VISABILITY™ MICRO INSERT SYSTEM

FDA ADVISORY COMMITTEE MEETING
EXECUTIVE SUMMARY

MEETING OF THE OPHTHALMIC DEVICES PANEL

CONFIDENTIAL OCTOBER 16, 2020

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ASI	Anterior Segment Ischemia
BCDVA	Best Corrected Distance Visual Acuity
CI	Confidence Interval
D	Diopter
DCNVA	Distance Corrected Near Visual Acuity
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
HOA	Higher Order Aberration
IN	Inferior Nasal
IOL	Intraocular lens
IOP	Intraocular Pressure
IT	Inferior Temporal
LASIK	Laser Assisted In-Situ Keratomileusis
LogMAR	Logarithm of the Minimum Angle of Resolution
MOA	Mechanism of Action
MRSE	Manifest Refraction Spherical Equivalent
NAVQ	Near Activity Visual Questionnaire
NSAID	Non-Steroidal Anti-Inflammatory Drug
OD	Oculus Dexter (Right Eye)
ODP	Ophthalmic Devices Panel
OS	Oculus Sinister (Left Eye)
OSDI	Ocular Surface Disease Index
OU	Oculus Uterque (Both Eyes)
PMA	Pre-market Approval
PRO	Patient Reported Outcome
SD	Standard Deviation
SN	Superior Nasal
ST	Superior Temporal
UCDVA	Uncorrected Distance Visual Acuity
UCNVA	Uncorrected Near Visual Acuity

1 SYNOPSIS

Refocus Group, Inc. (Refocus) is seeking approval of the VisAbility™ Micro Insert System for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years, 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. The VisAbility Micro Insert System is a treatment for presbyopia performed outside of the visual axis, that does not compromise the integrity of the cornea and lens, which is often the source of unwanted optical side effects such as glare, halos, starbursts, ghost images, or double vision . The VisAbility Micro Insert System is a novel Medical Device that meets the needs of a select subset of patients with presbyopia, reflected in the proposed indications for use, and is intended to allow patients to achieve functional near visual acuity while also preserving distance vision.

Presbyopia is the most prevalent of all visual deficiencies, affecting virtually everyone over the age of 45 years. Presbyopia is associated with substantial negative effects on vision-targeted health-related quality of life (McDonnell et al. 2003). First-line treatment of presbyopia with eyeglasses or contact lenses has limitations, and current surgical options are often associated with unwanted optical side effects. There remains an unmet need for a safe, bilateral procedure that will not affect the visual axis.

Data supporting the approval of the VisAbility Micro Insert System for the proposed indication come from the pivotal, prospective, multicenter VisAbility Study. The objective of the study was to evaluate the safety and effectiveness of the VisAbility Micro Insert for the improvement of near vision in patients with presbyopia. Refocus originally submitted the PMA for the VisAbility Micro Insert System based on a 12 month dataset. On September 12, 2018, FDA issued a not approvable letter indicating concerns that the PMA contained inadequate data to demonstrate a reasonable assurance of safety and effectiveness for the device. Following a meeting with FDA on January 28, 2019, Refocus submitted a Major Amendment to the PMA which included analyses of data through 24 months.

Following receipt of a second not approvable letter on October 22, 2019, Refocus requested a Supervisory Review of the PMA. The supervisory review, held on December 20, 2019, by William Maisel, M.D., 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 demonstrated that the probable benefits of the device outweighed the probable risks. The not approvable decision was officially set aside by Dr. Maisel, the PMA review 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.

This document summarizes the data for up to 24 months from the VisAbility Study supporting the conclusion that there is a reasonable assurance of the safety and effectiveness of the VisAbility Micro Insert System, as necessary to support FDA pre-market approval of the device.

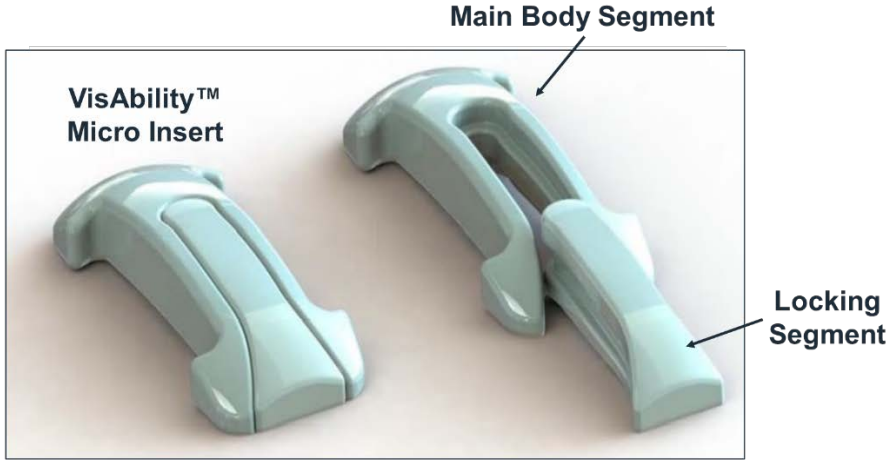
1.1 Device Description

The VisAbility Micro Insert System has been in development over the last 20 years as a treatment for presbyopia. The VisAbility Micro Insert System is unique among ocular surgeries to address this common condition. This surgery places a VisAbility Micro Insert into a scleral tunnel and has been classified as a Scleral Expansion Surgery. Refocus hypothesizes that the VisAbility Micro Inserts gently tent the scleral overlying the ciliary body. This action expands the circumlenticular space, tightening the zonular fibers that have become lax due to the age-related increase in the diameter of the lens.

The VisAbility Micro Insert System consists of the VisAbility Micro Insert, the VisAbility Scleratome, and the VisAbility Feeder Tube.

The **VisAbility Micro Insert** is a scleral implant that consists of a main body segment with 2 legs and a locking segment (Figure 1). The locking segment is designed to be smoothly clicked into place in the main body segment to prevent displacement or migration. Four VisAbility Micro Inserts are placed in a single presbyopic eye.

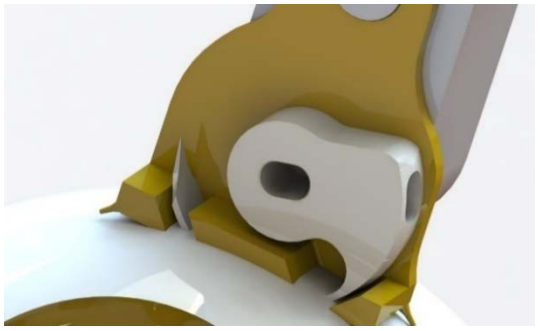
Figure 1: VisAbility Micro Insert Showing 2 Interlocking Pieces and Stabilization Feet



The **VisAbility Scleratome** (**Figures 2** and **3**) is a custom designed single-use surgical instrument used for creating precisely positioned scleral tunnel incisions into which the VisAbility Micro Inserts are placed.

Figure 2: VisAbility Scleratome

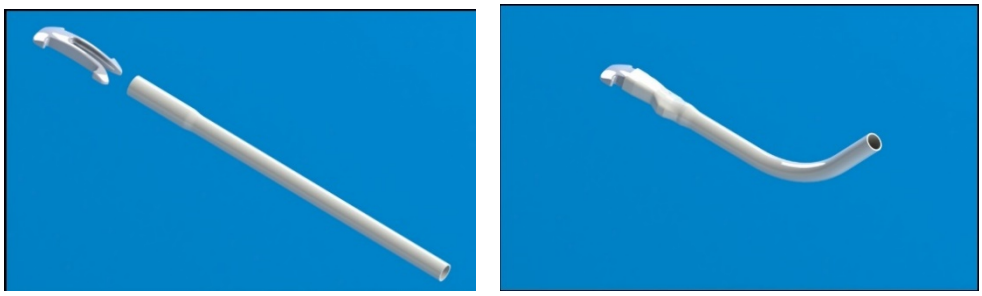
Figure 3: Scleratome Blade Creating a Tunnel[1]



[1] This view of the Scleratome would not be seen by the surgeon as the blade guard and docking station would be in the way

The **VisAbility Feeder Tube** is flexible tubing used to assist in placing the VisAbility Micro Inserts into the scleral tunnels (**Figures 4**).

Figures 4: VisAbility Feeder Tube and VisAbility Micro Insert Main Body Segment

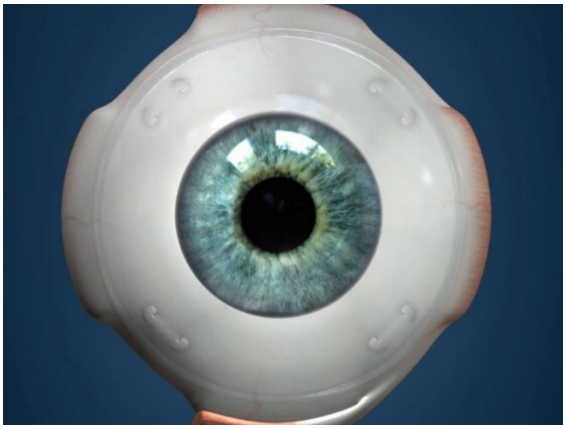


In addition, a docking station, which is a fixation device made of titanium and/or medical grade stainless steel, is used in conjunction with the VisAbility Micro Insert System. The docking station is supplied separately and is used for ocular fixation and as a docking location for the VisAbility Scleratome.

1.1.1 Implantation Procedure

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 meridians. **Figure 5** below shows a human eye implanted with the 4 VisAbility Micro Inserts.

Figure 5: Placement of VisAbility™ Micro Inserts



The surgical procedure involves the following basic steps:

- Marking – To indicate the correct rotational position of the docking station.
- Peritomy – Opening of the conjunctiva and Tenon's capsule at the limbus by standard techniques such as might be used in certain strabismus, glaucoma, or retina surgery to provide exposure of the sclera.
- Placement of the docking station – The docking station uses a four-point fixation system to provide ocular fixation and a fixed docking location for the VisAbility Scleratome.
- Scleral tunnel creation – The VisAbility Scleratome is activated to construct each of 4 scleral tunnels at a fixed position approximately 4 mm from the limbus and centered between adjacent recti muscles.
- Placement of the VisAbility Micro Insert – After each tunnel, the Main Body segment is pulled through the tunnel and the Locking segment is engaged to secure the VisAbility Micro Insert.
- Closing the conjunctiva – After re-checking each of the VisAbility Micro Inserts to assure that they do not impinge on the rectus muscle insertions, the docking station is removed, and the conjunctiva is secured to the limbus.

