3.0%)	7 (1.0%)	2 (0.3%)	8 (1.2%)	0 (0.0%)
Marked/Severe	0 (0.0%)	213 (30.2%)	137 (19.5%)	23 (3.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	1	0	0	0	0	0	0
Subconjunctival Hemorrhage										
n (Reported)	708	706	702	697	691	689	686	685	652	668
None	708 (100.0%)	0 (0.0%)	40 (5.7%)	531 (76.2%)	673 (97.4%)	685 (99.4%)	685 (99.9%)	683 (99.7%)	650 (99.7%)	666 (99.7%)
≤ 1 Quadrant	0 (0.0%)	3 (0.4%)	102 (14.5%)	140 (20.1%)	16 (2.3%)	4 (0.6%)	1 (0.1%)	2 (0.3%)	1 (0.2%)	2 (0.3%)
2 Quadrants	0 (0.0%)	27 (3.8%)	216 (30.8%)	22 (3.2%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3-4 Quadrants	0 (0.0%)	676 (95.8%)	344 (49.0%)	4 (0.6%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Not Reported	0	0	0	1	0	0	0	2	0	0
Conjunctival Edema										
n (Reported)	708	705	702	697	690	689	685	685	652	668
None	708 (100.0%)	85 (12.1%)	144 (20.5%)	490 (70.3%)	622 (90.1%)	662 (96.1%)	679 (99.1%)	677 (98.8%)	648 (99.4%)	668 (100.0%)
Trace	0 (0.0%)	70 (9.9%)	168 (23.9%)	116 (16.6%)	53 (7.7%)	23 (3.3%)	6 (0.9%)	8 (1.2%)	4 (0.6%)	0 (0.0%)
Mild	0 (0.0%)	164 (23.3%)	205 (29.2%)	83 (11.9%)	14 (2.0%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	0 (0.0%)	280 (39.7%)	128 (18.2%)	8 (1.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Marked/Severe	0 (0.0%)	106 (15.0%)	57 (8.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	1	0	1	1	0	1	2	0	0
Other Conjunctival Findings										
n (Reported)	708	706	702	697	691	689	686	687	652	668
None	591 (83.5%)	571 (80.9%)	637 (90.7%)	657 (94.3%)	659 (95.4%)	653 (94.8%)	639 (93.1%)	641 (93.3%)	592 (90.8%)	617 (92.4%)
Abnormal	114 (16.1%)	40 (5.7%)	42 (6.0%)	33 (4.7%)	27 (3.9%)	31 (4.5%)	46 (6.7%)	42 (6.1%)	51 (7.8%)	45 (6.7%)
Observations*	3 (0.4%)	95 (13.5%)	23 (3.3%)	7 (1.0%)	5 (0.7%)	5 (0.7%)	1 (0.1%)	4 (0.6%)	9 (1.4%)	6 (0.9%)
Not Reported	0	0	0	1	0	0	0	0	0	0

Percentage is based on the number of eyes reported with data.

* Observations include ocular notations that were not clinically significant and were not associated with any adverse events.

Table 23 Slit Lamp - Cornea - Safety Cohort

	Preop N = 708	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
Cornea Superficial Punctate Keratitis										
n (Reported)	708	705	701	697	691	689	686	687	652	668
None	683 (96.5%)	609 (86.4%)	642 (91.6%)	665 (95.4%)	638 (92.3%)	649 (94.2%)	654 (95.3%)	615 (89.5%)	591 (90.6%)	614 (91.9%)
Trace	24 (3.4%)	70 (9.9%)	40 (5.7%)	21 (3.0%)	36 (5.2%)	27 (3.9%)	24 (3.5%)	55 (8.0%)	52 (8.0%)	43 (6.4%)
Mild	1 (0.1%)	20 (2.8%)	19 (2.7%)	11 (1.6%)	16 (2.3%)	13 (1.9%)	7 (1.0%)	14 (2.0%)	9 (1.4%)	11 (1.6%)
Moderate	0 (0.0%)	5 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
Marked/Severe	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	1	1	1	0	0	0	0	0	0
Cornea Abrasion										
n (Reported)	708	706	702	696	691	689	686	687	650	668
None	708 (100.0%)	585 (82.9%)	693 (98.7%)	694 (99.7%)	691 (100.0%)	688 (99.9%)	686 (100.0%)	686 (99.9%)	650 (100.0%)	668 (100.0%)
Tiny	0 (0.0%)	87 (12.3%)	6 (0.9%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
1-2 mm	0 (0.0%)	23 (3.3%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2-3 mm	0 (0.0%)	6 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
>3 mm	0 (0.0%)	5 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	2	0	0	0	0	2	0
Cornea Edema										
n (Reported)	708	706	702	697	691	688	686	687	652	668
None (0%)	708 (100.0%)	646 (91.5%)	688 (98.0%)	697 (100.0%)	690 (99.9%)	688 (100.0%)	686 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
Trace (1-5%)	0 (0.0%)	40 (5.7%)	12 (1.7%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mild (6-25%)	0 (0.0%)	14 (2.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate (26-50%)	0 (0.0%)	5 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe (>50%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	1	0	1	0	0	0	0
Cornea Endothelial Guttata										
n (Reported)	708	706	700	697	690	687	686	687	652	668
None	703 (99.3%)	701 (99.3%)	694 (99.1%)	692 (99.3%)	685 (99.3%)	687 (100.0%)	686 (100.0%)	684 (99.6%)	652 (100.0%)	668 (100.0%)
Rare	5 (0.7%)	5 (0.7%)	6 (0.9%)	5 (0.7%)	5 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
Few	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Many	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mark/Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	2	1	1	2	0	0	0	0

	Preop N = 708	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
Other Corneal Findings										
n (Reported)	708	706	702	697	691	689	686	687	652	668
None	662 (93.5%)	672 (95.2%)	673 (95.9%)	671 (96.3%)	668 (96.7%)	668 (97.0%)	667 (97.2%)	663 (96.5%)	625 (95.9%)	637 (95.4%)
Abnormal	44 (6.2%)	23 (3.3%)	26 (3.7%)	22 (3.2%)	21 (3.0%)	19 (2.8%)	15 (2.2%)	14 (2.0%)	17 (2.6%)	21 (3.1%)
Observations*	2 (0.3%)	11 (1.6%)	3 (0.4%)	4 (0.6%)	2 (0.3%)	2 (0.3%)	4 (0.6%)	10 (1.5%)	10 (1.5%)	10 (1.5%)
Not Reported	0	0	0	1	0	0	0	0	0	0

Percentage is based on the number of eyes reported with data.

* Observations include ocular notations that were not clinically significant and were not associated with any adverse events.

Table 24 Slit Lamp - Anterior Chamber Cells - Safety Cohort

	Preop N = 708	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
n (Reported)	708	706	702	697	691	688	685	685	652	668
Grade 0 (<1)	708 (100.0%)	675 (95.6%)	699 (99.6%)	696 (99.9%)	690 (99.9%)	688 (100.0%)	685 (100.0%)	685 (100.0%)	650 (99.7%)	668 (100.0%)
Grade 0.5+ (1-5)	0 (0.0%)	23 (3.3%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 1+ (6-15)	0 (0.0%)	7 (1.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Grade 2+ (16-25)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Grade 3+ (26-50)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 4+ (50+)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	0	0	0	1	0	1	1	2	0	0

Percentage is based on the number of eyes reported with data.

Table 25 Micro Insert Segment Assessments - Safety Cohort

	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
Superior Temporal									
n (Reported)	704	701	697	691	689	686	687	652	668
Segment Present	703 (99.9%)	700 (99.9%)	696 (99.9%)	690 (99.9%)	688 (99.9%)	685 (99.9%)	687 (100.0%)	651 (99.8%)	667 (99.9%)
Segment Missing	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Shallow Segments	NA	NA	1 (0.1%)	1 (0.1%)	3 (0.4%)	2 (0.3%)	4 (0.6%)	4 (0.6%)	5 (0.7%)
Deep Segments	NA	NA	27 (3.9%)	28 (4.1%)	31 (4.5%)	33 (4.8%)	34 (4.9%)	29 (4.4%)	31 (4.6%)
Segment Non-Tangential to the Limbus	NA	NA	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	5 (0.7%)	3 (0.5%)	2 (0.3%)
Tilted Segments	NA	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Segment too Close to the Limbus	NA	NA	1 (0.1%)	3 (0.4%)	3 (0.4%)	4 (0.6%)	4 (0.6%)	7 (1.1%)	5 (0.7%)
Segment too far away from the Limbus	NA	NA	2 (0.3%)	5 (0.7%)	5 (0.7%)	4 (0.6%)	5 (0.7%)	5 (0.8%)	3 (0.4%)
Not Reported	2	1	1	0	0	0	0	0	0
Superior Nasal									
n (Reported)	704	701	697	691	689	686	687	652	668
Segment Present	704 (100.0%)	701 (100.0%)	697 (100.0%)	691 (100.0%)	689 (100.0%)	686 (100.0%)	687 (100.0%)	652 (100.0%)	667 (99.9%)
Segment Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Shallow Segments	NA	NA	1 (0.1%)	2 (0.3%)	4 (0.6%)	3 (0.4%)	3 (0.4%)	3 (0.5%)	4 (0.6%)
Deep Segments	NA	NA	20 (2.9%)	19 (2.7%)	19 (2.8%)	23 (3.4%)	21 (3.1%)	19 (2.9%)	19 (2.8%)
Segment Non-Tangential to the Limbus	NA	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.6%)	1 (0.1%)	2 (0.3%)	0 (0.0%)
Tilted Segments	NA	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Segment too Close to the Limbus	NA	NA	3 (0.4%)	1 (0.1%)	4 (0.6%)	2 (0.3%)	2 (0.3%)	5 (0.8%)	3 (0.4%)
Segment too far away from the Limbus	NA	NA	2 (0.3%)	5 (0.7%)	4 (0.6%)	6 (0.9%)	6 (0.9%)	5 (0.8%)	5 (0.7%)
Not Reported	2	1	1	0	0	0	0	0	0

Percentage is based on the number of eyes reported with data.

	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
Inferior Temporal									
n (Reported)	704	701	697	691	689	686	687	652	668
Segment Present	704 (100.0%)	701 (100.0%)	697 (100.0%)	691 (100.0%)	689 (100.0%)	686 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
Segment Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Shallow Segments	NA	NA	2 (0.3%)	3 (0.4%)	4 (0.6%)	5 (0.7%)	8 (1.2%)	6 (0.9%)	8 (1.2%)
Deep Segments	NA	NA	5 (0.7%)	6 (0.9%)	8 (1.2%)	8 (1.2%)	9 (1.3%)	7 (1.1%)	4 (0.6%)
Segment Non-Tangential to the Limbus	NA	NA	1 (0.1%)	1 (0.1%)	2 (0.3%)	3 (0.4%)	5 (0.7%)	2 (0.3%)	6 (0.9%)
Tilted Segments	NA	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Segment too Close to the Limbus	NA	NA	3 (0.4%)	3 (0.4%)	3 (0.4%)	8 (1.2%)	11 (1.6%)	11 (1.7%)	11 (1.6%)
Segment too far away from the Limbus	NA	NA	0 (0.0%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported	2	1	1	0	0	0	0	0	0
Inferior Nasal									
n (Reported)	704	701	697	691	689	686	687	652	668
Segment Present	703 (99.9%)	700 (99.9%)	696 (99.9%)	690 (99.9%)	688 (99.9%)	685 (99.9%)	687 (100.0%)	651 (99.8%)	667 (99.9%)
Segment Missing	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
Shallow Segments	NA	NA	3 (0.4%)	3 (0.4%)	6 (0.9%)	7 (1.0%)	10 (1.5%)	7 (1.1%)	11 (1.6%)
Deep Segments	NA	NA	5 (0.7%)	5 (0.7%)	6 (0.9%)	7 (1.0%)	7 (1.0%)	6 (0.9%)	2 (0.3%)
Segment Non-Tangential to the Limbus	NA	NA	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.3%)	9 (1.3%)	6 (0.9%)	7 (1.0%)
Tilted Segments	NA	NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Segment too Close to the Limbus	NA	NA	2 (0.3%)	3 (0.4%)	4 (0.6%)	4 (0.6%)	10 (1.5%)	9 (1.4%)	10 (1.5%)
Segment too far away from the Limbus	NA	NA	0 (0.0%)	2 (0.3%)	2 (0.3%)	1 (0.1%)	2 (0.3%)	1 (0.2%)	1 (0.1%)
Not Reported	2	1	1	0	0	0	0	0	0

Percentage is based on the number of eyes reported with data.

Table 26 Intraocular Pressure (IOP) and Change in IOP from Baseline Safety Cohort

	Preop N = 708	Day 1 N = 706	Week 1 N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
IOP (mmHg)										
n (Reported)	708	705	702	698	691	689	686	687	652	668
Mean (SD)	14.7 (2.5)	17.6 (4.1)	17.7 (4.3)	15.8 (3.4)	14.7 (2.8)	14.4 (2.8)	14.1 (2.8)	14.0 (2.8)	14.0 (2.6)	14.1 (2.6)
95% CI[1]	14.6, 14.9	17.3, 17.9	17.4, 18.0	15.5, 16.0	14.5, 14.9	14.2, 14.6	13.9, 14.3	13.8, 14.2	13.8, 14.1	13.9, 14.2
Median	14	18	17	15	14	14	14	14	14	14
Min, Max	9, 22	5, 41	6, 41	6, 30	6, 24	6, 26	6, 24	6, 23	6, 23	6, 22
Not Reported	0	1	0	0	0	0	0	0	0	0
IOP < 6 mmHg	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IOP > 30 mmHg	0 (0.0%)	3 (0.4%)	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Change in IOP (mmHg)										
n (Reported)		705	702	698	691	689	686	687	652	668
Mean (SD)		2.9 (4.0)	3.0 (4.1)	1.1 (3.3)	-0.0 (2.8)	-0.3 (2.8)	-0.6 (2.7)	-0.8 (2.6)	-0.7 (2.4)	-0.7 (2.5)
95% CI[1]		2.6, 3.1	2.6, 3.3	0.8, 1.3	-0.2, 0.2	-0.5, -0.1	-0.8, -0.4	-1.0, -0.6	-0.9, -0.6	-0.9, -0.5
Median		3	3	1	0	0	-1	-1	-1	-1
Min, Max		-8, 27	-9, 24	-8, 18	-9, 10	-8, 12	-9, 10	-9, 7	-8, 7	-8, 7
Decrease > 10 mmHg		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Decrease > 5 to ≤ 10 mmHg		5 (0.7%)	7 (1.0%)	8 (1.1%)	15 (2.2%)	16 (2.3%)	19 (2.8%)	20 (2.9%)	6 (0.9%)	14 (2.1%)
Decrease > 2 to ≤ 5 mmHg		36 (5.1%)	40 (5.7%)	73 (10.5%)	110 (15.9%)	123 (17.9%)	147 (21.4%)	145 (21.1%)	146 (22.4%)	134 (20.1%)
Change within ± 2 mmHg		305 (43.3%)	303 (43.2%)	415 (59.5%)	440 (63.7%)	450 (65.3%)	432 (63.0%)	447 (65.1%)	444 (68.1%)	445 (66.6%)
Increase > 2 to ≤ 5 mmHg		199 (28.2%)	180 (25.6%)	136 (19.5%)	105 (15.2%)	80 (11.6%)	80 (11.7%)	66 (9.6%)	52 (8.0%)	66 (9.9%)
Increase > 5 to ≤ 10 mmHg		134 (19.0%)	143 (20.4%)	60 (8.6%)	21 (3.0%)	19 (2.8%)	8 (1.2%)	9 (1.3%)	4 (0.6%)	9 (1.3%)
Increase > 10 mmHg		26 (3.7%)	29 (4.1%)	6 (0.9%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Reported		1	0	0	0	0	0	0	0	0
IOP > 30 mmHg or IOP Increase > 10 mmHg		26 (3.7%)	29 (4.1%)	6 (0.9%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Percentage is based on the number of eyes reported with data.

[1] 95% confidence interval was based on t-distribution.