1.2 Summary of VisAbility Study Design

The VisAbility Study was a prospective clinical study of 360 surgical patients at 13 clinical sites to evaluate the safety and effectiveness of the VisAbility Micro Insert System. This pivotal study consisted of a non-randomized treatment arm (n=306), as well as a randomized substudy arm (n=54) at 3 clinical sites. In the substudy arm, patients were randomized 1:1 to either an immediate treatment group, in which patients were implanted with the VisAbility Micro Insert System and followed for 24 months, or a deferred treatment (control) group, in which patients were observed for 6 months before surgery and were then eligible to be implanted with the VisAbility Micro Insert System.

The trial included 2 co-primary endpoints: (i) achievement of distance corrected near visual acuity (DCNVA) 20/40 or better and gain of ≥ 10 letters DCNVA in 75% of the primary eyes at 12 months; and (ii) achievement of a statistically significant (one-sided $p < 0.025$) difference in the proportion of eyes with DCNVA 20/40 or better and gain of ≥ 10 letters at 6 months in patients randomized to treatment versus deferred surgery as part of the randomized substudy.

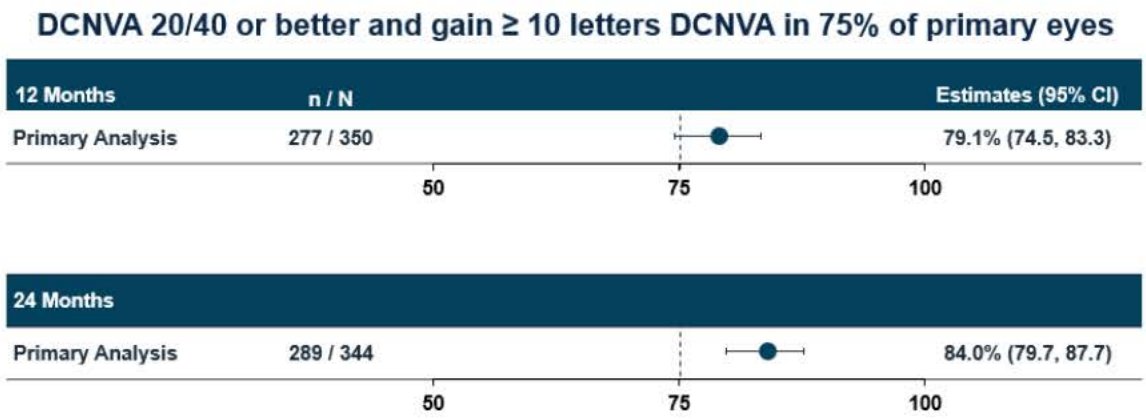
As noted in the study protocol, subjects were to be evaluated at one day, one week and at 1,2, 3, 6, 12, 18 and 24 months post operatively. Subjects were considered to have completed the study when they completed the 24 month exam. While the objective of 75%, as described above, was predefined for evaluation at 12 months, we believe the 24 month results are as valid and are important to consider in the totality of data. This time point is not based on selecting the best time point from multiple points, but rather it reflects the last pre-defined time point for the study and

defines the long term outcome for the endpoint. Additionally, this was an open label study with excellent follow-up through 24 months.

1.3 Summary of Effectiveness Data from the VisAbility Study

At 12 months, the first co-primary effectiveness endpoint was achieved in 79.1% of primary eyes, with a 95% CI lower bound of 74.5%, 0.5% below the prespecified threshold of 75%. At 24 months, the effectiveness endpoint criteria were achieved in 84% of primary eyes with a 95% CI lower bound of 79.7% (**Figure 6**).

Figure 6: First Co-Primary Effectiveness Endpoint in the VisAbility Study (Primary Eye)



Note: Explants at or before endpoint were imputed as failures. Other patients with missing values were excluded.

In addition, the VisAbility Study met the second co-primary effectiveness endpoint of a statistically significant (one-sided $p < 0.025$) difference in the proportion of eyes with DCNVA 20/40 or better and gain of ≥ 10 letters at 6 months in patients randomized to treatment versus deferred surgery as part of the randomized substudy of the pivotal trial. The results showed that 64.3% of eyes in the immediate treatment group met the effectiveness endpoint, while only 6.9% of eyes in the deferred treatment group met the same criteria (**Table 1**).

Table 1: Second Co-Primary Effectiveness Endpoint of DCNVA ≥ 20/40 and Gain of ≥ 10 Letters at 6 Months in the 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	< 0.001	

1. For patients 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 patients were excluded.
2. Explants at or before Month 6 were imputed as failures. For other patients 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 patients were excluded.
3. Exact binomial 95% confidence interval (CI)

Based on the totality of the effectiveness data collected from the pivotal trial of the VisAbility Micro Insert System, the data provided demonstrate a reasonable assurance of the effectiveness of the VisAbility Micro Insert System, supporting approval of the device.

1.4 Summary of Key Safety Data from the VisAbility Study

Safety data from the VisAbility Study demonstrate that the VisAbility Micro Insert System has a favorable safety profile. Safety data are reported for the safety cohort, which includes all implanted eyes (n=708). Ocular adverse events (AEs) were reported in 36.7% of implanted eyes, with the majority of events (70%) being related to ocular surface events such as onset or worsening to severe clinically significant lid margin disease after 3 months (64/260 events), dry eye signs requiring prescription medication after 6 months (87/260 events), and moderate or severe conjunctival injection after 3 months or more (32/260 events) associated with this type of surgery and the age of patients in the study. These events were effectively managed with treatments such as artificial tear supplementation, eyelid hygiene, and topical or oral therapeutic agents.

AEs of clinical concern in the pivotal trial were infrequent, and patients experienced no lasting symptoms or functional effects. Key findings related to AEs of clinical concern are as follows:

- Scleral Perforations – Eight intraoperative scleral perforations were observed in 8 patients in the trial, reflecting 1.1% of implanted eyes (8/708). Each of these perforations was successfully managed and resolved.
- Anterior segment ischemia (ASI) – Five events were observed in 5 patients in the trial, reflecting 0.7% of implanted eyes (5/708). Four patients recovered fully, and 1 pupillary abnormality resolved by 24 months with sequelae limited to 1–2 clock hours of stable iris transillumination.
- Conjunctival retraction that did not spontaneously resolve or resulted in an exposed Micro Insert therefore requiring re-approximation – Fifteen cases were observed in 15 patients in the trial, reflecting 2.1% of implanted eyes (15/708). All cases were managed successfully and resolved without sequelae in 1 to 10 days.
- Removals – Through 24 months, explantation was performed in 13 eyes of 8 patients, reflecting 1.8% of implanted eyes (13/708), and all explanted eyes recovered fully.
- Laser retinopexy for repair of retinal holes/tears – One retinal hole was observed in 1 patient and 1 retinal tear was observed in 1 patient in the study, reflecting 0.3% of implanted eyes (2/708). Neither event was deemed to be related to implantation of the VisAbility Micro Insert segments, in part because the events occurred in patients in whom scleral perforation had not occurred. Moreover, both conditions successfully resolved.

The VisAbility Micro Insert System demonstrates a favorable safety profile. In the pivotal study, most ocular AEs were generally mild in nature and resolved by the next postoperative visit. Events of clinical concern were infrequent, were managed effectively, and did not result in any long-term untoward effects. Importantly, at 24 months, 97% of patients with the VisAbility Micro Insert maintained best corrected distance visual acuity (BCDVA), and 99.6% were 20/20 or better.

1.5 Conclusion

In the pivotal trial of the VisAbility Micro Insert System, the first co-primary effectiveness endpoint at 12 months had a point estimate of 79.1% (74.5, 83.3). At 24 months, the criteria reflected in the first co-primary effectiveness endpoint (though not the endpoint itself, which was defined at 12 months) were achieved in 84% of primary eyes with a 95% CI lower bound of 79.7%. Even in the worst-case analysis, the point estimates at 12 and 24 months were greater than 75%. AEs of clinical concern (scleral perforations, ASI, re-approximation of the conjunctiva, removals, and laser retinopexy for repair of retinal holes/tears) occurred with low frequencies in the pivotal trial and resolved with no lasting functional effects. The potential sequelae of such AEs can be effectively mitigated or prevented. Moreover, occurrences of ASI, scleral perforation, and conjunctival re-approximation, in particular, can be prevented using proper surgical techniques. Other ocular AEs were effectively managed with common treatments and were primarily related to ocular surface effects associated with this type of surgery and the age of the study population. Following approval, Refocus will conduct a controlled introduction of the VisAbility Micro Insert System. Additionally, qualified surgeons will be trained and certified in the selection of appropriate patients, performance of VisAbility Micro Insert surgery, and management of potential complications.

Compared to alternative surgical treatments, the VisAbility Micro Insert System is less invasive, as it is implanted outside of the visual axis such that the crystalline lens and cornea remain intact. With respect to non-surgical alternatives, such as bifocals or reading glasses, approximately 10% of patients with presbyopia suffer such inconvenience from spectacle correction that they may consider surgical intervention (Luo et al. 2008). The VisAbility Micro Insert System may thus provide an attractive alternative to existing treatments.

2 BACKGROUND ON PRESBYOPIA

Summary

- Presbyopia is the gradual loss of the ability of the eye to focus on nearby objects.
- Presbyopia is the most prevalent visual deficiency.
- Presbyopia corrected with glasses is associated with a decrease in quality of life similar to that of treated systemic hypertension (Luo et al. 2008).
- Once presbyopia occurs, one will need an optical aid for near vision and may often ultimately require a correction for both distance and near vision.
- Current corrective surgical options may address near vision but are associated with visual loss and aberrations, such as halos and glare, as well as reduced distance vision, all of which are often irreversible.

2.1 Overview of Presbyopia

Presbyopia is characterized by a progressive, age-related loss of accommodation, or the ability of the unaided human eye to focus clearly on objects over a range of near to intermediate distances from the eye. (American Academy of Ophthalmology – Presbyopia Treatment 2019). Typically, people will begin to lose the ability to focus on objects at near and intermediate distances in their 40s. Over time this results in an almost complete inability to see near objects clearly.

Presbyopia is associated with reduced health-related quality of life (McDonnell et al. 2003). Approximately 10% of presbyopic patients suffer such inconvenience from spectacle correction that they may be candidates for surgical intervention (Luo et al. 2008).

According to a survey conducted by Kaiser Associates (January 2017), there is a high level of patient frustration with presbyopia in the 45–60 year old age group, and mixed satisfaction with current procedures among both patients and providers. Monovision laser assisted in-situ keratomileusis (LASIK) is the clear leader in the market, but patients view it as having significant downsides, including patient adjustment, depth of focus, and difficulties with halos and glare. Safety remains the biggest concern for patients and a procedure performed outside of the visual axis and one that is reversible is very important to a typical patient. On a scale from 1–7 with 7 being very frustrated, more than 75% of patients expressed a high degree of frustration with their presbyopia despite their current solutions; the average of 161 patients was 5.4.

2.2 Current Treatment Options

Treatment options for presbyopia include corrective non-surgical approaches such as eyeglasses or contact lenses, as well as surgical approaches such as refractive surgery.