Table 27 Intraocular Pressure (IOP) and Change in IOP from Baseline for Primary Eyes – Randomized Substudy

	Deferred Treatment Group (31 Randomized Eyes)			Immediate Treatment Group (29 Randomized Eyes)		
	Baseline N = 31	Month 3 N = 29	Month 6 N = 29	Preop N = 29	Month 3 N = 28	Month 6 N = 25
IOP (mmHg)						
n (Reported)	31	29	29	29	28	25
Mean (SD)	14.5 (2.1)	14.9 (2.6)	15.2 (2.7)	14.1 (1.6)	13.0 (2.1)	13.3 (2.4)
95% CI[1]	13.8, 15.3	13.9, 15.9	14.2, 16.2	13.5, 14.7	12.1, 13.8	12.3, 14.3
Median	14	15	16	14	12	13
Min, Max	10, 18	9, 20	9, 19	10, 17	9, 18	7, 18
Not Reported	0	0	0	0	0	0
Change in IOP (mmHg)						
n (Reported)		29	29		28	25
Mean (SD)		0.4 (2.6)	0.7 (2.3)		-1.0 (2.6)	-0.6 (2.5)
95% CI[1]		-0.5, 1.4	-0.1, 1.6		-2.0, -0.0	-1.6, 0.4
Median		0	0		-2	0
Min, Max		-5, 8	-5, 5		-7, 6	-7, 4
Decrease > 10 mmHg		0 (0%)	0 (0%)		0 (0%)	0 (0%)
Decrease > 5 to ≤ 10 mmHg		0 (0%)	0 (0%)		1 (4%)	2 (8%)
Decrease > 2 to ≤ 5 mmHg		3 (10%)	3 (10%)		5 (18%)	1 (4%)
Change within ± 2 mmHg		22 (76%)	20 (69%)		21 (75%)	20 (80%)
Increase > 2 to ≤ 5 mmHg		3 (10%)	6 (21%)		0 (0%)	2 (8%)
Increase > 5 to ≤ 10 mmHg		1 (3%)	0 (0%)		1 (4%)	0 (0%)
Increase > 10 mmHg		0 (0%)	0 (0%)		0 (0%)	0 (0%)
Not Reported		0	0		0	0

Percentage is based on the number of eyes reported with data.
[1] 95% confidence interval was based on t-distribution.

Table 28 BCDVA Over Time - Safety Cohort

	Preop N = 708	1 Week N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
n (Reported)	708	702	696	691	688	684	687	652	668
20/16 or better	449 (63.4%)	372 (53.0%)	442 (63.5%)	494 (71.5%)	533 (77.5%)	544 (79.5%)	581 (84.6%)	558 (85.6%)	552 (82.6%)
20/20 or better	708 (100.0%)	642 (91.5%)	676 (97.1%)	676 (97.8%)	684 (99.4%)	682 (99.7%)	683 (99.4%)	647 (99.2%)	665 (99.6%)
20/25 or better	708 (100.0%)	691 (98.4%)	696 (100.0%)	690 (99.9%)	687 (99.9%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/32 or better	708 (100.0%)	699 (99.6%)	696 (100.0%)	691 (100.0%)	687 (99.9%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/40 or better	708 (100.0%)	700 (99.7%)	696 (100.0%)	691 (100.0%)	687 (99.9%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/50 or better	708 (100.0%)	701 (99.9%)	696 (100.0%)	691 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/63 or better	708 (100.0%)	702 (100.0%)	696 (100.0%)	691 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/80 or better	708 (100.0%)	702 (100.0%)	696 (100.0%)	691 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/100 or better	708 (100.0%)	702 (100.0%)	696 (100.0%)	691 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/125 or better	708 (100.0%)	702 (100.0%)	696 (100.0%)	691 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/160 or better	708 (100.0%)	702 (100.0%)	696 (100.0%)	691 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
20/200 or better	708 (100.0%)	702 (100.0%)	696 (100.0%)	691 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	652 (100.0%)	668 (100.0%)
Not Reported	0	0	2	0	1	2	0	0	0

Percentage is based on the number of eyes reported with data.

Table 29 Change in BCDVA from Baseline - Safety Cohort

	1 Week N = 702	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
n (Reported)	702	696	691	688	684	687	652	668
Gained ≥ 5 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gained ≥ 4 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gained ≥ 3 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gained ≥ 2 lines	1 (0.1%)	2 (0.3%)	5 (0.7%)	8 (1.2%)	9 (1.3%)	18 (2.6%)	10 (1.5%)	15 (2.2%)
Gained ≥ 1 line	44 (6.3%)	57 (8.2%)	92 (13.3%)	109 (15.8%)	125 (18.3%)	170 (24.7%)	178 (27.3%)	185 (27.7%)
No Change	510 (72.6%)	565 (81.2%)	541 (78.3%)	553 (80.4%)	540 (78.9%)	503 (73.2%)	456 (69.9%)	463 (69.3%)
Lost ≥ 1 line	148 (21.1%)	74 (10.6%)	58 (8.4%)	26 (3.8%)	19 (2.8%)	14 (2.0%)	18 (2.8%)	20 (3.0%)
Lost ≥ 2 lines	40 (5.7%)	15 (2.2%)	7 (1.0%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	2 (0.3%)	0 (0.0%)
Lost ≥ 3 lines	10 (1.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 4 lines	3 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 5 lines	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean (SD) of line change	-0.30 (0.90)	-0.04 (0.71)	0.13 (0.70)	0.26 (0.66)	0.31 (0.65)	0.43 (0.70)	0.46 (0.68)	0.46 (0.71)
Not Reported	0	2	0	1	2	0	0	0

Percentage is based on the number of eyes reported with data.

Table 30 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months by Population

Population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Bilateral Effectiveness Cohort	275/340 (80.9%) (76.3%, 84.9%)	282/348 (81.0%) (76.5%, 85.0%)	277/348 (79.6%) (75.0%, 83.7%)
Intent-to-Treat	277/350 (79.1%) (74.5%, 83.3%)	285/360 (79.2%) (74.6%, 83.2%)	279/360 (77.5%) (72.8%, 81.7%)

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

2 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as successes.

3 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 31 Monocular DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months for Primary Eyes vs Fellow Eyes - All Implanted Eyes (Imputation per Primary Analysis Approach)

	Implanted Primary Eyes	Implanted Fellow Eyes	All Implanted Eyes
N[1]	350	342	692
20/40 or Better and Gain of ≥ 10 Letters	277 (79.1%)	266 (77.8%)	543 (78.5%)
95% CI[2]	74.5%, 83.3%	73.0%, 82.1%	74.2%, 81.6%
No Imputation for Missing Month 12	10	6	16

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

2 Binomial distribution for Implanted Primary Eyes and for Implanted Fellow Eyes; GEE with an unstructured working correlation matrix for All Implanted Eyes

Table 32 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months By Population

Population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Bilateral Effectiveness Cohort	287/335 (85.7%) (81.5%, 89.2%)	297/348 (85.3%) (81.2%, 88.9%)	289/348 (83.0%) (78.7%, 86.8%)
Intent-to-Treat	289/344 (84.0%) (79.7%, 87.7%)	301/360 (83.6%) (79.4%, 87.3%)	291/360 (80.8%) (76.4%, 84.8%)

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded. One subject (b) (6) excluded due to IOL implantation.

2 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as successes.

3 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 33 Monocular DCNVA ≥ 20/40 and Gain of 10 ≥ Letters at 24 Months for Primary Eyes vs Fellow Eyes - All Implanted Eyes - (Imputation per Primary Analyses Approach)

	Implanted Primary Eyes	Implanted Fellow Eyes	All Implanted Eyes
N[1]	344	334	678
20/40 or Better and Gain of ≥ 10 Letters	289 (84.0%)	275 (82.3%)	564 (83.2%)
95% CI[2]	79.7%, 87.7%	77.8%, 86.3%	79.2%, 86.0%
No Imputation for Missing Month 24	16	14	30

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.

2 Binomial distribution for Implanted Primary Eyes and for Implanted Fellow Eyes; GEE with an unstructured working correlation matrix for All Implanted Eyes

Table 34 Data Listing for Second Co-Primary Effectiveness Endpoint Requiring Imputation – Randomized Substudy – Primary Eyes of Treated Subjects

Subject Eye	Visit	DCNVA	Letters Change from Baseline	Revised Imputation Method	Second Co-Primary Effectiveness Endpoint
Deferred Treatment[1]					
(b) (6) OD	Baseline	20/50			
	3 Months	miss visit	miss visit		
	6 Months	miss visit	miss visit	Imputed by DCNVA at Baseline	Failure
(b) (6) OS	Baseline	20/50			
	3 Months	miss visit	miss visit		
	6 Months	miss visit	miss visit	Imputed by DCNVA at Baseline	Failure
Immediate Treatment[2]					
(b) (6) OD	Preop	20/80			
	3 Months	20/40	15		
	6 Months	miss visit	miss visit	Imputed by DCNVA at 12 Months	Success
	12 Months	20/32	21		
	18 Months	20/25	24		
(b) (6) OD	Preop	20/63			
	3 Months	20/63	1		
	6 Months	miss visit	miss visit	Imputed by DCNVA at 12 Months	Success
	12 Months	20/25	20		
(b) (6) OD	Preop	20/50			
	3 Months	20/40	5		
	6 Months	miss visit	miss visit	Imputed by DCNVA at 12 Months	Failure
	12 Months	20/50	0		
	18 Months	20/40	2		
(b) (6) , OS	Preop	20/63			
	3 Months	miss visit	miss visit		
	6 Months	miss visit	miss visit	Imputed by DCNVA at Baseline	Failure
Subject Eye	**Visit**	**DCNVA**	**Letters Change from Baseline**	**Pre-specified Protocol Defined Imputation Method**	**Second Co-Primary Effectiveness Endpoint**
Deferred Treatment[3]					
(b) (6) OD	Baseline	20/50			

	3 Months	miss visit	miss visit		
	6 Months	miss visit	miss visit	No imputation	
(b) (6), OS	Baseline	20/50			
	3 Months	miss visit	miss visit		
	6 Months	miss visit	miss visit	No imputation	
Immediate Treatment[4]					
(b) (6), OD	Preop	20/80			
	3 Months	20/40	15		
	6 Months	miss visit	miss visit	Imputed by DCNVA at 12 Months	Success
	12 Months	20/32	21		
	18 Months	20/25	24		
(b) (6) OD	Preop	20/63			
	3 Months	20/63	1		
	6 Months	miss visit	miss visit	Imputed by DCNVA at 12 Months	Success
	12 Months	20/25	20		
(b) (6) OD	Preop	20/50			
	3 Months	20/40	5		
	6 Months	miss visit	miss visit	Imputed by DCNVA at 12 Months	Failure
	12 Months	20/50	0		
	18 Months	20/40	2		
(b) (6) OS	Preop	20/63			
	3 Months	miss visit	miss visit		
	6 Months	miss visit	miss visit	No imputation	

1 For subjects with missing Month 6 values, the last observation carried forward (including baseline) was used.

2 Explants at or before Month 6 were imputed as failures. For other subjects with missing Month 6 values, the value closest to Month 6 collected from the protocol schedule visits after Month 6 up to and including Month 12 was used. If no data were observed between Month 6 and Month 12, the last observed data (including baseline) prior to 6 months was used.

3 For subjects with missing Month 6 values, the value closest to Month 6 collected between Month 3 and Month 6 was used. If no data were observed between Month 3 and Month 6, the subjects were excluded.

4 Explants at or before Month 6 were imputed as failures. For other subjects with missing Month 6 values, the value closest to Month 6 collected from the protocol schedule visits after Month 6 up to and including Month 12 was used. If no data were observed between Month 6 and Month 12, the subjects were excluded.

Table 35 Second Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 6 Months - Randomized Substudy

	Deferred Treatment[1] Group (31 Randomized Eyes)	Immediate Treatment[2] Group (29 Randomized Eyes)
Revised Imputation Method		
N	31	29
20/40 or Better and Gain of ≥ 10 Letters	2 (6.5%)	18 (62.1%)
95% CI[5]	0.8%, 21.4%	42.3%, 79.3%
Fisher's Exact Test p-value	<.001	
	Deferred Treatment[3] Group (31 Randomized Eyes)	**Immediate Treatment[4] Group (29 Randomized Eyes)**
Pre-specified Protocol Defined Imputation Method		
N	29	28
20/40 or Better and Gain of ≥ 10 Letters	2 (6.9%)	18 (64.3%)
95% CI[5]	0.8%, 22.8%	44.1%, 81.4%
Fisher's Exact Test p-value	<.001	

1 For subjects with missing Month 6 values, the last observation carried forward (including baseline) was used.

2 Explants at or before Month 6 were imputed as failures. For other subjects with missing Month 6 values, the value closest to Month 6 collected from the protocol schedule visits after Month 6 up to and including Month 12 was used. If no data were observed between Month 6 and Month 12, the last observed data (including baseline) prior to 6 months was used.

3 For subjects with missing Month 6 values, the value closest to Month 6 collected between Month 3 and Month 6 was used. If no data were observed between Month 3 and Month 6, the subjects were excluded.

4 Explants at or before Month 6 were imputed as failures. For other subjects with missing Month 6 values, the value closest to Month 6 collected from the protocol schedule visits after Month 6 up to and including Month 12 was used. If no data were observed between Month 6 and Month 12, the subjects were excluded.

5 Exact binomial 95% confidence interval (CI)

Table 36 Second Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 6 Months - Randomized Substudy

	Deferred Treatment[1] Group (31 Randomized Eyes)	Immediate Treatment[2] Group (29 Randomized Eyes)
N	29	28
20/40 or Better and Gain of ≥ 10 Letters	2 (6.9%)	18 (64.3%)
95% CI[3]	0.8%, 22.8%	44.1%, 81.4%
Fisher's Exact Test p-value	<.001	

1 For subjects with missing Month 6 values, the value closest to Month 6 collected between Month 3 and Month 6 was used. If no data were observed between Month 3 and Month 6, the subjects were excluded.

2 Explants at or before Month 6 were imputed as failures. For other subjects with missing Month 6 values, the value closest to Month 6 collected from the protocol schedule visits after Month 6 up to and including Month 12 was used. If no data were observed between Month 6 and Month 12, the subjects were excluded.

3 Exact binomial 95% confidence interval (CI)

Table 37 DCNVA for Primary Eyes Over Time - Intent-to-Treat Population

	Preop N = 360	Month 1 N = 357	Month 2 N = 350	Month 3 N = 352	Month 6 N = 347	Month 12 N = 346	Month 18 N = 326	Month 24 N = 337
n (Reported)	360	355	350	351	346	346	326	336
20/16 or better	0 (0.0%)	6 (1.7%)	8 (2.3%)	9 (2.6%)	10 (2.9%)	9 (2.6%)	8 (2.5%)	16 (4.8%)
20/20 or better	0 (0.0%)	20 (5.6%)	32 (9.1%)	40 (11.4%)	54 (15.6%)	84 (24.3%)	73 (22.4%)	86 (25.6%)
20/25 or better	0 (0.0%)	79 (22.3%)	105 (30.0%)	125 (35.6%)	146 (42.2%)	183 (52.9%)	170 (52.1%)	188 (56.0%)
20/32 or better	**1 (0.3%)**	**152 (42.8%)**	**180 (51.4%)**	**203 (57.8%)**	**238 (68.8%)**	**262 (75.7%)**	**258 (79.1%)**	**260 (77.4%)**
20/40 or better	**2 (0.6%)**	**243 (68.5%)**	**250 (71.4%)**	**268 (76.4%)**	**289 (83.5%)**	**313 (90.5%)**	**298 (91.4%)**	**314 (93.5%)**
20/50 or better	130 (36.1%)	311 (87.6%)	305 (87.1%)	325 (92.6%)	322 (93.1%)	332 (96.0%)	315 (96.6%)	331 (98.5%)
20/63 or better	277 (76.9%)	342 (96.3%)	340 (97.1%)	343 (97.7%)	338 (97.7%)	343 (99.1%)	326 (100.0%)	335 (99.7%)
20/80 or better	360 (100.0%)	353 (99.4%)	346 (98.9%)	350 (99.7%)	344 (99.4%)	346 (100.0%)	326 (100.0%)	336 (100.0%)
20/100 or better	360 (100.0%)	354 (99.7%)	348 (99.4%)	350 (99.7%)	345 (99.7%)	346 (100.0%)	326 (100.0%)	336 (100.0%)
20/125 or better	360 (100.0%)	355 (100.0%)	350 (100.0%)	351 (100.0%)	346 (100.0%)	346 (100.0%)	326 (100.0%)	336 (100.0%)
20/160 or better	360 (100.0%)	355 (100.0%)	350 (100.0%)	351 (100.0%)	346 (100.0%)	346 (100.0%)	326 (100.0%)	336 (100.0%)
20/200 or better	360 (100.0%)	355 (100.0%)	350 (100.0%)	351 (100.0%)	346 (100.0%)	346 (100.0%)	326 (100.0%)	336 (100.0%)
Not Reported	0	2	0	1	1	0	0	1

Percentage is based on the number of eyes reported with data.