Eyeglasses and contact lenses are typically the first line of treatment for symptoms of presbyopia. While single-vision eye wear is used, bifocals, trifocals, multifocal lenses, and monovision contact lenses may provide better functional utility.

There currently are no universally accepted surgical treatments available for presbyopia. Multifocal intraocular lenses, corneal implants, and monovision LASIK have been developed to improve near vision. Unfortunately, these methods may result in some compromise of distance vision in order to gain an improvement in uncorrected near vision. Moreover, while monovision correction of presbyopia is related to some improvements in health-related quality of life compared with single-vision correction, it is still worse than the quality of life of pre-presbyopic emmetropes (McDonnell et al. 2003).

2.3 Limitations to Current Treatment Options for Presbyopia

Once presbyopia occurs, patients need some sort of correction in order to function in their daily lives. The inconvenience and perceived negative social effects of wearing reading glasses can engender a strong motivational force for patients so that they seek surgical options for the correction of presbyopia. The popularity of monovision LASIK, and presbyopia-correcting intraocular lenses, despite their drawbacks, speaks to these patients' desire for a better solution. Current corrective surgical options may address near vision but are associated with visual loss and aberrations, such as halos and glare, as well as reduced distance vision, decreased contrast sensitivity, and compromised depth perception, all of which are often irreversible. Therefore, a need exists for a safe, bilateral procedure that does not negatively impact the quality of distance vision.

3 DEVICE DESCRIPTION

Summary

- The VisAbility Micro Insert System is a novel medical device that meets the needs of a select subset of patients with presbyopia, reflected in the proposed indications for use, and is a treatment for presbyopia that is performed outside of the visual axis in the anterior sclera.
- The VisAbility Micro Insert System was designed to restore near vision without compromising depth perception or distance vision.
- The VisAbility Micro Insert is a scleral implant with a curved anterior and posterior surface. Four Micro Inserts are placed into each eye in the oblique quadrants.
- The design of the VisAbility Micro Insert consists of a main body segment with 2 legs and a locking segment that is smoothly clicked into place in the main body segment. The VisAbility Micro Insert includes stabilization feet at each end intended to fixate at the entrance and exit sides of the scleral tunnel incision, thereby preventing displacement or migration of the implanted VisAbility Micro Insert.
- The VisAbility Scleratome is a custom designed disposable surgical instrument used for creating precisely positioned scleral tunnel incisions in which the VisAbility Micro Inserts are placed.
- The VisAbility Feeder Tube is then used to insert the VisAbility Micro Inserts into the scleral tunnels, providing the optimal means of traversing the lamellar scleral tunnels with the least amount of external stress on surrounding tissue.

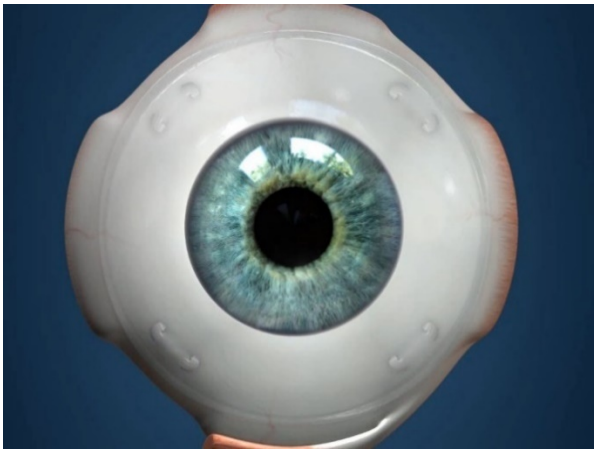
3.1 Indication

The VisAbility Micro Insert System 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.

3.2 Implantation Procedure

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 meridians. **Figure 7** illustrates a human eye implanted with the 4 VisAbility Micro Inserts.

Figure 7: Placement of VisAbility™ Micro Inserts.



The surgical procedure involves the following basic steps:

- Marking – In the pre-operative area, the patient is positioned upright. Following application of a topical anesthetic (Xylocaine 2% without epinephrine) to the ocular surface, the conjunctiva is marked with ink near the limbus at 12:00 and 6:00 o'clock.
- Peritomy – Once in the operating room the surgical eye is prepped and draped. In addition to topical anesthetic drops, Lidocaine 2% without epinephrine (to avoid pupil dilation and compromise intraoperative and postoperative pupil monitoring) is injected in the anterior subtenon's space for anesthesia and separation of tenons from the sclera. A 360-degree perimetry is completed and tenon's capsule are cleared from the anterior scleral surface.
- Placement of the docking station – The docking station is secured to the eye using a four-point fixation system. The docking station is centered around the limbus with its internal arrow points on the 6:00 and 12:00 o'clock positions. The surgeon should assess fixation and position to ensure that the tunnels will be centered between the insertions of the extraocular rectus muscles.
- Scleral tunnel creation – The VisAbility Scleratome locating ridge is docked to the docking station channel and the VisAbility Scleratome is used to create each of the 4 scleral tunnels 4 mm from the limbus and centered between adjacent recti muscles. Tunnels should be created in the following sequence to facilitate ergonomic hand positioning: 1st Inferior Nasal (IN), 2nd Superior Nasal (SN), 3rd Inferior Temporal (IT), and 4th Superior Temporal (ST).
- Placement of the VisAbility Micro Insert – After each tunnel is constructed, the Main Body segment is pulled through the tunnel and the Locking segment is engaged to secure the VisAbility Micro Insert.

Surgeons are trained in the following key elements of technique:

- Carefully assess the position of the extraocular muscle insertions for anterior insertions or altered anatomy to avoid impingement of the anterior ciliary arteries which can lead to ASI.
- Never push the VisAbility Micro Insert through the tunnel; only use the pull through technique to avoid perforation.
- Always keep the feeder tube assembly along the roof of the tunnel
- Never attempt a manual dissection of the tunnel.
- Remember that this is an elective surgery, and it is better to not place the VisAbility Micro Insert if conditions are not optimal.

- Closing the conjunctiva – After checking each of the VisAbility Micro Inserts to assure that they do not impinge on the rectus muscle insertions, the docking station is removed, and the conjunctiva is secured to the limbus.

3.3 Postoperative Care

Following surgery, pupil functionality is evaluated post-operatively using a NeurOptics Pupillometer every 15 to 30 minutes, until the percent pupil constriction reading is at least 25%. A second, confirmatory reading of 25% or greater may be taken as soon as 5 minutes after the first. If 2 pupil constriction readings of at least 25% are not achieved within the first 4 hours after surgery, preparation for removal of implants will commence. The investigator must remove all 4 implant segments no later than 6 hours after the implantation surgery if 2 pupil constriction readings of at least 25% are not achieved within 6 hours post-operatively.

During the first week after the surgery, patients are treated 3 to 4 times per day with topical antibiotic and steroid medications. Topical antibiotic therapy is usually stopped after one week and topical steroid medication is usually stopped after week 2. Conjunctival sutures may be removed at one week post-operatively or later as needed.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The pivotal study supporting approval of the VisAbility Micro Insert System was a prospective multi-center clinical trial conducted to evaluate the safety and effectiveness of the Refocus VisAbility Micro Insert System in presbyopic patients seeking improvement in near visual acuity.
- Refocus submitted the original PMA for the VisAbility Micro Insert System to FDA in 2017, containing data through 12 months of the pivotal study.
- Refocus submitted a Major Amendment in April 2019, which included the 24 month end of study data.

4.1 Regulatory Milestones

Refocus submitted a PMA for the VisAbility Micro Insert System to FDA on December 15, 2017. Per protocol, the PMA was submitted presenting the 12 month data set. Following receipt of a not approvable letter and a meeting with FDA on January 28, 2019, Refocus submitted a Major Amendment to the PMA on April 26, 2019. That amendment included analysis of data through 24 months per protocol and addressed concerns raised by FDA.

Following receipt of a second not approvable letter on October 22, 2019, Refocus requested a Supervisory Review of the PMA. The supervisory review, held on December 20, 2019, by William Maisel, M.D., 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 demonstrated that the probable benefits of the device outweighed the probable risks. The not approvable decision was officially set aside by Dr. Maisel, the PMA review 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.

4.2 Clinical Development Program

The pivotal study supporting the approval of the VisAbility Micro Insert System is the VisAbility Study (i.e., VIS-2014). The VisAbility Study was a prospective multi-center clinical trial conducted to evaluate the safety and effectiveness of the Refocus VisAbility Micro Insert System through 24 months in presbyopic patients seeking improvement in near visual acuity. Twelve month data were submitted in the original PMA submission in 2017; the current Major Amendment includes data from the VisAbility Study through 24 months.

5 CLINICAL EFFECTIVENESS

Summary

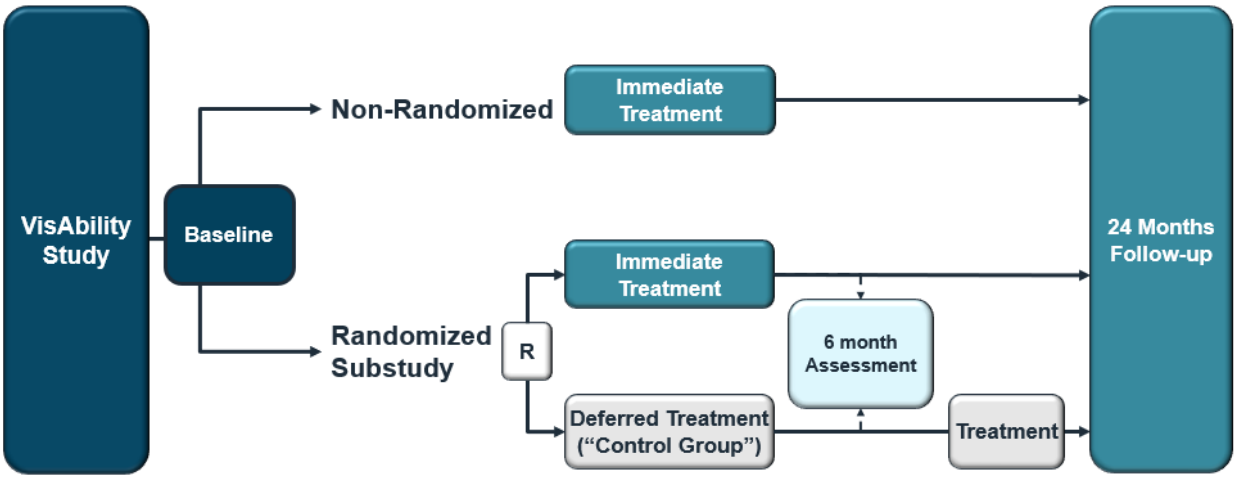
- The first co-primary effectiveness endpoint was the achievement of DCNVA of Snellen equivalent 20/40 or better (at 40 cm), and at least 10 letters (ETDRS) improvement in DCNVA in 75% of primary eyes at 12 months.
    - In the primary analysis, the 95% lower CI was 74.5%, 0.5% below the threshold of 75%. However, by 24 months, the performance target was met. At 24 months, 84.1% of patients achieved DCNVA ≥ 20/40 and a gain of ≥ 10 letters.
- The second co-primary effectiveness endpoint was the difference in the proportion of eyes with DCNVA 20/40 or better and gain of ≥ 10 letters at 6 months between groups in the randomized substudy.
    - The responder rate for the randomized surgery group at 6 months was 64%, significantly greater than the responder rate of 6.9% for the deferred treatment group ($p < 0.001$).
- 80% of eyes evaluated achieved a gain of at least 2 or more lines of binocular UCNVA at 24 months.
- The consistency of the results demonstrates that the VisAbility Micro Insert System meets its intended use by providing a clinically significant improvement in near visual acuity in presbyopic patients.