Table 38 DCNVA for Primary Eyes - Randomized Substudy

	Deferred Treatment Group (31 Randomized Eyes)			Immediate Treatment Group (29 Randomized Eyes)		
	Baseline N = 31	Month 3 N = 29	Month 6 N = 29	Preop N = 29	Month 3 N = 28	Month 6 N = 25
n (Reported)	31	29	29	29	28	25
20/16 or better	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
20/20 or better	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	2 (8.0%)
20/25 or better	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.3%)	7 (28.0%)
20/32 or better	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	12 (42.9%)	13 (52.0%)
20/40 or better	**0 (0.0%)**	**0 (0.0%)**	**3 (10.3%)**	**0 (0.0%)**	**21 (75.0%)**	**19 (76.0%)**
20/50 or better	5 (16.1%)	5 (17.2%)	7 (24.1%)	7 (24.1%)	25 (89.3%)	25 (100.0%)
20/63 or better	17 (54.8%)	16 (55.2%)	17 (58.6%)	19 (65.5%)	27 (96.4%)	25 (100.0%)
20/80 or better	31 (100.0%)	26 (89.7%)	29 (100.0%)	29 (100.0%)	28 (100.0%)	25 (100.0%)
20/100 or better	31 (100.0%)	29 (100.0%)	29 (100.0%)	29 (100.0%)	28 (100.0%)	25 (100.0%)
20/125 or better	31 (100.0%)	29 (100.0%)	29 (100.0%)	29 (100.0%)	28 (100.0%)	25 (100.0%)
20/160 or better	31 (100.0%)	29 (100.0%)	29 (100.0%)	29 (100.0%)	28 (100.0%)	25 (100.0%)
20/200 or better	31 (100.0%)	29 (100.0%)	29 (100.0%)	29 (100.0%)	28 (100.0%)	25 (100.0%)
Not Reported	0	0	0	0	0	0

Percentage is based on the number of eyes reported with data.

Table 39 Change in DCNVA from Baseline for Primary Eyes - Intent-to-Treat Population

	Month 1 N = 357	Month 2 N = 350	Month 3 N = 352	Month 6 N = 347	Month 12 N = 346	Month 18 N = 326	Month 24 N = 337
n (Reported)	355	350	351	346	346	326	336
Gained ≥ 5 lines	7 (2.0%)	14 (4.0%)	20 (5.7%)	26 (7.5%)	32 (9.2%)	30 (9.2%)	37 (11.0%)
Gained ≥ 4 lines	40 (11.3%)	52 (14.9%)	67 (19.1%)	84 (24.3%)	102 (29.5%)	97 (29.8%)	116 (34.5%)
Gained ≥ 3 lines	**98 (27.6%)**	**125 (35.7%)**	**147 (41.9%)**	**165 (47.7%)**	**209 (60.4%)**	**195 (59.8%)**	**216 (64.3%)**
Gained ≥ 2 lines	**196 (55.2%)**	**219 (62.6%)**	**239 (68.1%)**	**263 (76.0%)**	**280 (80.9%)**	**273 (83.7%)**	**294 (87.5%)**
Gained ≥ 1 line	275 (77.5%)	279 (79.7%)	295 (84.0%)	305 (88.2%)	322 (93.1%)	302 (92.6%)	324 (96.4%)
No Change	72 (20.3%)	61 (17.4%)	51 (14.5%)	36 (10.4%)	23 (6.6%)	24 (7.4%)	11 (3.3%)
Lost ≥ 1 line	8 (2.3%)	10 (2.9%)	5 (1.4%)	5 (1.4%)	1 (0.3%)	0 (0.0%)	1 (0.3%)
Lost ≥ 2 lines	2 (0.6%)	4 (1.1%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Lost ≥ 3 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 4 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 5 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean (SD) of line change	2.05 (1.50)	2.25 (1.59)	2.54 (1.57)	2.80 (1.52)	3.15 (1.44)	3.16 (1.39)	3.35 (1.33)
Not Reported	2	0	1	1	0	0	1

Percentage is based on the number of eyes reported with data.

Table 40 Change in DCNVA from Baseline for Primary Eyes - Randomized Substudy

	Deferred Treatment Group (31 Randomized Eyes)		Immediate Treatment Group (29 Randomized Eyes)	
	Month 3 N = 29	Month 6 N = 29	Month 3 N = 28	Month 6 N = 25
n (Reported)	29	29	28	25
Gained ≥ 5 lines	0 (0.0%)	0 (0.0%)	1 (3.6%)	1 (4.0%)
Gained ≥ 4 lines	0 (0.0%)	0 (0.0%)	2 (7.1%)	6 (24.0%)
Gained ≥ 3 lines	0 (0.0%)	1 (3.4%)	8 (28.6%)	10 (40.0%)
Gained ≥ 2 lines	**0 (0.0%)**	**4 (13.8%)**	**18 (64.3%)**	**18 (72.0%)**
Gained ≥ 1 line	7 (24.1%)	11 (37.9%)	25 (89.3%)	23 (92.0%)
No Change	16 (55.2%)	13 (44.8%)	2 (7.1%)	2 (8.0%)
Lost ≥ 1 line	6 (20.7%)	5 (17.2%)	1 (3.6%)	0 (0.0%)
Lost ≥ 2 lines	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)
Lost ≥ 3 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 4 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 5 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean (SD) of line change	-0.03 (1.00)	0.28 (1.27)	2.20 (1.32)	2.68 (1.42)
Not Reported	0	0	0	0

Percentage is based on the number of eyes reported with data.

Table 41 Binocular UCNVA Over Time - Intent-to-Treat Population

	Preop N = 360	Month 3 N = 337	Month 6 N = 339	Month 12 N = 341	Month 18 N = 326	Month 24 N = 331
n (Reported)	360	337	338	341	326	329
20/16 or better	0 (0.0%)	33 (9.8%)	29 (8.6%)	35 (10.3%)	35 (10.7%)	29 (8.8%)
20/20 or better	2 (0.6%)	109 (32.3%)	104 (30.8%)	107 (31.4%)	114 (35.0%)	126 (38.3%)
20/25 or better	8 (2.2%)	229 (68.0%)	221 (65.4%)	235 (68.9%)	239 (73.3%)	239 (72.6%)
20/32 or better	**23 (6.4%)**	**286 (84.9%)**	**282 (83.4%)**	**300 (88.0%)**	**293 (89.9%)**	**294 (89.4%)**
20/40 or better	**100 (27.8%)**	**318 (94.4%)**	**312 (92.3%)**	**328 (96.2%)**	**315 (96.6%)**	**316 (96.0%)**
20/50 or better	242 (67.2%)	336 (99.7%)	330 (97.6%)	333 (97.7%)	322 (98.8%)	324 (98.5%)
20/63 or better	341 (94.7%)	337 (100.0%)	337 (99.7%)	340 (99.7%)	324 (99.4%)	327 (99.4%)
20/80 or better	360 (100.0%)	337 (100.0%)	338 (100.0%)	341 (100.0%)	326 (100.0%)	329 (100.0%)
20/100 or better	360 (100.0%)	337 (100.0%)	338 (100.0%)	341 (100.0%)	326 (100.0%)	329 (100.0%)
20/125 or better	360 (100.0%)	337 (100.0%)	338 (100.0%)	341 (100.0%)	326 (100.0%)	329 (100.0%)
20/160 or better	360 (100.0%)	337 (100.0%)	338 (100.0%)	341 (100.0%)	326 (100.0%)	329 (100.0%)
20/200 or better	360 (100.0%)	337 (100.0%)	338 (100.0%)	341 (100.0%)	326 (100.0%)	329 (100.0%)
Not Reported	0	0	1	0	0	2

Percentage is based on the number of subjects reported with data.

Table 42 Change in Binocular UCNVA from Baseline - Intent-to-Treat Population

	Month 3 N = 337	Month 6 N = 339	Month 12 N = 341	Month 18 N = 326	Month 24 N = 331
n (Reported)	337	338	341	326	329
Gained ≥ 5 lines	20 (5.9%)	27 (8.0%)	17 (5.0%)	22 (6.7%)	19 (5.8%)
Gained ≥ 4 lines	68 (20.2%)	80 (23.7%)	88 (25.8%)	82 (25.2%)	91 (27.7%)
Gained ≥ 3 lines	**174 (51.6%)**	**155 (45.9%)**	**172 (50.4%)**	**179 (54.9%)**	**184 (55.9%)**
Gained ≥ 2 lines	**256 (76.0%)**	**249 (73.7%)**	**260 (76.2%)**	**263 (80.7%)**	**263 (79.9%)**
Gained ≥ 1 line	315 (93.5%)	301 (89.1%)	309 (90.6%)	299 (91.7%)	304 (92.4%)
No Change	20 (5.9%)	34 (10.1%)	30 (8.8%)	26 (8.0%)	23 (7.0%)
Lost ≥ 1 line	2 (0.6%)	3 (0.9%)	2 (0.6%)	1 (0.3%)	2 (0.6%)
Lost ≥ 2 lines	0 (0.0%)	0 (0.0%)	2 (0.6%)	1 (0.3%)	0 (0.0%)
Lost ≥ 3 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 4 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost ≥ 5 lines	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean (SD) of line change	2.84 (1.37)	2.78 (1.51)	2.85 (1.40)	2.97 (1.36)	3.02 (1.35)
Not Reported	0	1	0	0	2

Percentage is based on the number of subjects reported with data.

Table 43 Near Add and Change in Near Add from Baseline for Primary Eyes - Intent-to-Treat Population

	Preop N = 360	Month 3 N = 352	Month 6 N = 347	Month 12 N = 346	Month 18 N = 326	Month 24 N = 337
Add (D)						
n (Reported)	360	220	209	174	154	152
Mean (SD)	1.617 (0.312)	0.819 (0.415)	0.793 (0.428)	0.682 (0.453)	0.651 (0.442)	0.577 (0.447)
95% CI[1]	(1.585, 1.650)	(0.764, 0.874)	(0.735, 0.851)	(0.615, 0.750)	(0.581, 0.721)	(0.506, 0.649)
Median	1.50	0.75	0.75	0.63	0.50	0.50
Min, Max	1.25, 2.50	0.00, 2.25	0.00, 2.00	0.00, 2.00	0.00, 1.75	0.00, 1.75
Not Reported	0	132	138	172	172	185
Change in Add (D)						
n (Reported)		220	209	174	154	152
Mean (SD)		-0.835 (0.469)	-0.856 (0.519)	-0.994 (0.557)	-1.000 (0.558)	-1.067 (0.582)
95% CI[1]		(-0.897, -0.773)	(-0.927, -0.786)	(-1.078, -0.911)	(-1.089, -0.911)	(-1.161, -0.974)
Median		-0.75	-0.75	-1.00	-1.00	-1.25
Min, Max		-2.00, 1.00	-2.25, 0.50	-2.25, 0.50	-2.25, 0.25	-2.25, 0.50
Not Reported		132	138	172	172	185

[1] 95% confidence interval was based on t-distribution.

Table 44 Near Add and Change in Near Add from Baseline for Primary Eyes - Randomized Substudy

	Deferred Treatment Group (34 Randomized Eyes)			Immediate Treatment Group (33 Randomized Eyes)		
	Preop N = 31	Month 3 N = 29	Month 6 N = 29	Preop N = 29	Month 3 N = 28	Month 6 N = 25
Add (D)						
n (Reported)	31	29	29	29	28	25
Mean (SD)	1.815 (0.309)	1.828 (0.418)	1.819 (0.347)	1.767 (0.389)	1.098 (0.421)	0.840 (0.374)
95% CI[1]	(1.701, 1.928)	(1.669, 1.987)	(1.687, 1.951)	(1.619, 1.915)	(0.935, 1.262)	(0.686, 0.994)
Median	1.75	1.75	1.75	1.75	1.25	1.00
Min, Max	1.25, 2.25	1.25, 2.50	1.25, 2.50	1.25, 2.50	0.00, 1.75	0.00, 1.50
Not Reported	0	0	0	0	0	0
Change in Add (D)						
n (Reported)		29	29		28	25
Mean (SD)		-0.009 (0.195)	-0.017 (0.211)		-0.670 (0.436)	-0.920 (0.504)
95% CI[1]		(-0.083, 0.065)	(-0.097, 0.063)		(-0.839, -0.501)	(-1.128, -0.712)
Median		0.00	0.00		-0.75	-1.00
Min, Max		-0.50, 0.50	-0.50, 0.25		-1.50, 0.25	-2.00, 0.00
Not Reported		0	0		0	0

Table 45 Change in Mean Visual Acuity (LogMAR) at 6 Months by Lens Power - Primary Eyes - Randomized Substudy

Lens Power (Diopter)	Deferred Treatment (31 Randomized Eyes)			Immediate Treatment (29 Randomized Eyes)		
	N	Observation 6M (Mean±SD LogMAR)	95% CI	N	Postop 6M (Mean±SD LogMAR)	95% CI
-4.00	28	-0.081 ± 0.135	-0.134, -0.029	24	-0.112 ± 0.187	-0.191, -0.033
-3.50	28	-0.102 ± 0.150	-0.160, -0.044	24	-0.153 ± 0.189	-0.233, -0.073
-3.00	28	-0.074 ± 0.122	-0.121, -0.026	24	-0.177 ± 0.181	-0.253, -0.101
-2.50	28	-0.070 ± 0.148	-0.127, -0.012	24	-0.169 ± 0.189	-0.248, -0.089
-2.00	28	-0.041 ± 0.192	-0.116, 0.033	24	-0.144 ± 0.191	-0.225, -0.063
-1.50	28	-0.029 ± 0.168	-0.094, 0.036	24	-0.132 ± 0.140	-0.191, -0.073
-1.00	28	-0.020 ± 0.131	-0.070, 0.031	24	-0.110 ± 0.128	-0.165, -0.056
-0.50	28	0.001 ± 0.088	-0.033, 0.036	24	-0.049 ± 0.117	-0.098, 0.001
0.00	28	-0.017 ± 0.059	-0.040, 0.006	24	-0.024 ± 0.057	-0.048, 0.000
0.50	28	-0.058 ± 0.121	-0.105, -0.011	24	-0.087 ± 0.111	-0.134, -0.040
1.00	28	-0.069 ± 0.132	-0.120, -0.018	24	-0.101 ± 0.147	-0.163, -0.039
1.50	28	-0.064 ± 0.141	-0.119, -0.009	24	-0.120 ± 0.151	-0.184, -0.056
2.00	28	-0.070 ± 0.151	-0.129, -0.012	24	-0.142 ± 0.162	-0.210, -0.074

Table 46 Static Change in Wavefront Descriptors at 6 Months - PE Only

Group/Interval	N (eyes)	Mean (SD)	95% CI[2]	p-value
(b) Z1 Spherical Equivalent				
Deferred Treatment				
Baseline	27	0.33 (0.36)	0.190 – 0.470	
Observation 6 Months	26	0.31 (0.38)	0.180 – 0.440	0.61
Immediate Treatment				
Baseline	28	0.32 (0.40)	0.150 – 0.460	
6 Months	28	0.28 (0.38)	0.120 – 0.420	0.57
				0.71
(b) (6) C03 Oblique Astigmatism				
Deferred Treatment				
Baseline	27	0.00 (0.04)	-0.012 – 0.018	
Observation 6	26	0.01 (0.04)	-0.008 – 0.024	0.37
Immediate Treatment				
Baseline	28	-0.01 (0.04)	-0.019 – 0.001	
6 Months	28	-0.02 (0.05)	-0.040 – 0.000	0.02
				0.007
(b) (6) C05 Vertical Astigmatism				
Deferred Treatment				
Baseline	27	0.03 (0.06)	0.003 – 0.050	
Observation 6	26	0.03 (0.05)	0.009 – 0.050	0.2
Immediate Treatment				
Baseline	28	0.02 (0.06)	-0.007 – 0.040	
6 Months	28	0.00 (0.05)	-0.018 – 0.020	0.16
				0.08
(b) (6) C07 Vertical Coma				
Deferred Treatment				
Baseline	27	0.00 (0.01)	-0.001 – 0.007	
Observation 6	26	0.00 (0.01)	-0.004 – 0.007	0.8
Immediate Treatment				
Baseline	28	0.00 (0.01)	-0.003 – 0.007	
6 Months	28	-0.00(0.01)	-0.005 – 0.004	0.32
				0.47
(b) (6) C08 Horizontal Coma				
Deferred Treatment				
Baseline	27	0.003 (0.01)	-0.002 – 0.008	
Observation 6	26	0.002 (0.01)	-0.001 – 0.005	0.0001
Immediate Treatment				
Baseline	28	0.00 (0.01)	-0.004 – 0.003	
6 Months	28	0.00 (0.01)	-0.008 – 0.001	0.16

				0.05
(b) (6) C12 Spherical Aberration				
Deferred Treatment				
Baseline	27	0.00 (0.01)	0.002 – 0.007	
Observation 6	28	0.00 (0.01)	0.004 – 0.004	0.37
Immediate Treatment				
Baseline	28	0.00 (0.01)	-0.000 – 0.005	
6 Months	28	0.00 (0.01)	-0.001 – 0.004	0.55
				0.82
(b) (6) C13 Vertical Secondary Astigmatism				
Deferred Treatment				
Baseline	27	-0.00 (0.01)	-0.004 – 0.001	
Observation 6	26	-0.00 (0.01)	-0.003 – 0.001	0.96
Immediate Treatment				
Baseline	28	-0.00 (0.01)	-0.003 – 0.001	
6mo	28	0.00 (0.01)	-0.002 – 0.002	0.57
				0.76

* $p < 0.05$

Table 47 Dynamic Change - Vertical Coma (CO7)

Group	N	Mean (SD)	95% CI[2]	p-value
1 Meter				
Deferred Treatment	27	0.0006 (0.01)	-0.002 – 0.004	
Immediate Treatment	28	-0.005 (0.00)	-0.001 – - 0.008	0.03
66 Centimeters				
Deferred Treatment	27	0.00001 (0.001)	-0.004 – 0.0004	
Immediate Treatment	28	0.002 (0.012)	-0.006 – 0.009	0.69
50 Centimeters				
Deferred Treatment	27	0.004 (0.01)	-0.003 – 0.005	
Immediate Treatment	28	-0.002 (0.01)	-0.008 – 0.003	0.42
40 Centimeters				
Deferred Treatment	27	-0.002 (0.01)	-0.006 – 0.001	
Immediate Treatment	28	-0.004 (0.01)	-0.01 – 0.002	0.66
33 Centimeters				
Deferred Treatment	27	-0.002 (0.01)	-0.006 – 0.002	
Immediate Treatment	28	0.00 (0.01)	-0.005 – 0.006	0.36

Table 48 MRSE and Change in MRSE from Baseline - Safety Cohort

	Preop N = 708	Month 1 N = 698	Month 2 N = 691	Month 3 N = 689	Month 6 N = 686	Month 12 N = 687	Month 18 N = 652	Month 24 N = 668
MRSE (D)								
n (Reported)	708	697	691	688	684	687	652	668
Mean (SD)	0.126 (0.265)	-0.038 (0.345)	-0.047 (0.331)	0.034 (0.298)	0.144 (0.327)	0.203 (0.340)	0.232 (0.358)	0.252 (0.385)
95% CI[1]	(0.106, 0.145)	(-0.064, -0.012)	(-0.072, -0.023)	(0.011, 0.056)	(0.119, 0.168)	(0.178, 0.229)	(0.205, 0.260)	(0.222, 0.281)
Median	0.125	0.000	0.000	0.000	0.125	0.250	0.250	0.250
Min, Max	-0.750, 0.500	-1.375, 1.000	-1.250, 1.000	-1.000, 1.000	-1.250, 1.500	-0.875, 2.125	-1.250, 2.250	-1.000, 2.250
Not Reported	0	1	0	1	2	0	0	0
Change in MRSE (D)								
n (Reported)		697	691	688	684	687	652	668
Mean (SD)		-0.164 (0.305)	-0.175 (0.305)	-0.094 (0.277)	0.016 (0.278)	0.073 (0.310)	0.101 (0.318)	0.118 (0.330)
95% CI[1]		(-0.186, -0.141)	(-0.198, -0.153)	(-0.114, -0.073)	(-0.005, 0.037)	(0.050, 0.096)	(0.077, 0.126)	(0.093, 0.144)
Median		-0.125	-0.125	-0.125	0.000	0.000	0.000	0.125
Min, Max		-1.250, 0.875	-1.500, 1.000	-1.000, 1.000	-0.875, 1.125	-1.125, 1.875	-1.500, 1.875	-1.250, 2.000
Hyperopic Shift		7 (1.0%)	8 (1.2%)	9 (1.3%)	24 (3.5%)	38 (5.5%)	46 (7.1%)	56 (8.4%)
> 2.0 D		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
> 1.0 to ≤ 2.0 D		0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (0.4%)	4 (0.6%)	6 (0.9%)
> 0.5 to ≤ 1.0 D		7 (1.0%)	8 (1.2%)	9 (1.3%)	23 (3.4%)	35 (5.1%)	42 (6.4%)	50 (7.5%)
Change within 0.5 D		635 (91.1%)	621 (89.9%)	654 (95.1%)	655 (95.8%)	644 (93.7%)	601 (92.2%)	608 (91.0%)
Myopic Shift		55 (7.9%)	62 (9.0%)	25 (3.6%)	5 (0.7%)	5 (0.7%)	5 (0.8%)	4 (0.6%)
> 0.5 to ≤ 1.0 D		51 (7.3%)	58 (8.4%)	25 (3.6%)	5 (0.7%)	4 (0.6%)	4 (0.6%)	3 (0.4%)
> 1.0 to ≤ 2.0 D		4 (0.6%)	4 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.2%)	1 (0.1%)
> 2.0 D		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean Monthly Change		-0.164	-0.088	-0.031	0.003	0.006	0.006	0.005
Not Reported		1	0	1	2	0	0	0

Percentage is based on the number of eyes reported with data.

[1] 95% confidence interval was based on t-distribution.

Table 49 Stability of MRSE - Safety Cohort

	Preop to 1 Month	1 to 2 Months	2 to 3 Months	1 to 3 Months	3 to 6 Months	6 to 12 Months	12 to 18 Months	18 to 24 Months
Pairwise Sequential Visits								
N	697	682	674	679	669	670	649	644
Within ± 0.50D	635 (91.1%)	642 (94.1%)	640 (95.0%)	633 (93.2%)	635 (94.9%)	650 (97.0%)	635 (97.8%)	624 (96.9%)
95% CI[1]	88.7, 93.1	92.1, 95.8	93.0, 96.5	91.1, 95.0	93.0, 96.5	95.4, 98.2	96.4, 98.8	95.2, 98.1
Within ± 1.00D	693 (99.4%)	679 (99.6%)	673 (99.9%)	675 (99.4%)	668 (99.9%)	668 (99.7%)	649 (100.0%)	644 (100.0%)
95% CI[1]	98.5, 99.8	98.7, 99.9	99.2, 100.0	98.5, 99.8	99.2, 100.0	98.9, 100.0	99.4, 100.0	99.4, 100.0
Mean (SD)[2]	-0.164 (0.305)	-0.011 (0.292)	0.084 (0.266)	0.071 (0.309)	0.107 (0.262)	0.057 (0.262)	0.025 (0.233)	0.020 (0.242)
95% CI	-0.186, -0.141	-0.033, 0.011	0.064, 0.104	0.048, 0.094	0.087, 0.127	0.037, 0.077	0.007, 0.043	0.002, 0.039
Mean Monthly Change[3]	-0.164	-0.011	0.084	0.036	0.036	0.009	0.004	0.003
Mean Annual Change[3]	-1.965	-0.130	1.006	0.426	0.429	0.114	0.049	0.041

Pairwise Sequential Visits = Eyes that had two consecutive exams, but not necessarily every follow-up exam.
Consistent Cohort = All eyes examined at all scheduled postop visits through 12 months.
1 95% confidence interval is calculated by Clopper-Pearson method.
2 95% confidence interval is based on t-distribution.
3 Mean Monthly Change = Mean/(number of months of the period). Mean Annual Change = Mean Monthly Change *12.

Table 50 Vector Stability of Cylinder - Safety Cohort

	Preop to 1 Month	1 to 2 Months	2 to 3 Months	1 to 3 Months	3 to 6 Months	6 to 12 Months	12 to 18 Months	18 to 24 Months
Pairwise Sequential Visits								
N	697	682	674	679	669	670	649	644
≤ 0.50D Vector Change	532 (76.3%)	543 (79.6%)	580 (86.1%)	523 (77.0%)	597 (89.2%)	610 (91.0%)	589 (90.8%)	598 (92.9%)
95% CI[1]	73.0, 79.4	76.4, 82.6	83.2, 88.6	73.7, 80.1	86.6, 91.5	88.6, 93.1	88.3, 92.9	90.6, 94.7
≤ 1.00D Vector Change	670 (96.1%)	669 (98.1%)	664 (98.5%)	662 (97.5%)	668 (99.9%)	668 (99.7%)	648 (99.8%)	637 (98.9%)
95% CI[1]	94.4, 97.4	96.8, 99.0	97.3, 99.3	96.0, 98.5	99.2, 100.0	98.9, 100.0	99.1, 100.0	97.8, 99.6
Mean (SD)[2]	0.347 (0.344)	0.281 (0.304)	0.241 (0.265)	0.322 (0.303)	0.220 (0.232)	0.226 (0.229)	0.212 (0.225)	0.211 (0.245)
95% CI	0.321, 0.372	0.259, 0.304	0.221, 0.261	0.299, 0.344	0.202, 0.238	0.209, 0.244	0.194, 0.229	0.192, 0.230
Mean Monthly Change[3]	0.347	0.281	0.241	0.161	0.073	0.038	0.035	0.035
Mean Annual Change[3]	4.161	3.377	2.895	1.929	0.880	0.453	0.424	0.422

Pairwise Sequential Visits = Eyes that had two consecutive exams, but not necessarily every follow-up exam.
Consistent Cohort = All eyes examined at all scheduled postop visits through 12 months.
1 95% confidence interval is calculated by Clopper-Pearson method.
2 95% confidence interval is based on t-distribution.
3 Mean Monthly Change = Mean/(number of months of the period). Mean Annual Change = Mean Monthly Change *12.

Table 51 First Co-Primary Effectiveness Endpoint at 12 Months by Site - Intent-to-Treat Population

Site	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
001	8	8 (100.0%)	63.1%, 100.0%
002	45	32 (71.1%)	55.7%, 83.6%
003	31	29 (93.5%)	78.6%, 99.2%
004	11	7 (63.6%)	30.8%, 89.1%
005	13	11 (84.6%)	54.6%, 98.1%
006	36	34 (94.4%)	81.3%, 99.3%
007	33	21 (63.6%)	45.1%, 79.6%
008	68	54 (79.4%)	67.9%, 88.3%
009	36	35 (97.2%)	85.5%, 99.9%
010	13	5 (38.5%)	13.9%, 68.4%
012	15	12 (80.0%)	51.9%, 95.7%
013	32	22 (68.8%)	50.0%, 83.9%
014	9	7 (77.8%)	40.0%, 97.2%
p-value[3]			<.001
Average over Site[4]		77.9%	73.0%, 82.8%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 value were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for site difference using Monte Carlo method

4 Percentage was the simple average of the percentages over all sites. Normal approximation was used to calculate the 95% CI.

Table 52 First Co-Primary Effectiveness Endpoint at 24 Months by Site - Intent-to-Treat Population

Site	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
001	8	6 (75.0%)	34.9%, 96.8%
002	45	38 (84.4%)	70.5%, 93.5%
003	29	28 (96.6%)	82.2%, 99.9%
004	11	7 (63.6%)	30.8%, 89.1%
005	11	10 (90.9%)	58.7%, 99.8%
006	36	30 (83.3%)	67.2%, 93.6%
007	33	22 (66.7%)	48.2%, 82.0%
008	67	59 (88.1%)	77.8%, 94.7%
009	36	36 (100.0%)	90.3%, 100.0%
010	14	13 (92.9%)	66.1%, 99.8%
012	15	11 (73.3%)	44.9%, 92.2%
013	30	23 (76.7%)	57.7%, 90.1%
014	9	6 (66.7%)	29.9%, 92.5%
p-value[3]			0.001
Average over Site[4]		81.4%	76.2%, 86.5%

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded. One subject (b) (6) excluded due to IOL implantation.

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for site difference using Monte Carlo method

4 Percentage was the simple average of the percentages over all sites. Normal approximation was used to calculate the 95% CI.

Table 53 Second Co-Primary Effectiveness Endpoint at 6 Months by Site - Randomized Substudy

Site	Deferred Treatment[1] Group (31 Randomized Eyes)			Immediate Treatment[2] Group (29 Randomized Eyes)		
	N	20/40 or Better and Gain of ≥10 Letters n (%)	95% CI[3]	N	20/40 or Better and Gain of ≥10 Letters n (%)	95% CI[3]
003	12	0 (0.0%)	0.0%, 26.5%	12	11 (91.7%)	61.5%, 99.8%
007	10	1 (10.0%)	0.3%, 44.5%	10	2 (20.0%)	2.5%, 55.6%
008	7	1 (14.3%)	0.4%, 57.9%	6	5 (83.3%)	35.9%, 99.6%
Logistic Regression[4]						
Treatment p-value	<.001					
Site p-value	0.269					
Treatment-by-Site p-value	0.084					
Gail-Simon p-value[5]	0.750					
CMH p-value[6]	<.001					

1 For subjects with missing Month 6 values, the value closest to Month 6 collected between Month 3 and Month 6 was used. If no data were observed between Month 3 and Month 6, the subjects were excluded.

2 Explants at or before Month 6 were imputed as failures. For other subjects with missing Month 6 values, the value closest to Month 6 collected after Month 6 up to and including Month 12 was used. If no data were observed between Month 6 and Month 12, the subjects were excluded.

3 Exact binomial 95% confidence interval (CI)

4 Logistic regression for the primary effectiveness endpoint with covariates treatment, site and treatment-by-site interaction and using Firth's penalized maximum likelihood estimation to resolve quasi-complete separation.