5.1 Study Design

The VisAbility Study was a prospective multi-center clinical trial conducted to evaluate the safety and effectiveness of the VisAbility Micro Insert System in presbyopic patients seeking improvement in near visual acuity. This study was conducted at 13 sites in the US with a total enrollment of 360 patients (708 surgical eyes) treated with the VisAbility Micro Insert System. Eligible patients were ages 45 to 60 years with DCNVA and uncorrected near visual acuity (UCNVA) of 20/50 to 20/80 (inclusive).

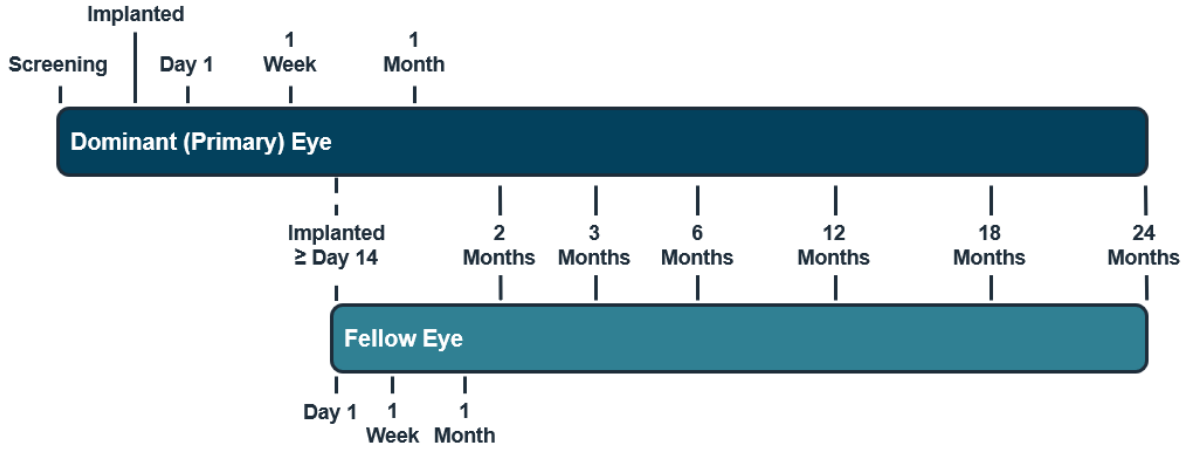
The VisAbility study consisted of a non-randomized arm and a randomized substudy arm (**Figure 8**). Patients in the non-randomized arm received immediate treatment while those in the randomized substudy arm were randomized 1:1 to either an immediate treatment group or a deferred treatment (control) group.

Figure 8: VisAbility Study Design



In the non-randomized arm, patients were implanted with the VisAbility Micro Insert System in the dominant eye first, which was designated as the primary eye. The fellow eye was implanted no sooner than 14 days after the primary eye and only in the absence of unresolved AEs in the primary eye (**Figure 9**). The protocol required that patients be followed for 24 months; the primary eye was examined at 1 day, 1 week, and at 1, 2, 3, 6, 12, 18 and 24 months, post-operatively. The fellow eye was examined at 1 day, 1 week, and 1 month post-operatively and then examined in accordance with the subsequent primary eye examination visits.

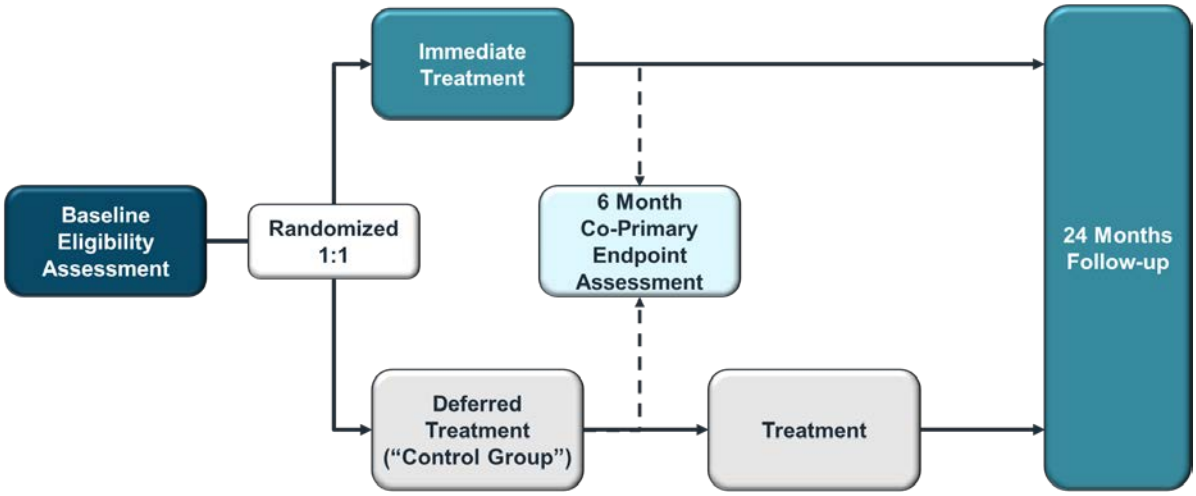
Figure 9: VisAbility Study (Non-Randomized Arm) Primary and Fellow Eye Implantation Schedule



Those patients randomized to the immediate treatment group were implanted and followed for 24 months, in the same manner as the non-randomized treatment group. The deferred treatment (control) group was observed for 6 months prior to surgery to compare the effect of not having had VisAbility surgery at 6 months preoperative to having had VisAbility surgery at 6 months postoperative (**Figure 10**). The deferred treatment (control) patients who elected to have surgery were implanted and followed for 24 months, in the same manner as the non-randomized treatment

group. Those deferred patients who chose not to have surgery were exited from the study at the end of the 6 month deferred treatment observation period.

Figure 10: VisAbility Study (Randomized Substudy) 24 Month Study Design



5.1.1 Inclusion and Exclusion Criteria

Inclusion criteria included the following:

1. Patients must be between ages of 45 to 60 at the time of enrollment.
2. Patients must have BCDVA of 20/20 in each eye.
3. Patients must have DCNVA at 40 cm of 20/50, 20/63 or 20/80 in each eye.
4. Patients must have uncorrected near visual acuity (UCNVA) at 40 cm of 20/50, 20/63 or 20/80 in each eye.
5. Patients must have pre-operative 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 should be ≤ 0.50 diopter.
6. Patients must require a minimum near add of +1.25 or greater to read 20/20 at near (40 cm).
7. Patients must be phakic in each eye.
8. Patients 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. Patients must be able to provide written informed consent.

Exclusion criteria included the following:

1. Patients in whom 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 a NeurOptics Pupillometer.
2. Patients with ocular inflammation, chronic uveitis, or other recurrent anterior or posterior segment inflammatory conditions in either eye; patients 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. Patients with scleral thickness of less than 530 microns as measured 3.5 to 4.0 mm posterior to the ST quadrant limbus in either eye.
4. Patients 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. Patients with any history of prior extraocular muscle surgery or orbital surgery.
6. Patients 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. Patients with any acute ocular disease that has not been completely treated and resolved for at least 3 months such as conjunctivitis, blepharitis, chalazion, corneal abrasion or keratitis in either eye.
8. Patients 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. Patients 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 10 days prior to surgery.
10. Patients with 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.
11. Patients who are allergic to any medications used in the protocol.
12. Patients who are pregnant, lactating, or of child-bearing age and not practicing a medically approved method of birth control.

5.1.2 Endpoints

The primary effectiveness endpoint consisted of 2 co-primary endpoints as follows:

- Achievement of DCNVA 20/40 or better **and** gain ≥ 10 letters DCNVA in 75% of the primary eyes.
- Achievement of a statistically significant (one-sided $p < 0.025$) difference in the proportion of eyes with DCNVA 20/40 or better **and** gain of ≥ 10 letters at 6 months in patients randomized to treatment versus deferred surgery as part of the randomized sub-study.

Both endpoints were required to be statistically significant (two-sided significance level of 0.05, or, one-sided significance level of 0.025). Any other p-values are nominal and not adjusted for multiple comparisons.

5.1.3 Statistical Analyses

5.1.3.1 Sample Size Calculation

The sample size calculation for the first co-primary effectiveness objective is based on the following criteria:

- The two-sided significance level equals 0.05 (or one-sided significance level equals 0.025)
- The statistical power equals 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
- Binomial distribution is used for sample size calculation

For the effectiveness and safety cohort, a sample size of 333 treated primary eyes was needed to meet the sample size requirements for both safety and effectiveness assuming a dropout rate of 10% by approximately 12 months.

No site was allowed to enroll and perform surgery on more than 20% of the patient cohort.

The sample size calculation for the second co-primary effectiveness endpoint is based on the following criteria:

- The two-sided significance level equals 0.05 (or one-sided significance level equals 0.025).
- The statistical power equals 90%, with the assumption that the 6 month responder rate is estimated as 10% for the randomized deferred treatment group and that the 6 month responder rate of the randomized immediate treatment group in this study will be approximately 0.75.
- Fisher's exact test is used for sample size calculation.

For the randomized substudy, a sample of at least 14 randomized immediate treatment group primary eyes and 14 randomized deferred treatment group primary eyes ensured a power greater

than 90% for the second co-primary effectiveness endpoint, using a one-sided alpha of 0.025. Therefore, a sample size of 30 randomized immediate treatment group patients and 30 randomized deferred treatment group patients were selected to account for a possible 10% patient dropout rate and allow for greater accuracy in point estimates for both groups. The randomized substudy was conducted at 3 clinical sites and the target enrollment at each was 20 eligible patients to provide an even distribution. However, no site was permitted to enroll and determine eligible more than half of the randomized substudy cohort or 30 patients.