5 Gail-Simon test for qualitative treatment-by-site interaction

6 Cochran-Mantel-Haenszel test for treatment difference adjusting for site

12 Figures

Figure 1: VisAbility Micro Insert

Figure 2: Placement of VisAbility Micro Insert

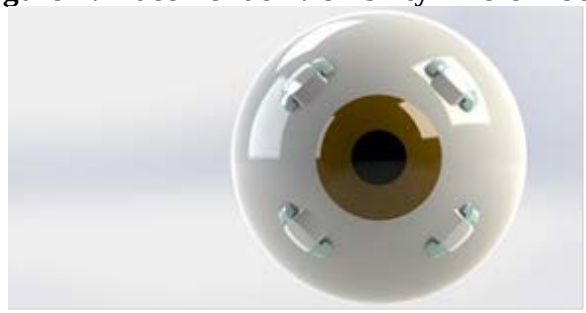


Figure 3: VisAbility Scleratome

Figure 4: VisAbility Feeder Tube Assembly

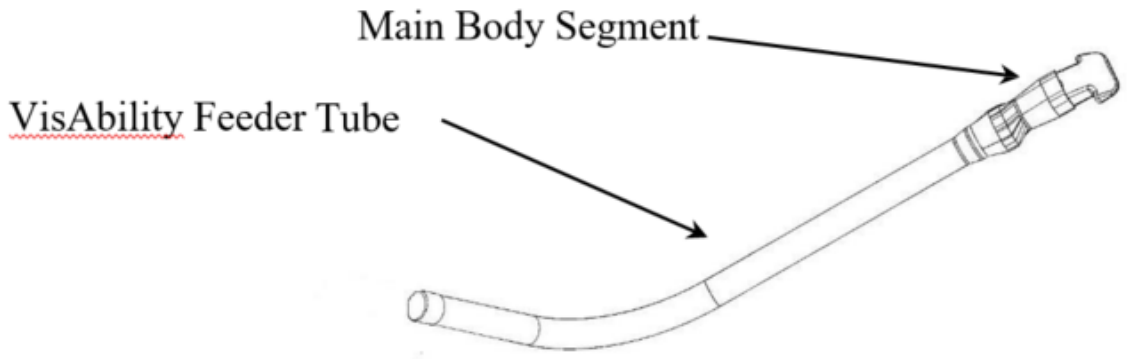


Figure 5: VisAbility Feeder Tube Assembly with Optional Shuttle or Trocar

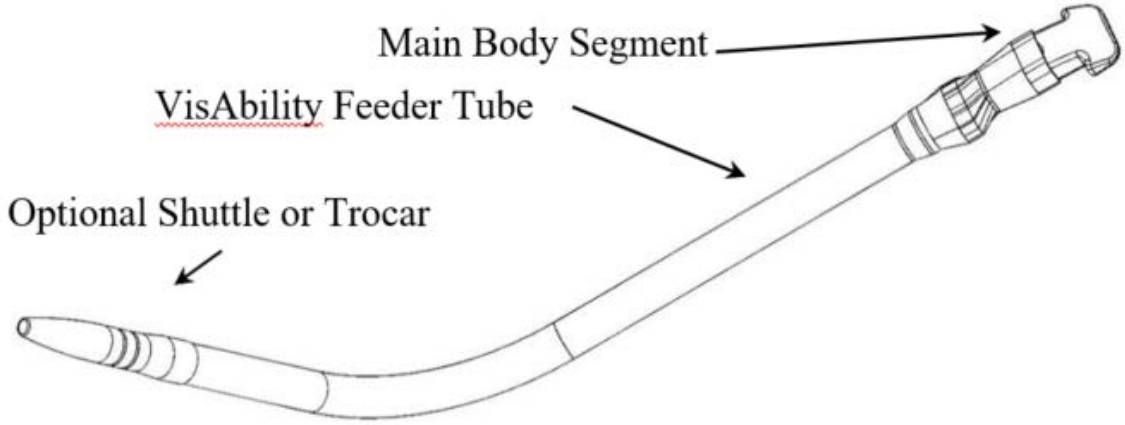


Figure 6 Placement of VisAbility Micro Inserts with VisAbility Feeder Tube

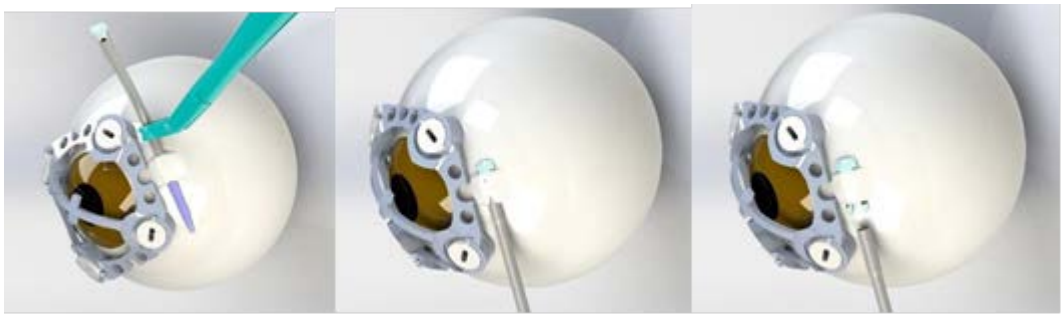


Figure 7: Docking Station

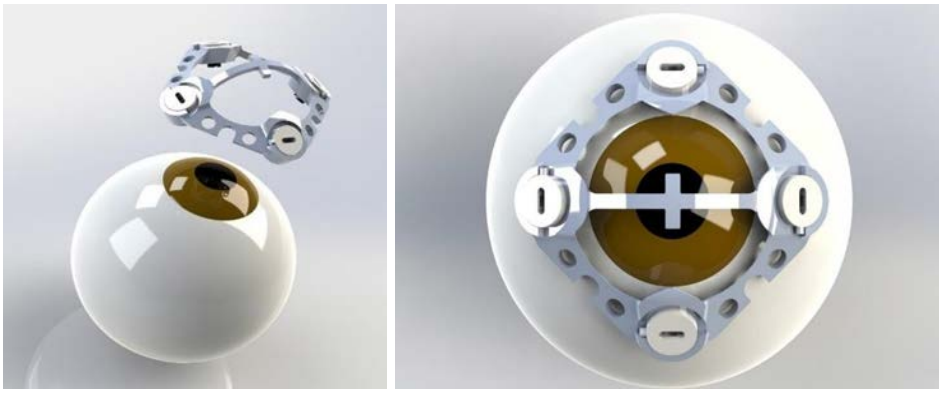


Figure 8: VisAbility Scleratome Used With Docking Station

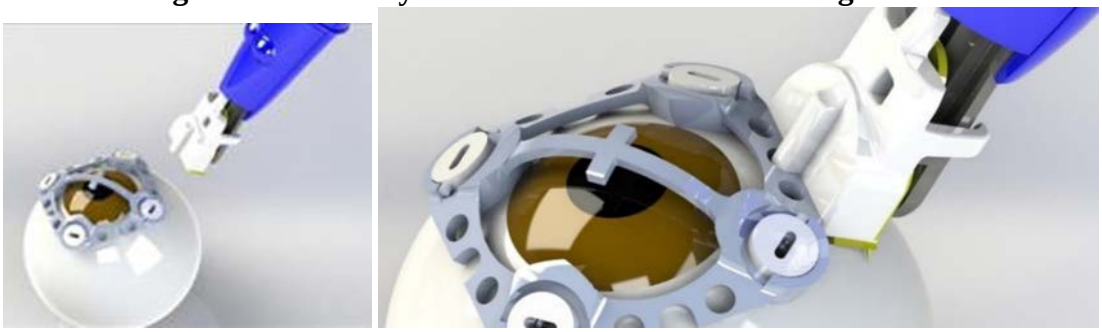


Figure 9 VisAbility Implant Removal Procedure

Figure 10 Clinical Trial Design (FDA Generated Figure)

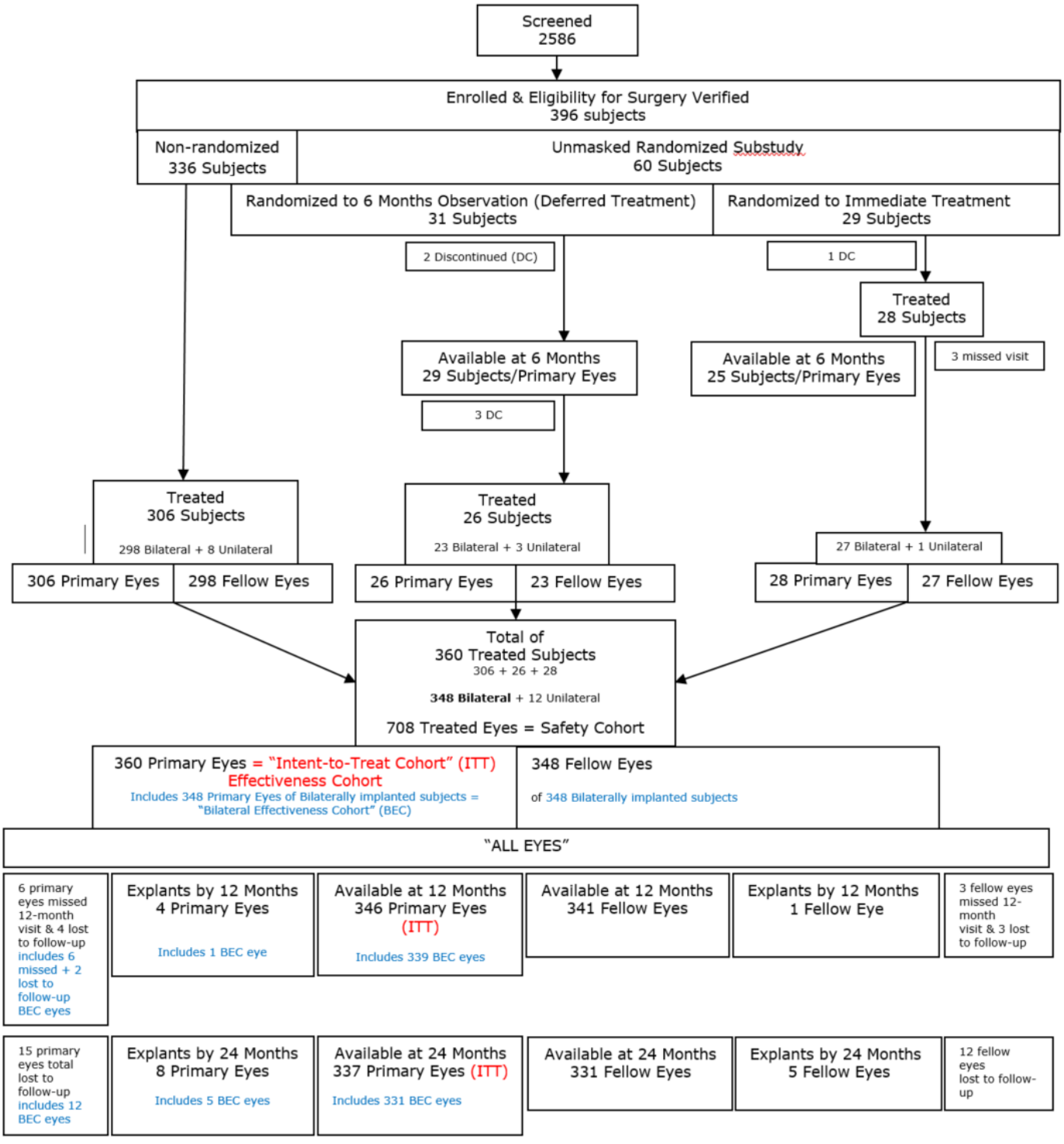


Figure 11 Tipping Point Analysis of First Co-Primary Effectiveness Endpoint at 12 Months, Intent-to-Treat Population

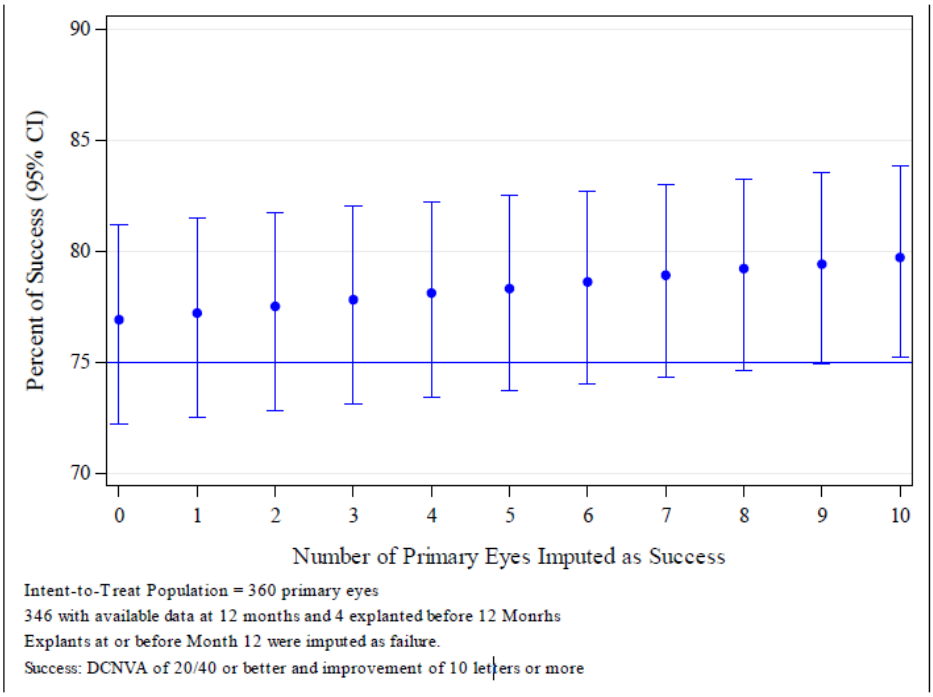


Figure 12 Tipping Point Analysis of First Co-Primary Effectiveness Endpoint at 12 Months, Bilateral Effectiveness Cohort

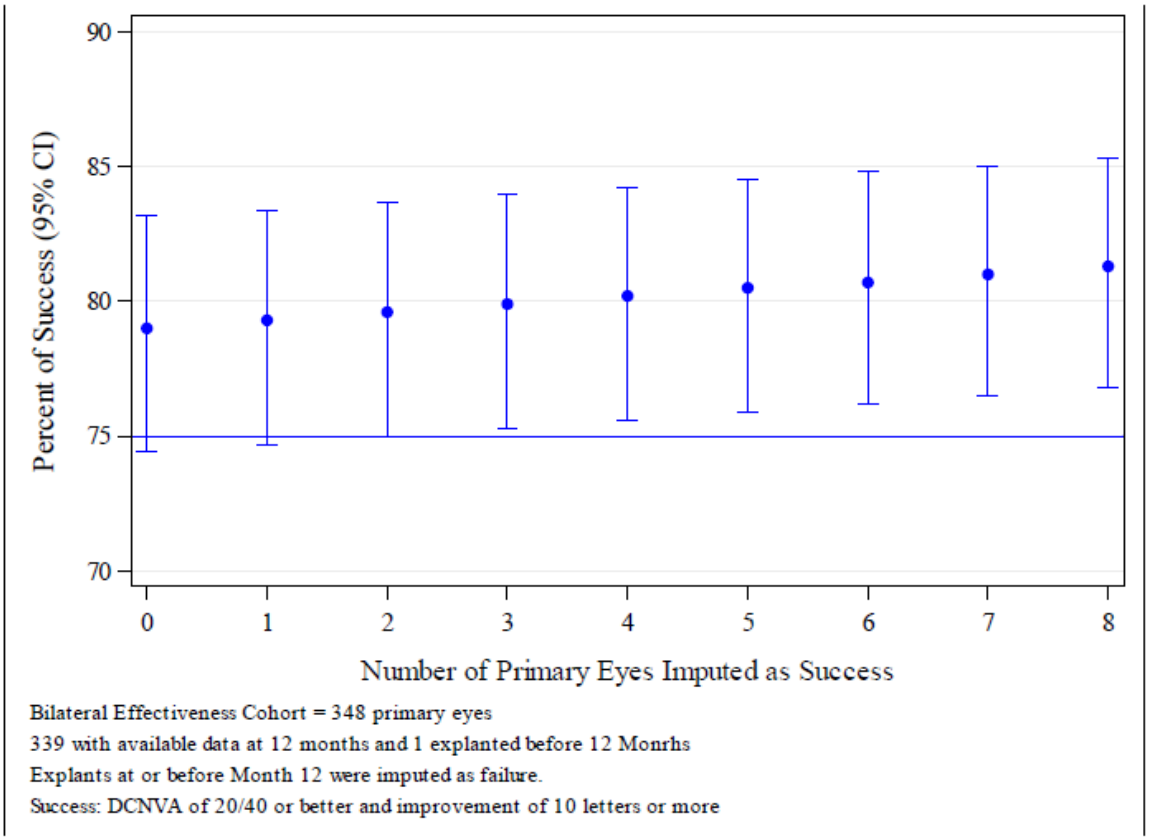


Figure 13 Box and Whisker Plot of Uncorrected Near Visual Acuity (UCNVA) at the Pre-Operative and 6, 12, 18 and 24 Month Post-Operative Visits. (Better vision is indicated by a higher score for UCNVA)

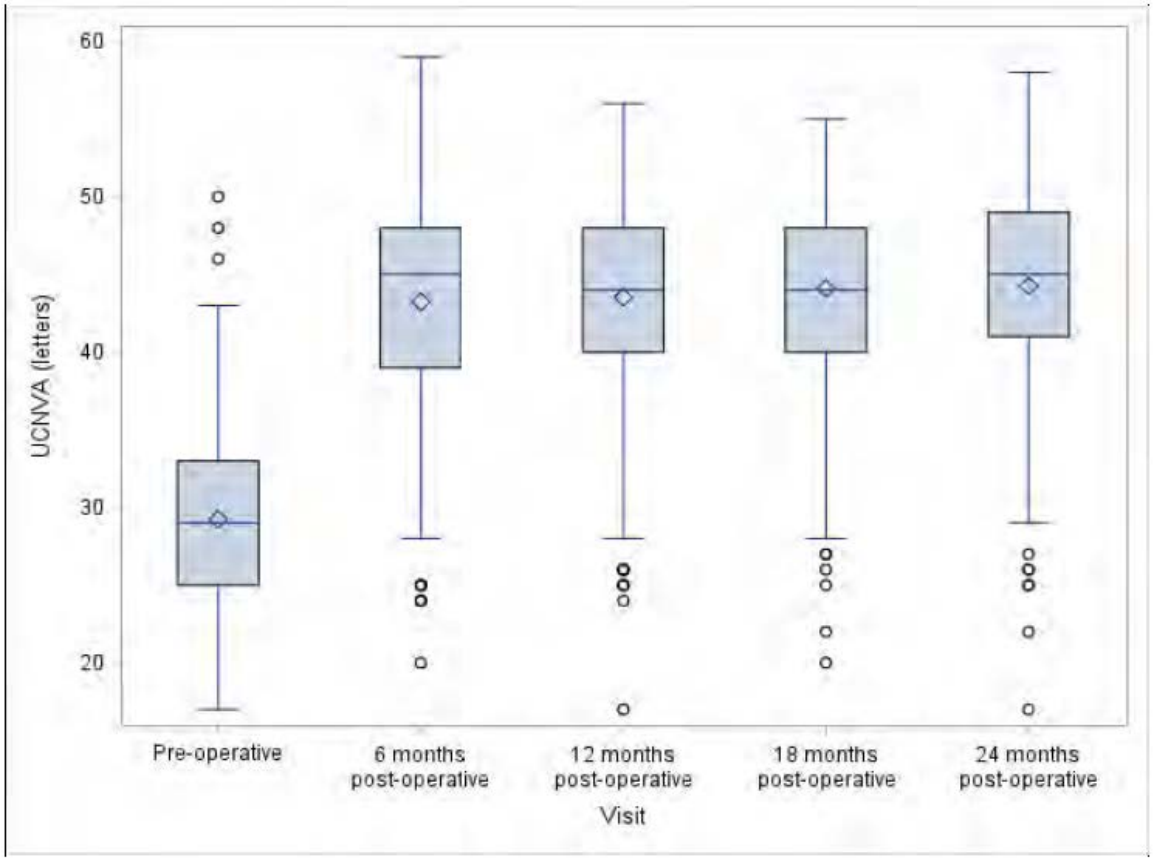


Figure 14 UCNVA versus UCDVA Change from Baseline at 12 Months, Intent-to-Treat Population

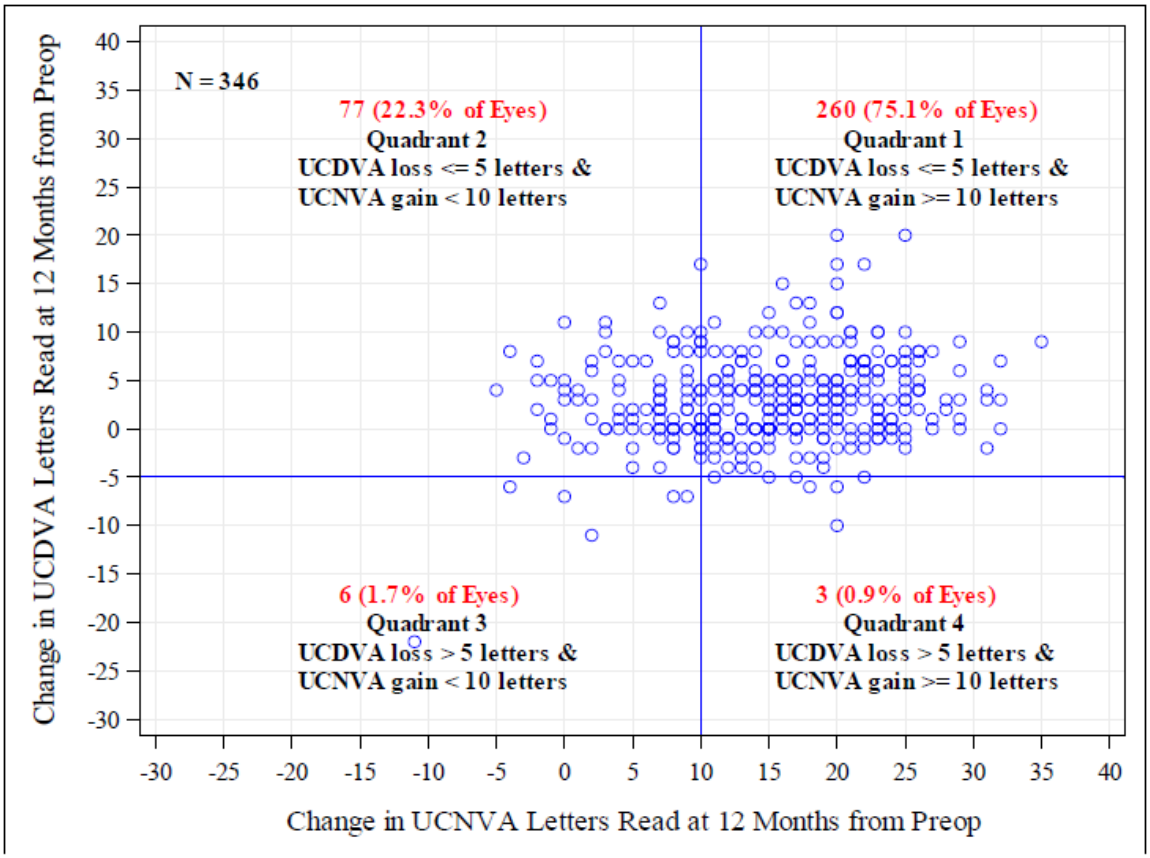


Figure 15 UCNVA versus UCDVA Change from Baseline at 24 Months, Intent-to-Treat Population

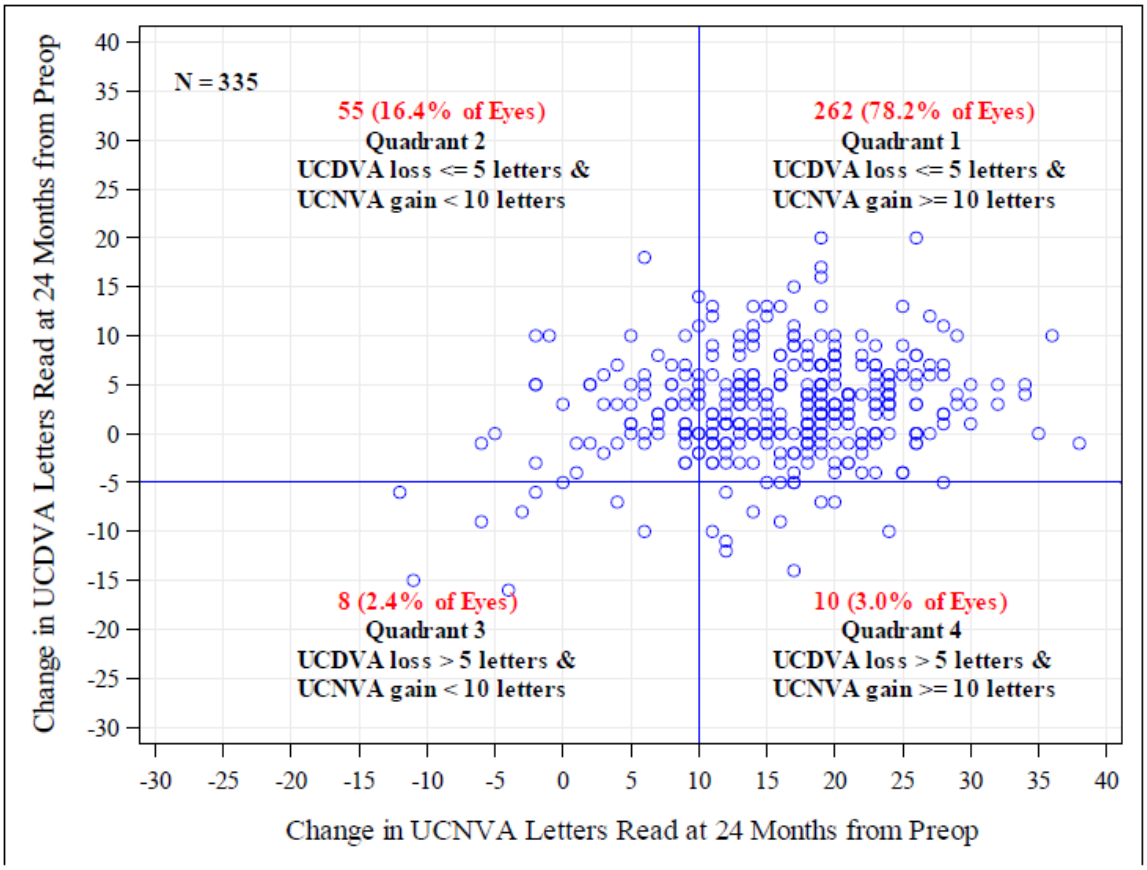
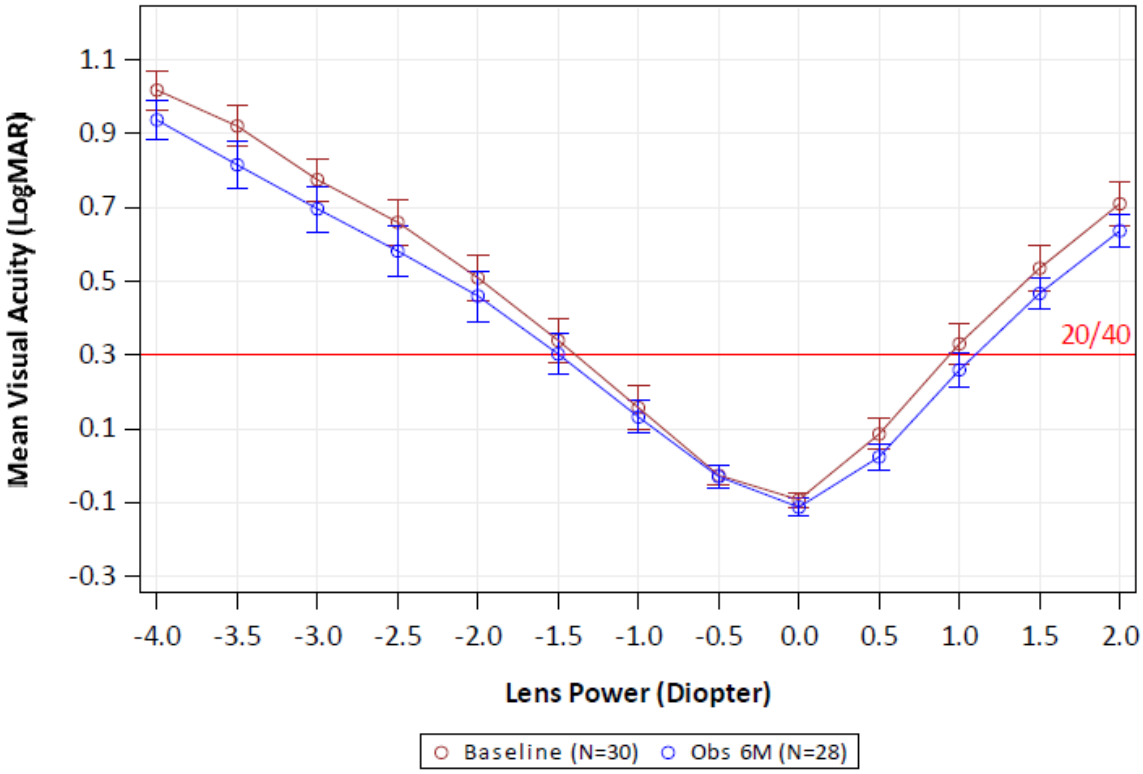


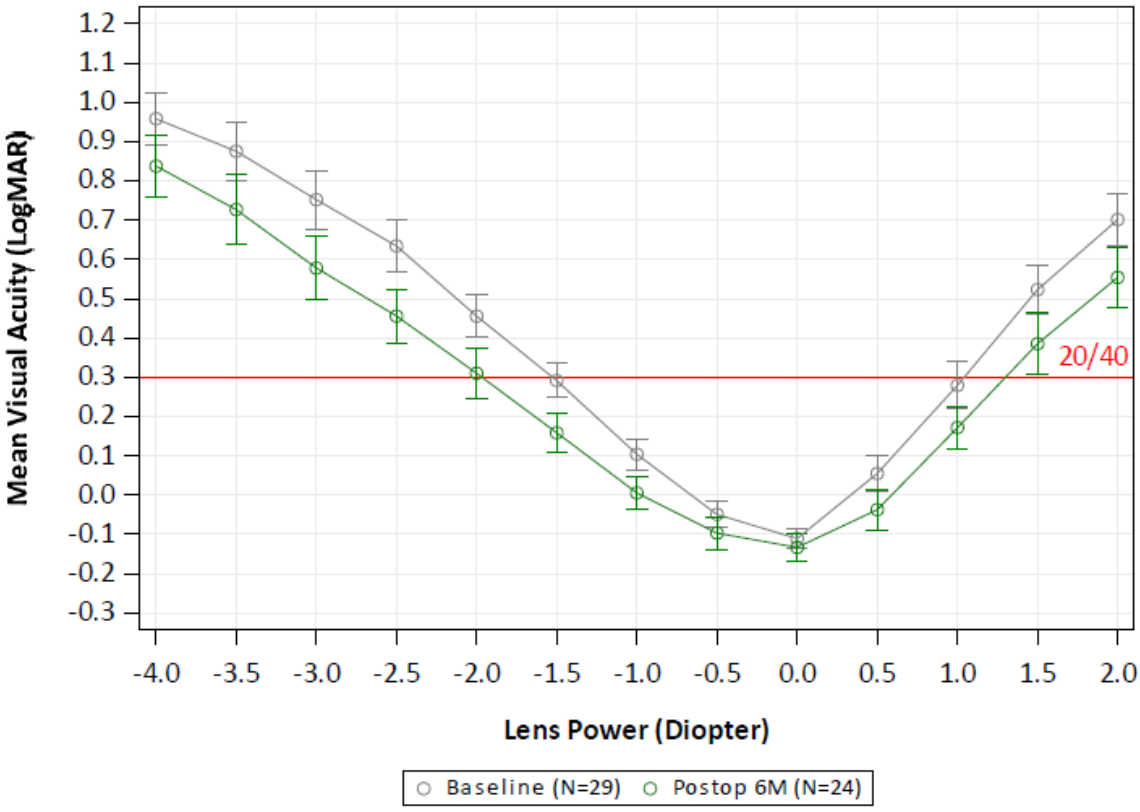
Figure 16 Mean (95% CI) Defocus Curve for Primary Eyes - Randomized Substudy - Deferred Treatment



Baseline = average Baseline #1 and Baseline #2

00844065 in the Deferred-Treatment group did not have the defocus test.

Figure 17 Mean (95% CI) Defocus Curve for Primary Eyes - Randomized Substudy - Immediate Treatment



Baseline = average Baseline #1 and Baseline #2

13 Appendices

13.1 Appendix 1 – List of Abbreviations and Definitions of Terms

Abbreviation	Represents
AE	Adverse Event
ASI	Anterior Segment Ischemia
BCDVA	Best Corrected Distance Visual Acuity
BCNVA	Best Corrected Near Visual Acuity
BEC	Bilateral Effectiveness Cohort
BSS	Balanced Salt Solution
CPS	Critical Print Size
CRF	Case Report Form
CRO	Clinical Research Organization
CRSE	Cycloplegic Refraction Spherical Equivalent
CSR	Clinical Study Report
dB	Decibel
DCNVA	Distance Corrected Near Visual Acuity
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICD	International Classification of Diseases
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
IU	Intended Use Cohort
LASIK	Laser Assisted In-Situ Keratomileusis
LogMAR	Logarithm of the Minimum Angle of Resolution
LST	Lamellar Scleral Tunnel
MD	Mean Deviation
mm	millimeters
mmHg	Millimeters of Mercury
MRSE	Manifest Refraction Spherical Equivalent
NAVQ	Near Acuity Visual Questionnaire
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCT	Optical Coherence Tomography
OD	Right Eye
OS	Left Eye
PG	Prostaglandin
PI	Principal Investigator
PMA	Premarket Approval
PMMA	Polymethylmethacrylate
PRO	Patient Reported Outcomes

13.2 Appendix 2 – List of PMA Effectiveness Tables and Figures

The list below represents the full list of effectiveness analyses provided by the applicant within their PMA and includes each original table number and page reference in the PMA. Highlighted items represent tables that FDA has replicated and discussed within this summary. Note that the table numbers have been modified accordingly based on their presentation within this summary. Furthermore, FDA has presented modified versions of Tables 16b, 66, and 69 where Table 16b was modified to remove the IU Cohort results (as this is not the indication being sought) and Tables 66 and 69 were modified to remove the 12-Month Consistent Cohort results.

Figures

Tables

13.3 Appendix 3 - Dynamic Wavefront Tables

Table 54 Dynamic Change at 6 Months - Spherical Equivalent (Z1)

Group	N (eyes)	Mean (SD)	95% CI[2]	p-value
1 Meter				
Deferred Treatment	27	-0.05 (0.15)	-0.110 – 0.010	
Immediate Treatment	28	-0.04 (0.12)	-0.100 –0.020	0.88
66 Centimeters				
Deferred Treatment	27	-0.05 (0.16)	-0.100 – 0.010	
Immediate Treatment	28	-0.01 (0.2)	-0.090 – 0.060	0.40
50 Centimeters				
Deferred Treatment	27	-0.07 (0.2)	-0.103 – -0.005	
Immediate Treatment	28	-0.06 (0.02)	-0.140 – 0.009	0.95
40 Centimeters				
Deferred Treatment	27	-0.07 (0.14)	-0.12 – 0.010	
Immediate Treatment	28	-0.06 (0.16)	-0.12 – 0.003	0.89
33 Centimeters				
Deferred Treatment	27	-0.05 (0.16)	-0.12 – 0.000	
Immediate Treatment	28	-0.06 (0.20)	-0.13 – 0.020	0.93

Table 55 Dynamic Change at 6 Months – Oblique Astigmatism (CO3)

Group	N (eyes)	Mean (SD)	95% CI[2]	p-value
1 Meter				
Deferred Treatment	27	-0.01 (0.03)	-0.020 – 0.010	
Immediate Treatment	28	-0.00 (0.03)	-0.140 – 0.010	0.73
66 Centimeters				
Deferred Treatment	27	-0.01 (0.02)	-0.020 – 0.000	
Immediate Treatment	28	0.00 (0.02)	-0.010 – 0.010	0.42
50 Centimeters				
Deferred Treatment	27	0.01 (0.03)	-0.000 – 0.010	
Immediate Treatment	28	0.00 (0.03)	-0.010 – 0.010	0.24
40 Centimeters				
Deferred Treatment	27	-0.00 (0.03)	-0.01 – 0.01	
Immediate Treatment	28	-0.005 (0.03)	-0.02 – 0.01	0.24
33 Centimeters				
Deferred Treatment	27	-0.004 (0.02)	-0.01 – 0.01	
Immediate Treatment	28	-0.002 (0.03)	-0.02 – 0.01	0.84

Table 56 Dynamic Change - Vertical Astigmatism (C05)

Group	N	Mean (SD)	95% CI[2]	p-value
1 Meter				
Deferred Treatment	27	0.0003 (0.04)	-0.01 – 0.02	
Immediate Treatment	28	-0.002(0.03)	-0.02 – 0.01	0.63
66 Centimeters				
Deferred Treatment	27	-0.002 (0.03)	-0.02 – 0.03	
Immediate Treatment	28	-0.006 (0.04)	-0.01 – 0.02	0.78
50 Centimeters				
Deferred Treatment	27	-0.002 (0.03)	0.007 – 0.011	
Immediate Treatment	28	-0.0003 (0.04)	-0.02 – 0.02	0.90
40 Centimeters				
Deferred Treatment	27	0.002 (0.06)	-0.001 – 0.015	
Immediate Treatment	28	0.002 (0.03)	-0.01 – 0.01	0.97
33 Centimeters				
Deferred Treatment	27	0.004 (0.04	-0.01 – 0.02	
Immediate Treatment	28	0.002 (0.04)	-0.01 – 0.02	0.85

Table 57 Dynamic Change at 6 Months - Horizontal Coma (CO8)