5.1.3.2 Handling of Missing Data

For the primary analysis of the first co-primary effectiveness endpoint, all observed 12 and 24 month exam data of the surgical primary eyes were included in the effectiveness analysis. Missing data were not imputed; however, explanted primary eyes were imputed as failures.

For the primary analysis of the second co-primary effectiveness endpoint, all reported 6 month data of the randomized primary eyes were included in the analysis. Missing data were imputed as follows:

- Randomized Deferred Treatment Group: In the absence of any observed data and including the 3 month and 6 month visits, the last observation was carried forward (including data at baseline).
- Randomized Immediate Treatment Group:
    - Explanted primary eyes at or before the 6 month endpoint were imputed as failures.
    - In the absence of observed data between and including the 6 month and 12 month visits, data recorded between and including the 3 month visit and up to the 6 month visit were used.

5.1.3.3 Sensitivity Analyses

The primary analysis for the first co-primary effectiveness endpoint criteria at 12 months post-operatively was met if the lower bound of the 95% CI was at least 75%. Each of the sensitivity analyses also met the effectiveness endpoint when missing data for the 12 month postoperative exam were imputed with a lower CI of at least 75%.

Sensitivity analyses were performed for the first co-primary effectiveness endpoint using the following imputation methods for missing 12 and 24 month data:

- Best-Case Analysis: All discontinued primary eyes were imputed as effectiveness failures. For primary eyes lost to follow-up or for primary eyes missing the endpoint exam visit data, the best value from any protocol scheduled visit at 1 month or later (1 month, 3 months, 6 months, and 12 months or 18 months if applicable) was used. In cases where the values were the same at more than 1 visit, the previous visit data that was most proximal to the endpoint exam visit was used. If such visit data did not exist for a primary eye, the effectiveness was imputed as a success.

- Worst-Case Analysis: All discontinued primary eyes were imputed as effectiveness failures. For primary eyes lost to follow-up or missing the endpoint exam visit data, the worst value from any protocol scheduled visit at 1 month or later (1 month, 3 months or 6 months, and 12 months or 18 months if applicable) was used. In cases where the values were the same at more than 1 visit, the previous visit data most proximal to the endpoint exam visit was used. If such visit data did not exist for a primary eye, the effectiveness was imputed as a failure.
- Tipping Point Analysis: All discontinued primary eyes were imputed as effectiveness failures. For primary eyes missing 12 and 24 month visit data for reasons other than discontinuation, effectiveness was initially set to success. At this step, the lower limit of the one-sided 97.5% confidence interval (CI) was calculated. Serial calculations were 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.

Sensitivity analyses were also performed for the second co-primary effectiveness endpoint using the following imputation methods:

- Tipping Point Analysis: All discontinued primary eyes were iteratively imputed as effectiveness success or failures. Letting n1 and n2 be the number of discontinued primary eyes for the randomized surgery group and the randomized control group, respectively, the n1 discontinued randomized surgery group primary eyes could be imputed as 0 failures, 1 failure, 2 failures, and up to n1 failures, for a total of (n1+1) possible imputations. For the n2 discontinued randomized control group primary eyes, there were (n2+1) possible imputations. Therefore, there were (n1+1) × (n2+1) possible combinations of success and failure imputations for the discontinued primary eyes. For each of these possible imputations, the lower limit of the one-sided 97.5% CI was calculated. The imputations that had the lower one-sided 97.5% CI < 75% were identified.

5.1.3.4 Additional Effectiveness Analyses

Additional effectiveness analyses were performed in the randomized substudy including the following:

- DCNVA
- Near Add and Change in Near Add from baseline
- Defocus Curve
- Wavefront Aberrometry

All the above statistical analyses were exploratory since no formal secondary objectives were specified.

5.1.4 Study Population

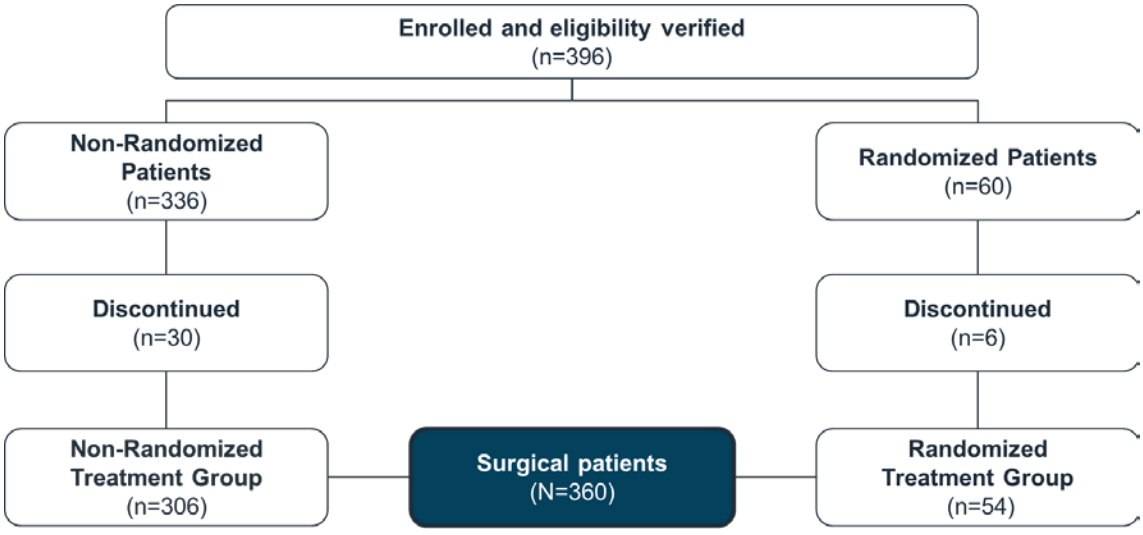
5.1.4.1 Patient Disposition and Accountability

A total of 565 patients met the initial screening criteria, were consented, and enrolled in the VisAbility Micro Insert clinical study. Of the enrolled patients, 28.8% (163/565) were deemed ineligible upon further examination, one was lost to follow-up, and 5 patients withdrew consent. Of these 396 patients, 336 were enrolled as part of the non-randomized treatment group and 60 were enrolled as part of the randomized substudy (**Figure 11**).

Of the 336 patients enrolled in the non-randomized treatment group, 3 were lost to follow-up and 27 did not proceed with surgery (e.g., withdrawal by patient or inability to continue). The remaining 306 patients were successfully implanted with the VisAbility Micro Insert System.

In the randomized substudy arm, 29 patients were randomized to immediate treatment, and 31 patients were randomized to deferred treatment (i.e., control). One patient from the immediate treatment group withdrew consent prior to primary eye surgery. In the deferred treatment group, 4 patients withdrew prior to primary eye surgery and one patient discontinued prior to primary eye surgery due to an AE. The remaining 54 patients were successfully implanted with the VisAbility Micro Insert System.

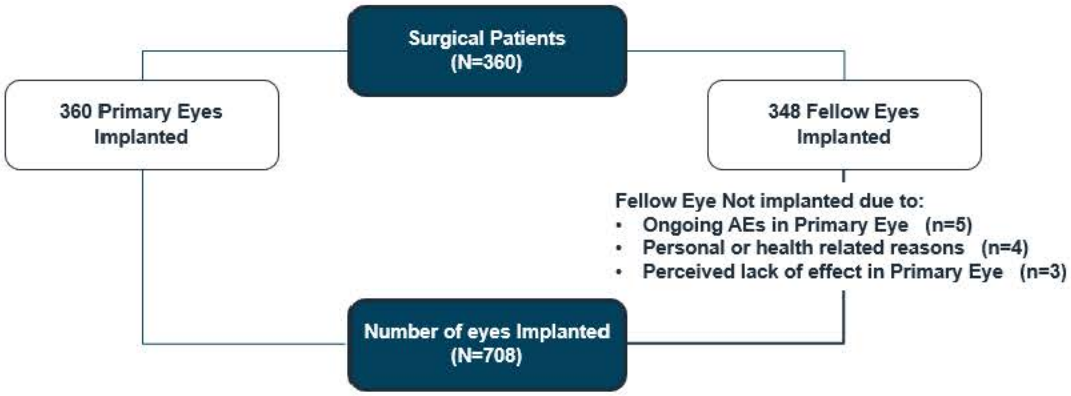
Figure 11: Patient Disposition in VisAbility Study



5.1.4.2 Eyes Implanted

A total of 360 patients (306 in the non-randomized treatment group and 54 in the randomized substudy) were successfully implanted in the primary eye with the VisAbility Micro Insert System. Twelve of the fellow eyes were not treated due to either ongoing AEs in the primary eye (5 patients), personal or health-related concerns (4 patients), or perceived lack of effect in the primary eye (3 patients) (**Figure 12**). Thus, the total number of eyes implanted among the 360 treated patients was 708 eyes.

Figure 12: Eyes Implanted in VisAbility Study



98% accountability at 12 months
96% accountability at 24 months

Patient accountability in the VisAbility Study was high for all postoperative visits in all patient populations. At the 12 month exam visit, patient accountability was 97.7%, with 97.0% available for analysis; similarly, at the 24 month exam visit, patient accountability was 96.1%, with 94.4% available for analysis (**Table 2**).

The VisAbility Micro Insert was explanted from 8 patients (13 eyes) through 24 months. More details on explants through 24 months can be found in **Section 6.4.3.**

Table 2: Patient Accountability in VisAbility Study

	Pre-op	12 Month Exam	24 Month Exam
Available for Analysis	708, (100.0%)	687, (97.0%)	668, (94.4%)
Explant	0	5, (0.7%)	13, (1.8%)
Lost to Follow-up1[1]	0	7, (1.0%)	27, (3.8%)
Missed Visit[2]	0	9, (1.3%)	0, (0.0%)
% Accountability[3]	708, (100.0%)	687, (97.7%)	668, (96.1%)

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

Table 3 shows the accountability by postoperative visit for 360 primary eyes of all implanted patients. At the 12 month exam, patient accountability was 97.2%, with 96.1% available for analysis. At the 24 month exam, patient accountability was 95.7%, with 93.6% available for analysis.

Table 3: Patient Accountability (Primary Eyes) in VisAbility Study

	Pre-op	12 Month Exam	24 Month Exam
Available for Analysis	360, (100.0%)	346, (96.1%)	337, (93.6%)
Explant	0	4, (1.1%)	8, (2.2%)
Lost to Follow-up[1]	0	4, (1.1%)	15, (4.2%)
Missed Visit[2]	0	6, (1.7%)	0, (0.0%)
% Accountability[3]	360, (100.0%)	346, (97.2%)	337, (95.7%)

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

5.1.4.3 Demographics and Baseline Characteristics

Table 4 shows demographics of all patients implanted in the VisAbility Study. The mean age of implanted patients was 51.6 years, with a range of 45 to 60 years. There were more males (60%) than females, and the majority of patients were Caucasian (85%). The right eye was dominant in 66.4% of the implanted patients.