Group	N (eyes)	Mean (SD)	95% CI[2]	p-value
1 Meter				
Deferred Treatment	27	-0.004 (0.02)	-0.010 – 0.003	
Immediate Treatment	28	-0.003 (0.01)	-0.009 – 0.002	0.87
66 Centimeters				
Deferred Treatment	27	-0.004 (0.01)	-0.009 – 0.001	
Immediate Treatment	28	-0.003 (0.01)	-0.006 – 0.0004	0.81
50 Centimeters				
Deferred Treatment	27	-0.003 (0.01)	-0.009 – 0.002	
Immediate Treatment	28	-0.003 (0.01)	-0.003 – 0.004	0.28
40 Centimeters				
Deferred Treatment	27	-0.00 (0.01)	-0.007 – 0.004	
Immediate Treatment	28	-0.00 (0.01)	-0.004 – 0.003	0.59
33 Centimeters				
Deferred Treatment	27	-0.00 (0.02)	-0.007 – 0.005	
Immediate Treatment	28	-0.00 (0.01)	-0.007 – 0.002	0.59

Table 58 Dynamic Change at 6 Months – Spherical Aberration (C12)

Group	N	Mean (SD)	95% CI[2]	p-value
1 Meter				
Deferred Treatment	27	-0.00 (0.00)	-0.003 – 0.000	
Immediate Treatment	28	-0.00 (0.00)	-0.003 – 0.000	0.75
66 Centimeters				
Deferred Treatment	27	-0.00 (0.00)	-0.002 – 0.001	
Immediate Treatment	28	-0.00 (0.00)	-0.003 – 0.001	0.64
50 Centimeters				
Deferred Treatment	27	-0.00 (0.01)	-0.002 – 0.000	
Immediate Treatment	28	-0.00 (0.01)	-0.007 – 0.000	0.43
40 Centimeters				
Deferred Treatment	27	-0.00 (0.01)	-0.003 – 0.000	
Immediate Treatment	28	-0.00 (0.01)	-0.004 – 0.000	0.83
33 Centimeters				
Deferred Treatment	27	0.00 (0.01)	-0.002 – 0.002	
Immediate Treatment	28	-0.00 (0.01)	-0.004 – 0.002	0.51

Table 59 Dynamic Change at 6 Months – Secondary Astigmatism (C13)

Group	N	Mean (SD)	95% CI[2]	p-value
1 Meter				
Deferred Treatment	27	0.00 (0.01)	-0.003 – 0.004	
Immediate Treatment	28	0.00 (0.01)	-0.002 – 0.002	0.92
66 Centimeters				
Deferred Treatment	27	0.00 (0.01)	-0.001 – 0.006	
Immediate Treatment	28	-0.00 (0.01)	-0.003 – 0.003	0.85
50 Centimeters				
Deferred Treatment	27	0.00 (0.01)	-0.003 – 0.004	
Immediate Treatment	28	-0.00 (0.01)	-0.003 – 0.005	0.88
40 Centimeters				
Deferred Treatment	27	0.00 (0.01)	-0.004 – 0.004	
Immediate Treatment	28	0.01 (0.01)	-0.003 – 0.004	0.89
33 Centimeters				
Deferred Treatment	27	-0.00 (0.01)	-0.004 – 0.002	
Immediate Treatment	28	0.00 (0.01)	-0.002 – 0.004	0.34

13.4 Appendix 4 – Covariate Analyses – Effectiveness Tables

Table 60 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months By Baseline Manifest Refraction Axis Using Negative Cylinder Convention - Intent-to-Treat Population

Baseline MR Axis	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No Astigmatism	137	119 (86.9%)	80.0%, 92.0%
60° - 120°	130	91 (70.0%)	61.3%, 77.7%
0° - 30° or 150° - 180°	39	33 (84.6%)	69.5%, 94.1%
31° - 59° or 121° - 149°	44	34 (77.3%)	62.2%, 88.5%
p-value[3]			0.006
Average over Baseline MR Axis[4]		79.7%	74.8%, 84.5%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for site difference
4 Percentage was the simple average of the percentages over all axis groups. Normal approximation was used to calculate the 95% CI.

Table 61 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months By Baseline Manifest Refraction Axis Using Negative Cylinder Convention - Intent-to-Treat Population

Baseline MR Axis	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No Astigmatism	137	119 (86.9%)	80.0%, 92.0%
60° - 120°	126	101 (80.2%)	72.1%, 86.7%
0° - 30° or 150° - 180°	38	34 (89.5%)	75.2%, 97.1%
31° - 59° or 121° - 149°	43	35 (81.4%)	66.6%, 91.6%
p-value[3]			0.369
Average over Baseline MR Axis[4]		84.5%	80.1%, 88.9%

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for site difference
4 Percentage was the simple average of the percentages over all axis groups. Normal approximation was used to calculate the 95% CI.

Table 62 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months By Baseline Keratometry Axis - Intent-to-Treat Population

Baseline Keratomery Axis	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No Astigmatism	5	4 (80.0%)	28.4%, 99.5%
60° - 120°	241	196 (81.3%)	75.8%, 86.0%
0° - 30° or 150° - 180°	35	27 (77.1%)	59.9%, 89.6%
31° - 59° or 121° - 149°	69	50 (72.5%)	60.4%, 82.5%
p-value[3]			0.380
Average over Baseline Keratomery Axis[4]		77.7%	67.9%, 87.6%

Axis = the axis of the larger amount of the horizontal and vertical K-readings

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for site difference

4 Percentage was the simple average of the percentages over all axis groups. Normal approximation was used to calculate the 95% CI.

Table 63 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months By Baseline Keratometry Axis - Intent-to-Treat Population

Baseline Keratomery Axis	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No Astigmatism	5	5 (100.0%)	47.8%, 100.0%
60° - 120°	235	194 (82.6%)	77.1%, 87.2%
0° - 30° or 150° - 180°	35	29 (82.9%)	66.4%, 93.4%
31° - 59° or 121° - 149°	69	61 (88.4%)	78.4%, 94.9%
p-value[3]			0.625
Average over Baseline Keratomery Axis[4]		88.5%	84.6%, 92.3%

Axis = the axis of the larger amount of the horizontal and vertical K-readings

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for site difference

4 Percentage was the simple average of the percentages over all axis groups. Normal approximation was used to calculate the 95% CI.

Table 64 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months By Baseline Manifest Refraction Cylinder Amount - Intent-to-Treat Population

Baseline MR Cylinder Amount	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No Astigmatism	137	119 (86.9%)	80.0%, 92.0%
< 0.75 D	170	131 (77.1%)	70.0%, 83.1%
≥ 0.75	43	27 (62.8%)	46.7%, 77.0%
p-value[3]			0.002
Average over Baseline MR Cylinder Amount[4]		75.6%	70.0%, 81.2%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for site difference
4 Percentage was the simple average of the percentages over the cylinder groups. Normal approximation was used to calculate the 95% CI.

Table 65 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months By Baseline Manifest Refraction Cylinder Amount - Intent-to-Treat Population

Baseline MR Cylinder Amount	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No Astigmatism	137	119 (86.9%)	80.0%, 92.0%
< 0.75 D	167	141 (84.4%)	78.0%, 89.6%
≥ 0.75	40	29 (72.5%)	56.1%, 85.4%
p-value[3]			0.101
Average over Baseline MR Cylinder Amount[4]		81.3%	76.0%, 86.6%

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for site difference
4 Percentage was the simple average of the percentages over the cylinder groups. Normal approximation was used to calculate the 95% CI.

Table 66 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months By Baseline Meibomian Gland Disease (MGD) – Intent-to-Treat Population

Baseline MGD	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No MGD	250	197 (78.8%)	73.2%, 83.7%
Any MGD	100	80 (80.0%)	70.8%, 87.3%
p-value[3]			0.885
Average over Baseline MGD[4]		79.4%	74.7%, 84.1%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for site difference
4 Percentage was the simple average of the percentages over the MGD groups. Normal approximation was used to calculate the 95% CI.

Table 67 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months By Baseline Meibomian Gland Disease (MGD) – Intent-to-Treat Population

Baseline MGD	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
No MGD	244	203 (83.2%)	77.9%, 87.7%
Any MGD	100	86 (86.0%)	77.6%, 92.1%
p-value[3]			0.627
Average over Baseline MGD[4]		84.6%	80.5%, 88.7%

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for site difference
4 Percentage was the simple average of the percentages over the MGD groups. Normal approximation was used to calculate the 95% CI.

Table 68 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months By Baseline Manifest Refraction Cylinder Amount – Intent-to-Treat Population

Baseline MR Cylinder Amount	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
0.00D	119/137 (86.9%) (80.0%, 92.0%)	124/143 (86.7%) (80.0%, 91.8%)	120/143 (83.9%) (76.9%, 89.5%)
≤ 0.25 D	182/218 (83.5%) (77.9%, 88.2%)	189/226 (83.6%) (78.1%, 88.2%)	184/226 (81.4%) (75.7%, 86.3%)
≤ 0.50 D	250/307 (81.4%) (76.6%, 85.6%)	258/317 (81.4%) (76.7%, 85.5%)	252/317 (79.5%) (74.6%, 83.8%)
≤ 0.75 D	271/336 (80.7%) (76.0%, 84.7%)	279/346 (80.6%) (76.1%, 84.7%)	273/346 (78.9%) (74.2%, 83.1%)
≤ 1.00 D	277/349 (79.4%) (74.7%, 83.5%)	285/359 (79.4%) (74.8%, 83.5%)	279/359 (77.7%) (73.1%, 81.9%)
≤ 1.25 D	277/350 (79.1%) (74.5%, 83.3%)	285/360 (79.2%) (74.6%, 83.2%)	279/360 (77.5%) (72.8%, 81.7%)

[1] Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

[2] Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as successes.

[3] Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as failures.

[4] Exact binomial 95% confidence interval (CI)

Table 69 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months By Baseline Manifest Refraction Cylinder Amount – Intent-to-Treat Population

Baseline MR Cylinder Amount	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
0.00D	119/137 (86.9%) (80.0%, 92.0%)	124/143 (86.7%) (80.0%, 91.8%)	120/143 (83.9%) (76.9%, 89.5%)
≤ 0.25 D	184/216 (85.2%) (79.7%, 89.6%)	192/226 (85.0%) (79.6%, 89.4%)	186/226 (82.3%) (76.7%, 87.0%)
≤ 0.50 D	260/304 (85.5%) (81.1%, 89.3%)	269/317 (84.9%) (80.4%, 88.6%)	262/317 (82.6%) (78.0%, 86.7%)
≤ 0.75 D	282/330 (85.5%) (81.2%, 89.1%)	294/346 (85.0%) (80.8%, 88.6%)	284/346 (82.1%) (77.6%, 86.0%)
≤ 1.00 D	289/343 (84.3%) (80.0%, 87.9%)	301/359 (83.8%) (79.6%, 87.5%)	291/359 (81.1%) (76.6%, 85.0%)
≤ 1.25 D	289/344 (84.0%) (79.7%, 87.7%)	301/360 (83.6%) (79.4%, 87.3%)	291/360 (80.8%) (76.4%, 84.8%)

[1] Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.

[2] Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as successes.

[3] Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as failures.

[4] Exact binomial 95% confidence interval (CI)

Table 70 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months By Baseline Scleral Thickness – Intent-to-Treat Population

Baseline Scleral Thickness*	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
≤ 551 um	118/141 (83.7%) (76.5%, 89.4%)	123/146 (84.2%) (77.3%, 89.7%)	120/146 (82.2%) (75.0%, 88.0%)
≤ 594 um	232/274 (84.7%) (79.9%, 88.7%)	239/282 (84.8%) (80.0%, 88.7%)	234/282 (83.0%) (78.1%, 87.2%)
≤ 637 um	260/319 (81.5%) (76.8%, 85.6%)	268/329 (81.5%) (76.8%, 85.5%)	262/329 (79.6%) (74.9%, 83.9%)
≤ 680 um	273/341 (80.1%) (75.4%, 84.2%)	281/351 (80.1%) (75.5%, 84.1%)	275/351 (78.3%) (73.7%, 82.5%)
≤ 723 um	276/347 (79.5%) (74.9%, 83.7%)	284/357 (79.6%) (75.0%, 83.6%)	278/357 (77.9%) (73.2%, 82.1%)
≤ 766 um	276/348 (79.3%) (74.7%, 83.4%)	284/358 (79.3%) (74.8%, 83.4%)	278/358 (77.7%) (73.0%, 81.9%)
≤ 809 um	277/350 (79.1%) (74.5%, 83.3%)	285/360 (79.2%) (74.6%, 83.2%)	279/360 (77.5%) (72.8%, 81.7%)

* The scleral thickness ranged from 530 to 800 Groups were constructed based on Mean (572) and SD (43) as ≤Mean-1.5*SD, ≤Mean-0.5*SD, ≤Mean + 0.5*SD, ≤Mean + 1.5*SD, etc..

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

2 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as successes.

3 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 71 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months By Baseline Scleral Thickness – Intent-to-Treat Population

Baseline Scleral Thickness*	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
≤ 551 um	111/136 (81.6%) (74.1%, 87.7%)	119/146 (81.5%) (74.2%, 87.4%)	113/146 (77.4%) (69.7%, 83.9%)
≤ 594 um	232/268 (86.6%) (81.9%, 90.4%)	243/282 (86.2%) (81.6%, 90.0%)	234/282 (83.0%) (78.1%, 87.2%)
≤ 637 um	262/313 (83.7%) (79.1%, 87.6%)	274/329 (83.3%) (78.8%, 87.2%)	264/329 (80.2%) (75.5%, 84.4%)
≤ 680 um	280/335 (83.6%) (79.2%, 87.4%)	292/351 (83.2%) (78.9%, 87.0%)	282/351 (80.3%) (75.8%, 84.4%)
≤ 723 um	286/341 (83.9%) (79.5%, 87.6%)	298/357 (83.5%) (79.2%, 87.2%)	288/357 (80.7%) (76.2%, 84.6%)
≤ 766 um	287/342 (83.9%) (79.6%, 87.6%)	299/358 (83.5%) (79.3%, 87.2%)	289/358 (80.7%) (76.3%, 84.7%)
≤ 809 um	289/344 (84.0%) (79.7%, 87.7%)	301/360 (83.6%) (79.4%, 87.3%)	291/360 (80.8%) (76.4%, 84.8%)

* The scleral thickness ranged from 530 to 800 Groups were constructed based on Mean (572) and SD (43) as ≤Mean-1.5*SD, ≤Mean-0.5*SD, ≤Mean + 0.5*SD, ≤Mean + 1.5*SD, etc..

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.

2 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as successes.

3 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 72 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months – Intent-to-Treat Population With Baseline UCNVA ≤ 20/63

Sub-population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Baseline UCNVA ≤ 20/63	207/258 (80.2%) (74.8%, 84.9%)	212/265 (80.0%) (74.7%, 84.6%)	209/265 (78.9%) (73.5%, 83.6%)

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

2 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as successes.

3 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 73 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months – Intent-to-Treat Population With Baseline UCNVA ≤ 20/63

Sub-population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Baseline UCNVA ≤ 20/63	214/254 (84.3%) (79.2%, 88.5%)	221/265 (83.4%) (78.4%, 87.7%)	215/265 (81.1%) (75.9%, 85.7%)

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.

2 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as successes.

3 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 74 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months – Intent-to-Treat Population With Baseline DCNVA ≤ 20/63

Sub-population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Baseline DCNVA ≤ 20/63	189/222 (85.1%) (79.8%, 89.5%)	196/230 (85.2%) (80.0%, 89.5%)	190/230 (82.6%) (77.1%, 87.3%)

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

2 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as successes.

3 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 75 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months – Intent-to-Treat Population With Baseline DCNVA ≤ 20/63

Sub-population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Baseline DCNVA ≤ 20/63	189/218 (86.7%) (81.5%, 90.9%)	199/230 (86.5%) (81.4%, 90.7%)	191/230 (83.0%) (77.6%, 87.7%)

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.

2 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as successes.

3 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 76 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 12 Months – Intent-to-Treat Population With Baseline Scleral Thickness ≤ 680 and Baseline Manifest Refraction Cylinder ≤ 0.75D

Sub-population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Baseline Scleral Thickness ≤ 680 um and Baseline MRCYL ≤ 0.75 D	268/328 (81.7%) (77.1%, 85.7%)	276/338 (81.7%) (77.1%, 85.6%)	270/338 (79.9%) (75.2%, 84.0%)

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded.

2 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as successes.

3 Explants at or before Month 12 were imputed as failures. For other subjects with missing Month 12 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, or 6-month) was used. If no data were observed between Month 1 and Month 12, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 77 First Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 24 Months – Intent-to-Treat Population With Baseline Scleral Thickness ≤ 680 and Baseline Manifest Refraction Cylinder ≤ 0.75D

Sub-population	Primary Analysis[1] n/N (%), 95% CI[4]	Best Case Sensitivity Analysis[2] n/N (%), 95% CI[4]	Worst Case Sensitivity Analysis[3] n/N (%), 95% CI[4]
Baseline Scleral Thickness ≤ 680 um and Baseline MRCYL ≤ 0.75 D	274/322 (85.1%) (80.7%, 88.8%)	286/338 (84.6%) (80.3%, 88.3%)	276/338 (81.7%) (77.1%, 85.6%)

1 Explants at or before Month 24 were imputed as failures. Other subjects with missing Month 24 values were excluded.

2 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the best value from the protocol scheduled visits at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as successes.