Table 4: Demographics and Eye Status (All Implanted Patients) in VisAbility Study

	N=360
Age at Consent (years)	
N	360
Mean (SD)	51.6 (3.5)
Min, Max	45, 60
Sex	
Female	143 (39.7%)
Male	217 (60.3%)
Race	
Asian	18 (5.0%)
Black or African American	15 (4.2%)
Caucasian	307 (85.3%)
Other	20 (5.5%)
Ethnicity	
Hispanic or Latino	38 (10.6%)
Not Hispanic or Latino	319 (88.6%)
Not Reported	3 (0.8%)
Dominant Eye	
OD	239 (66.4%)
OS	121 (33.6%)

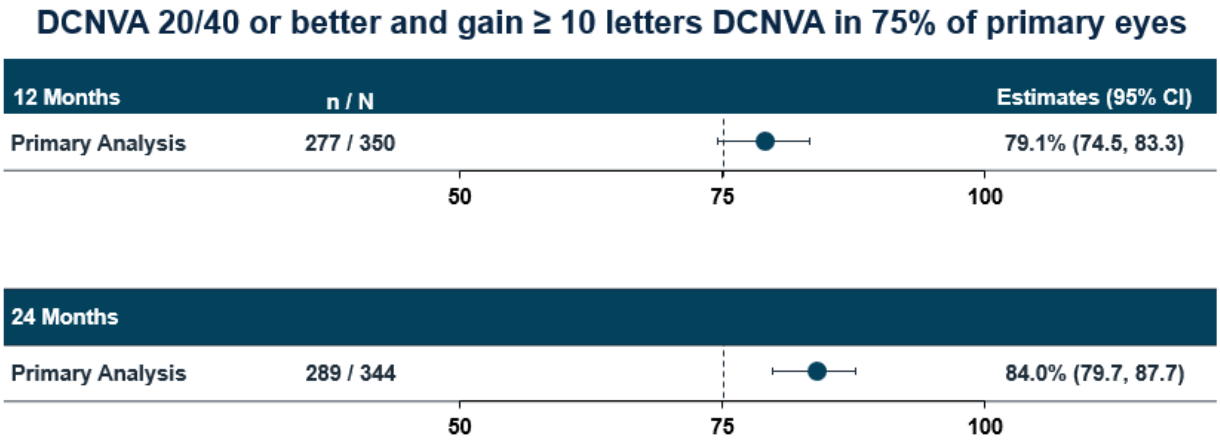
5.2 Effectiveness Results

5.2.1 First Co-Primary Endpoint

Figure 13 shows the first co-primary endpoint at the 12 month exam. At 12 months, the responder rate for the primary effectiveness endpoint was 79.1%, although the 95% lower bound of the CI was 74.5%. **Figure 13** also shows the criteria reflected in the first co-primary endpoint at the 24 month exam, and at that point, the effectiveness endpoint criteria were achieved in 84% of primary eyes with a 95% CI lower bound of 79.7%. These data demonstrate that patients had continued improvement in visual acuity regardless of the methods used to analyze the data.

As noted in the study protocol, subjects were to be evaluated at one day, one week and at 1,2, 3, 6, 12, 18 and 24 months post operatively. Subjects were considered to have completed the study when they completed the 24 month exam. While the predefined evaluation timepoint was 12 months, we believe the 24 month results are as valid and are important to consider in the totality of data. The 24 month time point reflects the last pre-defined time point for the study and defines the long term outcome for the endpoint. Additionally, this was an open label study with excellent follow-up through 24 months.

Figure 13: First Co-Primary Effectiveness Endpoint in VisAbility Study (Primary Eyes)



Note: Explants at or before endpoint were imputed as failures. Other patients with missing values were excluded.

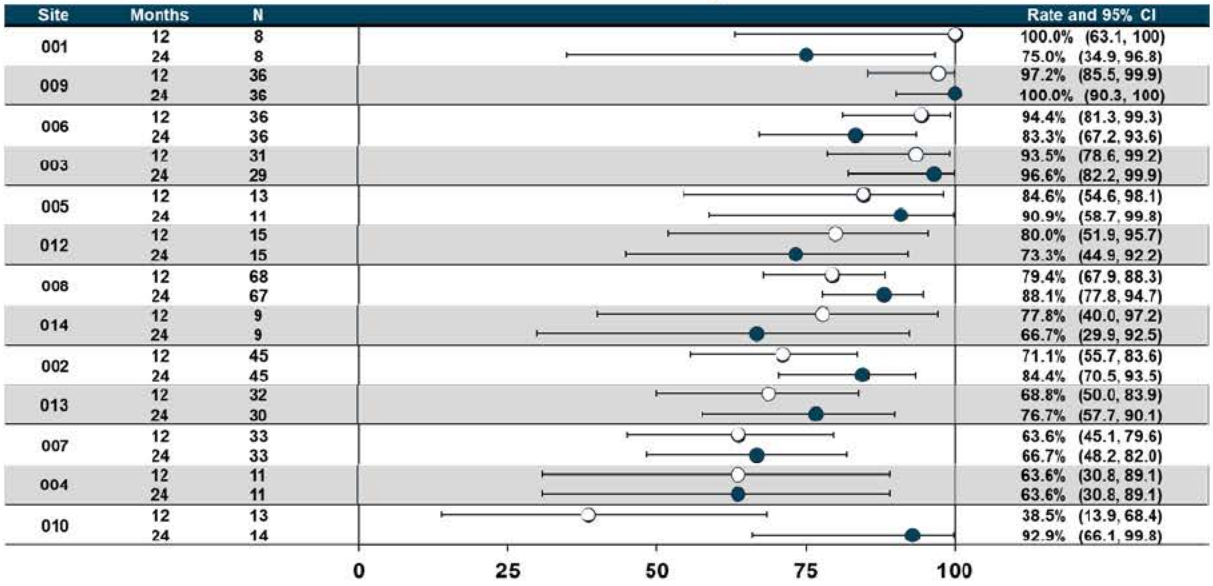
5.2.1.1 First Co-Primary Endpoint by Site

The percentage of primary eyes achieving the first co-primary effectiveness endpoint at the 12 month and 24 month exam was compared among the 13 study sites using the Fisher's Exact test. Since the site effect was significant (p-value ≤ 0.15), the 12 and 24 month responder rates were also stratified by study site, and the average of the 12 and 24 month responder rates was also calculated by site. The normal distribution approximation was used to estimate 95% CIs for the average 12 and 24 month responder rate.

Figure 14 shows the data at the 12 month and 24 month exam by site. At the 12 month exam, all individual site results demonstrated clinically relevant improvements in vision with the exception of Site 10. Eight of the 14 patients at Site 10 did not achieve the co-primary effectiveness endpoint at the 12 month exam. All 8 of these patients demonstrated trace to mild degrees of lid margin disease and/or conjunctival injection and all reported subjective symptoms of dry eye. These patients were subsequently treated for lid margin and/or ocular surface disease over the course of the study. At 24 months, 13 of the 14 patients at Site 10 had no conjunctival injection noted, and all 13 met the co-primary effectiveness endpoint criteria. One patient was noted to have remaining conjunctival injection at 24 months and did not meet the co-primary effectiveness endpoint criteria at the 24 month exam.

While Refocus has not identified any significant covariates that account for the variation in effectiveness findings seen across the trial sites, individually, each site enrolled a very small subset of the total patients. With the exception of one site which treated more than 60 patients (and at which more than 75% of primary eyes achieved DCNVA 20/40 or better with a gain of ≥ 10 letters DCNVA at 24 months), effectiveness data were obtained from roughly 10 to 45 patients at each site. The small number of patients at each site allowed for significant variation in the site-by-site results, and indeed, the individual sites were not powered to demonstrate effectiveness. Nonetheless, the results collectively demonstrated statistically and clinically significant improvement in the primary endpoint criteria at 24 months.

Figure 14: First Co-Primary Effectiveness Endpoint at the 12 Month and 24 Month Exam by Site



Note: Error bars represent 95% CI

5.2.2 Second Co-Primary Endpoint

For the second co-primary endpoint, treatment differences in the effectiveness endpoint in this non-blinded substudy of DCNVA 20/40 or better and gain of ≥ 10 letters in DCNVA at 6 months were compared between the immediate treatment group (n=28) and the deferred treatment group (n=29) using a two-sided Fisher's Exact test. The responder rate for the randomized immediate treatment group at 6 months was 64.3% (95% CI: 44.1%, 81.4%), which was significantly greater than the responder rate of 6.9% (95% CI: 0.8%, 22.8%) for the randomized deferred treatment group ($p < 0.001$) (**Table 5**).

Table 5: Second Co-Primary Effectiveness Endpoint in the VisAbility Study (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	< 0.001	

[1] For the (2) patients missing Month 6 values, since no data were observed between Month 3 and Month 6, the patients were excluded.

[2] There were no explants at or before Month 6. For the (3) patients 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.

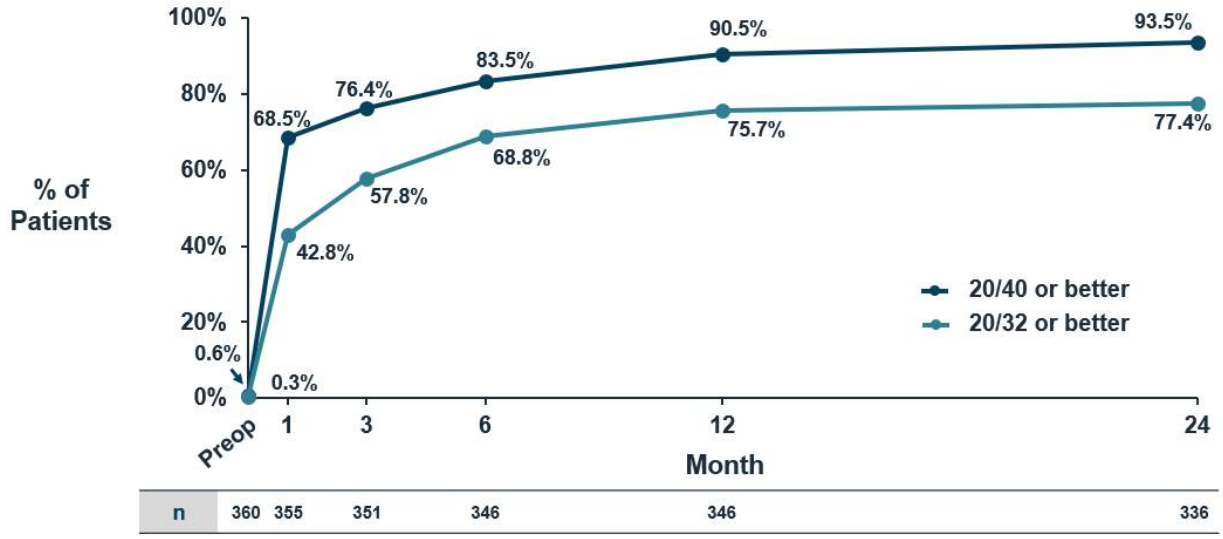
[3] Exact binomial 95% CI.