3 Explants at or before Month 24 were imputed as failures. For other subjects with missing Month 24 value, the worst value from the protocol scheduled visit at Month 1 to later (1-month, 2-month, 3-month, 6-month, 12-month, or 18-month) was used. If no data were observed between Month 1 and Month 24, the subjects were imputed as failures.

4 Exact binomial 95% confidence interval (CI)

Table 78 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline Maximum Pupil Size – Effectiveness Cohort

Pupil Size	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
≤ 5.0 mm	97	77 (79.4%)	70.0%, 86.9%
>5.0 to 5.5 mm	66	58 (87.9%)	77.5%, 94.6%
>5.5 to 6.0 mm	91	65 (71.4%)	61.0%, 80.4%
>6.0 mm	87	75 (86.2%)	77.1%, 92.7%
p-value[3]			0.033
Average over Pupil Size[4]		81.2%	77.2%, 85.3%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for pupil size difference

4 Percentage was the simple average of the percentages over all pupil size groups. Normal approximation was used to calculate the 95% CI.

Table 79 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline Minimum Pupil Size – Effectiveness Cohort

Pupil Size	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
≤ 2.7 mm	81	63 (77.8%)	67.2%, 86.3%
>2.7 to 3.0 mm	68	55 (80.9%)	69.5%, 89.4%
>3.0 to 3.5 mm	118	92 (78.0%)	69.4%, 85.1%
>3.5 mm	74	65 (87.8%)	78.2%, 94.3%
p-value[3]			0.316
Average over Pupil Size[4]		81.1%	76.9%, 85.3%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for pupil size difference
4 Percentage was the simple average of the percentages over all pupil size groups. Normal approximation was used to calculate the 95% CI.

Table 80 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline MRSE– Effectiveness Cohort

MRSE	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
<0.00 D	73	56 (76.7%)	65.4%, 85.8%
0.00 D	63	53 (84.1%)	72.7%, 92.1%
>0.00 D	205	166 (81.0%)	74.9%, 86.1%
p-value[3]			0.563
Average over MRSE[4]		80.6%	75.8%, 85.4%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for MRSE difference
4 Percentage was the simple average of the percentages over all MRSE groups. Normal approximation was used to calculate the 95% CI.

Table 81 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline Near Add - Effectiveness Cohort

Near Add	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
1.25 D	93	74 (79.6%)	69.9%, 87.2%
1.50 D	90	70 (77.8%)	67.8%, 85.9%
1.75 D	88	65 (73.9%)	63.4%, 82.7%
>1.75 D	70	66 (94.3%)	86.0%, 98.4%
p-value[3]			0.004
Average over Near Add[4]		81.4%	77.4%, 85.4%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for near add difference
4 Percentage was the simple average of the percentages over all near add groups. Normal approximation was used to calculate the 95% CI.

Table 82 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline ACD - Effectiveness Cohort

ACD*	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
< 3.00 mm	70	52 (74.3%)	62.4%, 84.0%
3.00 - 3.25 mm	85	68 (80.0%)	69.9%, 87.9%
3.26 - 3.50 mm	98	82 (83.7%)	74.8%, 90.4%
> 3.50 mm	83	69 (83.1%)	73.3%, 90.5%
p-value[3]			0.444
Average over ACD*[4]		80.3%	76.0%, 84.6%

* 5 subjects without baseline ACD were excluded from the analyses. The corresponding n (%) = 4 (80.0%) and 95% CI = (28.4%, 99.5%).
1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for ACD difference
4 Percentage was the simple average of the percentages over all ACD groups. Normal approximation was used to calculate the 95% CI.

Table 83 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline Axial Length – Effectiveness Cohort

Axial Length	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
< 23.0 mm	75	64 (85.3%)	75.3%, 92.4%
23.0 - < 23.5 mm	80	64 (80.0%)	69.6%, 88.1%
23.5 - < 24.0 mm	96	78 (81.3%)	72.0%, 88.5%
≥ 24.0 mm	90	69 (76.7%)	66.6%, 84.9%
p-value[3]			0.583
Average over Axial Length[4]		80.8%	76.6%, 85.0%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for axial length difference
4 Percentage was the simple average of the percentages over all axial length groups. Normal approximation was used to calculate the 95% CI.

Table 84 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline Astigmatism – Effectiveness Cohort

Astigmatism	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
-0.75 D or Higher	40	27 (67.5%)	50.9%, 81.4%
-0.50 D	88	68 (77.3%)	67.1%, 85.5%
-0.25 D	80	63 (78.8%)	68.2%, 87.1%
0.00 D	133	117 (88.0%)	81.2%, 93.0%
p-value[3]			0.018
Average over Astigmatism[4]		77.9%	72.9%, 82.9%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for astigmatism difference
4 Percentage was the simple average of the percentages over all astigmatism groups. Normal approximation was used to calculate the 95% CI.

Table 85 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline Keratometry – Effectiveness Cohort

Keratometry	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
≤ 42.80 D	85	68 (80.0%)	69.9%, 87.9%
>42.80 - 43.75 D	89	68 (76.4%)	66.2%, 84.8%
>43.75 - 44.65 D	86	73 (84.9%)	75.5%, 91.7%
>44.65 D	81	66 (81.5%)	71.3%, 89.2%
p-value[3]			0.563
Average over Keratometry[4]		80.7%	76.5%, 84.9%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for keratometry difference
4 Percentage was the simple average of the percentages over all keratometry groups. Normal approximation was used to calculate the 95% CI.

Table 86 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline Scleral Thickness – Effectiveness Cohort

Scleral Thickness	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
≤ 530 um	57	46 (80.7%)	68.1%, 90.0%
>530 - 560 um	130	115 (88.5%)	81.7%, 93.4%
>560 - 580 um	67	55 (82.1%)	70.8%, 90.4%
>580 um	87	59 (67.8%)	56.9%, 77.4%
p-value[3]			0.003
Average over Scleral Thickness[4]		79.8%	75.3%, 84.2%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for scleral thickness difference
4 Percentage was the simple average of the percentages over all scleral thickness groups. Normal approximation was used to calculate the 95% CI.

Table 87 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline IOP – Effectiveness Cohort

IOP	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
≤ 13 mmHg	95	75 (78.9%)	69.4%, 86.6%
>13 - 14 mmHg	78	70 (89.7%)	80.8%, 95.5%
>14 - 16 mmHg	86	65 (75.6%)	65.1%, 84.2%
≥ 16 mmHg	82	65 (79.3%)	68.9%, 87.4%
p-value[3]			0.101
Average over IOP[4]		80.9%	76.8%, 85.0%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for IOP difference
4 Percentage was the simple average of the percentages over all IOP groups. Normal approximation was used to calculate the 95% CI.

Table 88 First Co-Primary Effectiveness Endpoint at 12 Months by Severity of Blepharitis – Effectiveness Cohort

Blepharitis	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
None	298	241 (80.9%)	75.9%, 85.2%
Trace	33	27 (81.8%)	64.5%, 93.0%
≥ Mild	10	7 (70.0%)	34.8%, 93.3%
p-value[3]			0.623
Average over Blepharitis[4]		77.6%	67.0%, 88.1%

For subjects without the 12-month slit lamp findings the last available data before the 12 month was used.
1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded
2 Exact binomial 95% confidence interval (CI)
3 Fisher's exact test for Blepharitis difference
4 Percentage was the simple average of the percentages over all Blepharitis groups. Normal approximation was used to calculate the 95% CI.

Table 89 First Co-Primary Effectiveness Endpoint at 12 Months by Severity of Meibomian Gland Dysfunction - Effectiveness Cohort

Meibomian Gland Dysfunction	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
None	216	179 (82.9%)	77.2%, 87.6%
Trace	104	84 (80.8%)	71.9%, 87.8%
≥ Mild	21	12 (57.1%)	34.0%, 78.2%
p-value[3]			0.024
Average over Meibomian Gland Dysfunction[4]		73.6%	65.9%, 81.3%

For subjects without the 12-month slit lamp findings the last available data before the 12 month was used.

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for Meibomian Gland Dysfunction difference

4 Percentage was the simple average of the percentages over all Meibomian Gland Dysfunction groups. Normal approximation was used to calculate the 95% CI.

Table 90 First Co-Primary Effectiveness Endpoint at 12 Months by Severity of Superficial Punctate Keratitis

SPK	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
None	307	247 (80.5%)	75.6%, 84.7%
Trace	26	21 (80.8%)	60.6%, 93.4%
≥ Mild	8	7 (87.5%)	47.3%, 99.7%
p-value[3]			1.000
Average over SPK[4]		82.9%	73.6%, 92.2%

For subjects without the 12-month slit lamp findings the last available data before the 12 month was used.

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for SPK

4 Percentage was the simple average of the percentages over all SPK groups. Normal approximation was used to calculate the 95% CI.

Table 91 First Co-Primary Effectiveness Endpoint at 12 Months by Severity of Conjunctival Injection - Effectiveness Cohort

Conjunctival Injection	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
None	196	164 (83.7%)	77.7%, 88.6%
Trace	112	85 (75.9%)	66.9%, 83.5%
≥ Mild	33	26 (78.8%)	61.1%, 91.0%
p-value[3]			0.219
Average over Conjunctival Injection[4]		79.5%	73.8%, 85.1%

For subjects without the 12-month slit lamp findings the last available data before the 12 month was used.

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for conjunctival injection difference

4 Percentage was the simple average of the percentages over all conjunctival injection groups. Normal approximation was used to calculate the 95% CI.

Table 92 First Co-Primary Effectiveness Endpoint at 12 Months by Conjunctival Abnormality at 12 Months - Effectiveness Cohort

Other Conjunctival Abnormality	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
Without Abnormality	319	257 (80.6%)	75.8%, 84.8%
With Abnormality	22	18 (81.8%)	59.7%, 94.8%
p-value[3]			1.000
Average over Other Conjunctival Abnormality[4]		81.2%	72.8%, 89.5%

For subjects without the 12-month slit lamp findings the last available data before the 12 month was used. The Without Abnormality group includes clinical observations via slit lamp examination.

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for with and without other conjunctival abnormality difference

4 Percentage was the simple average of the percentages over with and without conjunctival abnormality groups. Normal approximation was used to calculate the 95% CI.

Table 93 First Co-Primary Effectiveness Endpoint at 12 Months by Ocular Surface Signs[5] – Effectiveness Cohort

Ocular Surface Signs	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
Without	152	131 (86.2%)	79.7%, 91.2%
With	189	144 (76.2%)	69.5%, 82.1%
p-value[3]			0.027
Average over Ocular Surface Signs[4]		81.2%	77.1%, 85.3%

For subjects without the 12-month slit lamp findings the last available data before the 12 month was used.

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for with and without ocular surface symtoms

4 Percentage was the simple average of the percentages over with and without ocular surface Signs. Normal approximation was used to calculate the 95% CI.

5 Ocular Surface Signs include the following; Blepharitis, Meibomian Gland Dysfunction, SPK, or Conjunctival Injection at 12 months.

Table 94 First Co-Primary Effectiveness Endpoint at 12 Months by Severity of Ocular Surface Signs[5] - Effectiveness Cohort

Ocular Surface Signs	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
< Mild	268	220 (82.1%)	77.0%, 86.5%
≥ Mild	73	55 (75.3%)	63.9%, 84.7%
p-value[3]			0.241
Average over Ocular Surface Signs[4]		78.7%	73.3%, 84.2%

For subjects without the 12-month slit lamp findings the last available data before the 12 month was used.

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for with and without ocular surface symtoms

4 Percentage was the simple average of the percentages over with and without ocular surface Signs. Normal approximation was used to calculate the 95% CI.

5 Ocular Surface Signs include the following; Blepharitis, Meibomian Gland Dysfunction, SPK, or Conjunctival Injection at 12 months.

Table 95 First Co-Primary Effectiveness Endpoint at 12 Months by Baseline DCNVA - Effectiveness Cohort

Baseline DCNVA	N	20/40 or Better and Gain of ≥ 10 Letters[1] n (%)	95% CI[2]
20/50 or Better	124	87 (70.2%)	61.3%, 78.0%
20/63	141	122 (86.5%)	79.8%, 91.7%
20/80	76	66 (86.8%)	77.1%, 93.5%
p-value[3]			0.001
Average over Baseline DCNVA[4]		81.2%	77.0%, 85.3%

1 Explants at or before Month 12 were imputed as failures. Other subjects with missing Month 12 values were excluded

2 Exact binomial 95% confidence interval (CI)

3 Fisher's exact test for DCNVA difference

4 Percentage was the simple average of the percentages over all DCNVA groups. Normal approximation was used to calculate the 95% CI.

13.5 Appendix 5 – Covariate Analyses – Safety Tables List

- BCDVA Over Time IU Safety Cohort
- Change in BCDVA from Baseline IU Safety Cohort
- UCDVA Over Time IU Safety Cohort
- Change in UCDVA from Baseline IU Safety Cohort
- Distance Cycloplegic Visual Acuity IU Safety Cohort
- Change in Distance Cycloplegic Visual Acuity from Baseline IU Safety Cohort MRSE and Change in
- MRSE from Baseline IU Safety Cohort
- Stability of MRSE IU Safety Cohort
- Normal Aging Adjusted MRSE and Change from Baseline IU Safety Cohort
- Cycloplegic Refraction Spherical Equivalent and Change from Baseline IU Safety Cohort
- Vector Stability of Cylinder IU Safety Cohort

- Slit Lamp - Lids Findings IU Safety Cohort
- Eyes with Other Lids Abnormality IU Safety Cohort (N = 117 Eyes)
- Slit Lamp - Cornea IU Safety Cohort
- Eyes with Other Cornea Abnormality IU Safety Cohort (N = 53 Eyes)
- Slit Lamp - Conjunctiva IU Safety Cohort
- Eyes with Other Conjunctiva Abnormality IU Safety Cohort (N = 214 Eyes)
- Slit Lamp - Anterior Chamber Cells IU Safety Cohort
- Slit Lamp - Anterior Chamber Flare IU Safety Cohort
- Slit Lamp - Iris Appearance IU Safety Cohort
- Eyes with Abnormal Iris IU Safety Cohort (N = 6 Eyes)
- Slit Lamp - Crystalline Lens Status IU Safety Cohort
- Slit Lamp – Change from Preop in Crystalline Lens Status IU Safety Cohort
- Eyes with Postoperative Worsening of Crystalline Lens Status IU Safety Cohort (N = 63 Eyes)
- Eyes with Lens Abnormality Other than Opacity IU Safety Cohort (N = 2 Eyes)
- Intraocular Pressure (IOP) and Change in IOP from Baseline IU Safety Cohort
- Stability of IOP IU Safety Cohort
- Postoperative Intraocular Pressure Increase >10 mmHg or Postoperative IOP > 30 mmHg IU Safety
- Cohort (N = 51 Eyes)
- Intraocular Pressure (IOP) and Change in IOP from Baseline for Primary Eyes IU Randomized Substudy
- Gonioscopy IU Safety Cohort
- Change in Angle on Gonioscopy IU Safety Cohort
- Axial Length and Change in Axial Length from Baseline IU Safety Cohort

- Ophthalmoscopy – Fundus Findings IU Safety Cohort
- Eyes with Abnormal Fundus Findings IU Safety Cohort (N = 42 Eyes)
- Change in Cup/Disk Ratio IU Safety Cohort
- Pupillometry – Maximum Pupil Size IU Safety Cohort
- Pupillometry – Minimum Pupil Size IU Safety Cohort
- Pupillometry – Percent Constriction IU Safety Cohort
- Pupillometry – Pupil Reaction - Latency IU Safety Cohort
- Pupillometry – Pupil Reaction - Maximum Constriction Velocity IU Safety Cohort
- Pupillometry – Pupil Shape IU Safety Cohort
- Number of Micro Insert Segments IU Safety Cohort
- Micro Insert Segment Assessments IU Safety Cohort
- Surgical Complications IU Safety Cohort
- Ocular Adverse Events IU Safety Cohort
- Reported Ocular Adverse Events by Implanted Eyes IU Safety Cohort
- Reported Ocular Adverse Events by Event Type IU Safety Cohort
- Ocular Adverse Events by Exam Period IU Safety Cohort
- Device-related Ocular Adverse Events IU Safety Cohort
- Ocular Adverse Events for Dominant Eyes of Control Subjects IU Randomized Substudy
- Non-Ocular Adverse Events IU Safety Cohort
- Ocular Adverse Events by Maximum Severity IU Safety Cohort
- Device-related Ocular Adverse Events by Maximum Severity IU Safety Cohort

- Serious Ocular and Non-Ocular Adverse Events IU Safety Cohort