5.2.3 Additional Results of Clinical Benefit

5.2.3.1 DCNVA Over Time

Pre-operatively, less than 1% (2/360) of study patients had DCNVA 20/40 or better in the primary eye. These 2 enrolled patients were included as a result of the study design, which used the 6 month observation data as the baseline comparator of the deferred treatment randomized study patients to allow for a visual acuity assessment more proximal to the surgical intervention, rather than 6 months prior to the intervention. These 2 patients met the study criteria and were enrolled in the study at the time of the initial baseline but did not meet the near visual acuity study criteria at the 6 month observation visit. By 1 month postoperative, 68.5% (243/355) of eyes achieved DCNVA 20/40 or better in the primary eye. At 12 months, 90.5% (313/346) of primary eyes achieved DCNVA of 20/40 or better and that percentage increased to 93.5% (314/336) at 24 months. Correspondingly, 75.7% (262/346) at 12 months and 77.4% (260/336) of patients at 24 months achieved a DCNVA of 20/32 or better (**Figure 15**).

Figure 15: DCNVA for Primary Eyes Over Time

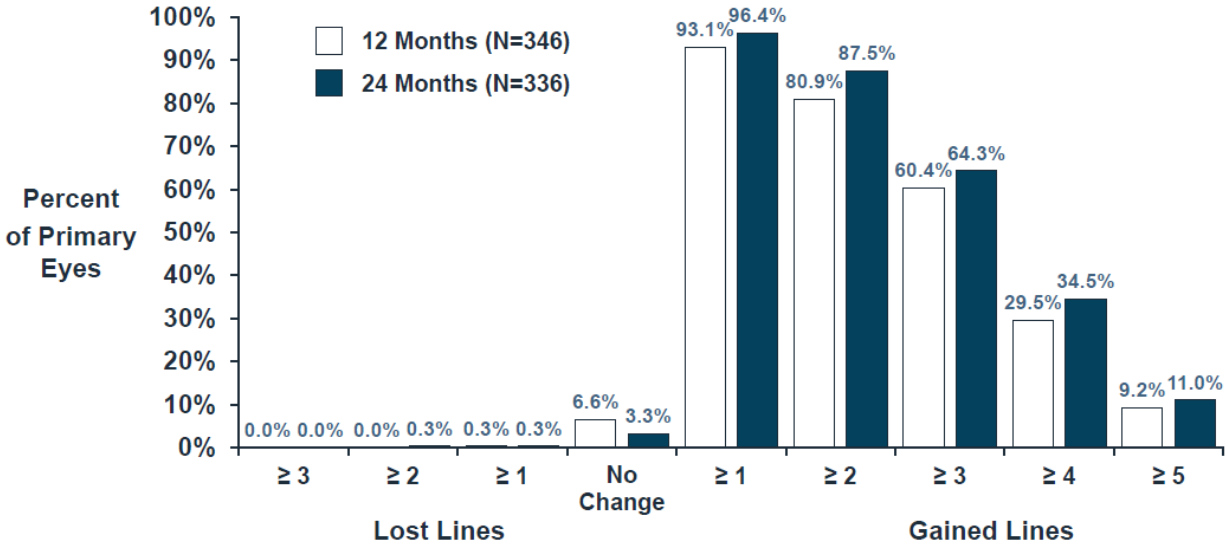


Note: preoperatively, < 1% of patients had DCNVA of 20/40 or better in the primary eye due to 6 month observation data being used as the baseline analyses, per study design.

5.2.3.2 Change in DCNVA Lines from Baseline

At the 12 month exam, 80.9% (280/346) of the eyes gained at least 2 or more lines of DCNVA. At the 24 month exam, the percentage of eyes with a gain of at least 2 or more lines of DCNVA increased to 87.5% (294/336) (**Figure 16**).

Figure 16: Change in DCNVA from Baseline for Primary Eyes



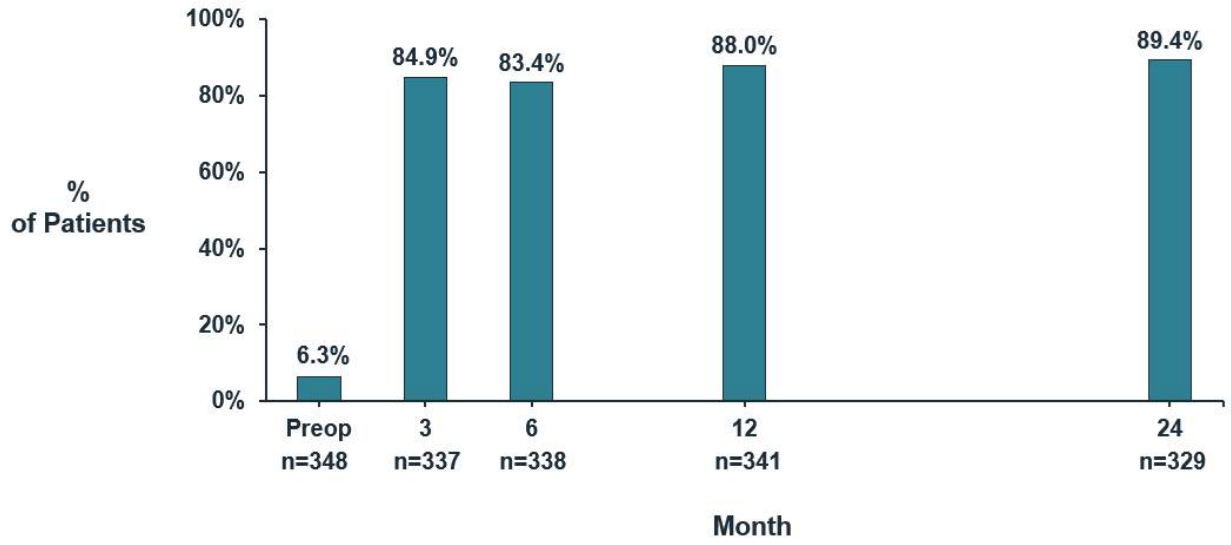
Note: Percentage is based on the number of eyes reported with data.

5.2.3.3 Binocular UCNVA

UCNVA does not account for patients' distance refractive errors that might falsely aid or limit the near visual acuity measurements and is therefore not used to determine the effectiveness of the device. Binocular UCNVA does, however, provide a valuable indicator of functional vision because it simulates the patient's everyday vision with both eyes open and no distance correction. Given that these patients have minimal refractive error, they are unlikely to wear glasses for distance correction in everyday life.

Binocular UCNVA is presented in **Figure 17**. At the 12 month and 24 month exams, 88.0% and 89.4% of patients achieved 20/32 or better binocular UCNVA, respectively.

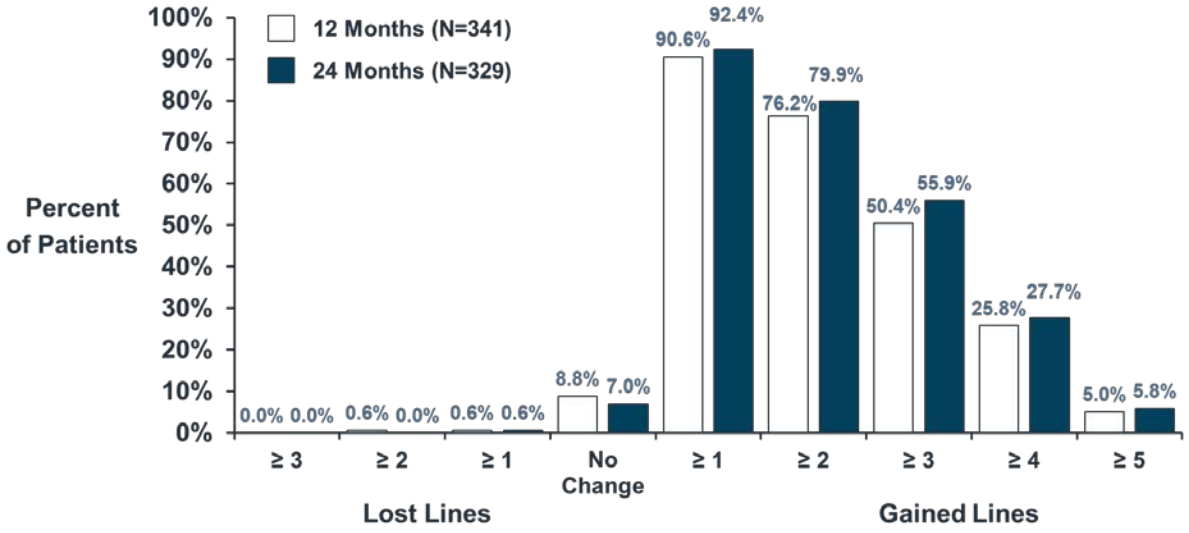
Figure 17: Binocular UCNVA Over Time, 20/32 or Better



Binocularly implanted patients = 348

As shown in **Figure 18**, 76.2% (260/341) of eyes that were evaluated for change in binocular UCNVA had a gain of ≥ 2 lines of binocular UCNVA at the 12 month exam. UCNVA continued to improve over time with gains of ≥ 2 lines of binocular UCNVA in 79.9% (263/329) of patients at the 24 month exam.

Figure 18: Change in Binocular UCNVA from Baseline



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

5.3 Patient Preferred Distance

Changes in preferred reading distance without near vision correction, which is the distance at which the smallest selected near visual acuity line appears clearest, were observed over the course of the study (**Table 6**). In presbyopia, reduced or absent accommodation results in an inability to recognize letters clear up close. At 12 months, the mean decrease from baseline was 16.66 cm. This difference corresponds to a mean decrease in just over 6.56 inches, and it reflects the ability to move reading material from the baseline distance of 23.2 inches (mean 58.98 cm), almost the fully stretched arm's length of the average person, to 16.4 inches (mean 42.20 cm), which is the typical non-presbyopic reading distance. Slightly better results were seen at 24 months. These findings have significant functional implications as the pre-operative preferred reading distance of almost 60 cm is typical of the presbyopic population and is often manifest by the complaint that one's "arms are not long enough" to read clearly.

Table 6: Patient Preferred Distance and Change from Baseline in Patient Preferred Distance – Binocular UCNVA

	Pre-op N=348	Month 3 N=337	Month 6 N=339	Month 12 N=341	Month 18 N=326	Month 24 N=331
Distance (cm)						
n (Reported)	348	337	338	341	326	329
Mean (SD)	58.97 (7.85)	43.77 (10.16)	43.65 (10.73)	42.20 (11.09)	41.98 (11.57)	41.59 (11.30)
Median	60	43	42	41	42	42
Min, Max	37, 99	15, 72	10, 72	14, 73	12, 71	15, 74
Not Reported	0	0	1	0	0	2
Change in Distance (cm)						
n (Reported)		337	338	341	326	329
Mean (SD)		-15.13 (11.06)	-15.42 (12.27)	-16.66 (12.20)	-16.78 (12.72)	-17.19 (12.26)
Median		-15	-16	-17	-17	-18
Min, Max		-45, 14	-54, 23	-49, 14	-50, 21	-52, 16
Not Reported		0	1	0	0	2

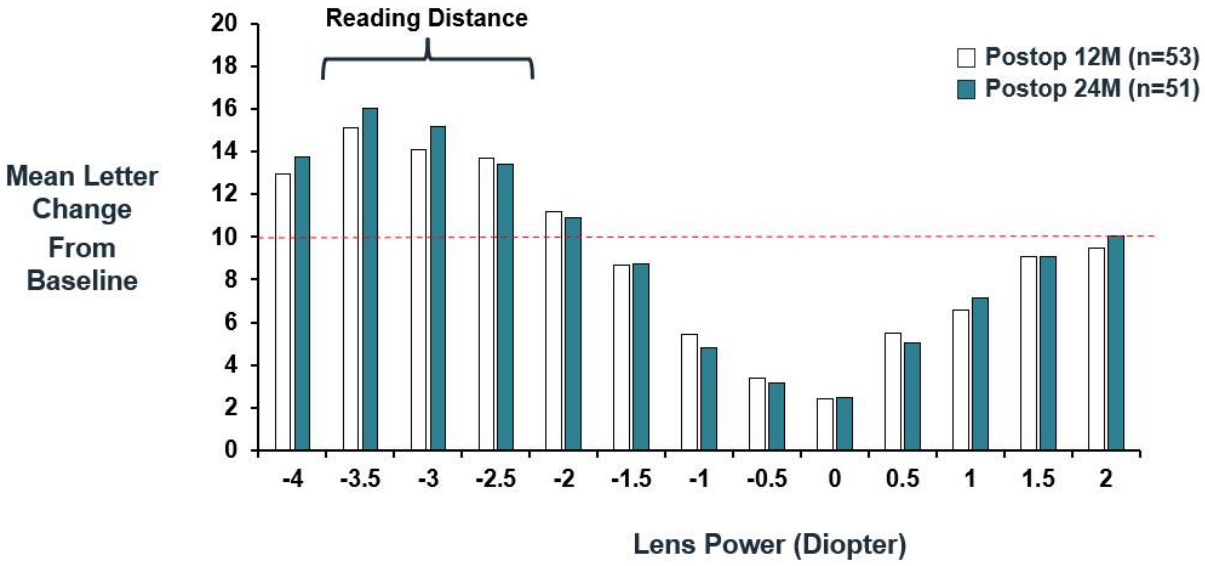
5.4 Defocus Curve

Defocus curve testing was performed in the randomized substudy patients as an exploratory analysis to subjectively measure the effectiveness of presbyopia correction by using minus and plus lenses. Per the protocol, only observed data were used for analysis and only descriptive statistics were performed.

Defocus curves were generated for all patients enrolled in the randomized substudy. Defocus measurements were made at 2 baseline visits, at 3 and 6 months after baseline during the observation phase and 3, 6, 12, 18, and 24 months after surgery for the deferred treatment group. Patients in the immediate treatment group of the randomized substudy were followed at 3, 6, 12, 18, and 24 months postoperative. At each visit, BCDVA was measured using a computer controlled ETDRS chart at a 6 m/20 ft distance, and a range of lens powers from -4.00D to +2.00D were introduced in increments of 0.50D

The improvement in defocus for all implanted primary eyes can be seen in **Figure 19**. When the change in the average Logarithm of the Minimum Angle of Resolution (LogMAR) acuity for each of the minus lens stimuli from baseline to the 12 month and 24 month exam converted to letters of improvement, a change of greater than 10 letters of improvement is seen for all minus lenses from -2.00 through -4.00.

Figure 19: Mean LogMAR at Each Lens Power by Visit in Primary Eyes in the VisAbility Study (Randomized Substudy)



5.4.1 Wavefront Aberrometry

This was set up as an exploratory study, with no formal endpoint specified. The findings were as follows:

- There were no clinically significant lower order changes in distance sphere or astigmatism (axis or power). These iTrace findings support the stability of the distance refraction over the 24 month study.
- No significant pupil size changes over the course of the study ruling this out as a possible MOA.
- No clinically significant HOA changes were seen in any of the Zernike measures in the static distance iTrace measures over the course of the study. This finding supports the statement that there were no induced visual side effects such a coma, glare, or halos.
- From the analyses provided in Amendment 5 of the PMA, examination of the lower order or higher order change with near targets failed to show any statistically significant changes in any of the Zernike functions with the exception of the C4 defocus term where there were statistically significant changes, but the maximum mean change corresponded to approximately 0.165 D.

6 CLINICAL SAFETY

Summary

- The VisAbility Micro Insert System is implanted outside the visual axis, avoiding vision loss and aberrations, while preserving distance vision.
- The VisAbility Micro Insert System has a favorable safety profile. Ocular AEs were reported in 36.7% (260/708) of implanted eyes in the pivotal study, with a majority of events being related to ocular surface.
    - These events were typically mild in nature and were effectively managed with treatments such as aqueous tear supplementation, eyelid hygiene, and topical or oral therapeutic agents.
- Surgical complications occurred in 1.8% (13/708) of eyes, with perforation of the sclera noted in 8 (1.1%) eyes.
    - There was no permanent loss of lines of BCDVA.
    - Scleral perforation was determined to be related to improper surgical technique, therefore, proper training and continued attention to insertion technique was identified as the primary measure to mitigate scleral perforation.
- The VisAbility Micro Insert System AEs of clinical concern included ASI (0.7% of eyes), scleral perforation (1.1% of eyes), re-approximation of the conjunctiva due to exposed implants and conjunctival retraction (2.1% of eyes), removals (1.8 % of eyes), and laser retinopexy for repair of retinal holes/tears (0.3% of eyes).
    - In each type of AE of clinical concern, the occurrences of the AEs observed were infrequent, and patients experienced no lasting symptoms or functional effects. Events were managed safely and other than cases of bilateral explantation, none of these AEs were observed in both eyes of a single patient.
- The VisAbility Micro Insert System can be safely implanted with no deleterious impact on vision. Most AEs were mild in nature and either resolved immediately or were managed without a long-term impact on vision.

6.1 Safety Population

Safety analysis was conducted in the safety cohort (N=360; 708 eyes), which includes all eyes of all patients that underwent surgical implantation. This cohort includes patients from both the randomized and non-randomized arms of the study.

6.2 Safety Results

6.2.1 Ocular Surface Findings

Over the course of the study, postoperative ocular AEs were reported in 36.7% (260/708) of eyes, with the most commonly reported events involving the ocular surface – the conjunctiva, cornea, and the eyelids (**Table 7**).

Dry eye signs requiring prescription medication after 6 months postoperative were observed in approximately 12.3% (87/708) of all implanted eyes and in 12.2% (44/360) of study patients. Many of these patients were treated with prescription medication for symptoms in the absence of dry eye signs; approximately 47.1% (41/87 eyes) had no corneal punctate staining and 24.1% (21/87 eyes) showed little to no conjunctival injection. This study population also showed preoperative signs of dry eye such as trace or mild degrees of corneal superficial punctate keratitis in 3.5% (25/708) of all study eyes, and trace or mild degrees of conjunctival injection in 18.8% (133/708) of eyes. Dry eye signs and symptoms in this study were either considered resolved by 24 months or were managed with ongoing treatment.

Conjunctival injection was observed in all eyes in the early postoperative period as a result of the conjunctival peritomy which was required for placement of the VisAbility Micro Inserts. Moderate or severe conjunctival injection (as determined by using the Efron Grading Scale photos) persisting at study visits of 3 month or later was considered an AE and was observed in 4.5% (32/708) of all implanted eyes. Over half of these eyes, 19 (59.4%), achieved resolution within 3 months.

Lid margin disease was reported as an AE in 9.0% (64/708) of eyes, with all but 5 events resolving within 24 months.

Post-market, pre-operative detection and management of ocular surface disease will be strongly recommended. Specifically, use of survey tools such as the Ocular Surface Disease Index (OSDI) as well as diagnostic instrumentation will help to detect pre-existing subclinical or low-grade ocular surface conditions that should be treated and resolved prior to consideration for the VisAbility procedure. In addition, careful attention to anticipated implant positioning with regard to lid exposure will be advised in order to minimize the risk of dry eye related to segment lid exposure.

Ocular AEs of decreased visual acuity, VisAbility Micro Insert removals, ASI, scleral perforation, laser retinopexy for repair of retinal holes/tears, and re-approximation of the conjunctiva due to conjunctival retraction with occasional exposed implants, are discussed in Sections 6.2.2, 6.2.3, and 6.2.4.

Table 7: Lid, Cornea, or Conjunctiva Adverse Events

Events	Through 24 Months			
	% of Patients (N=360)		% of Eyes (N=708)	
	n	%	n	%
Any ocular adverse events	**170**	**(47.2%)**	**260**	**(36.7%)**
Lid	**33**	**(9.2%)**	**64**	**(9.0%)**
Ptosis	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%)
Cornea/Conjunctiva	**89**	**(24.7%)**	**143**	**(20.2%)**
Corneal dellen after 1 week	1	(0.3%)	1	(0.1%)
Corneal abrasion > 2mm after 1 week	5	(1.4%)	5	(0.7%)
Corneal edema (moderate or severe) after 1 month	0	(0.0%)	0	(0.0%)
Corneal infiltrate or ulcer	1	(0.3%)	1	(0.1%)
Dry eye signs requiring prescription medication after 6 months	44	(12.2%)	87	(12.3%)
Conjunctival Cyst	15	(4.2%)	15	(2.1%)
Conjunctival thinning or erosion	0	(0.0%)	0	(0.0%)
Conjunctival Injection-moderate or severe @ 3 months or more	20	(5.6%)	32	(4.5%)
Subconjunctival hemorrhage after 3 months	15	(4.2%)	16	(2.3%)

Note: This table corresponds to Table 103, A005, Vol. 1, pp. 310-311

6.2.2 BCDVA

BCDVA was measured in the study population to ensure that treatment was not associated with a negative effect on distance vision.

From 3 to 24 months post-operatively, BCDVA was 20/20 or better in greater than 99% of all study eyes, and 20/25 or better in all study eyes (100%) from 6 to 24 months (**Table 8**).

Table 8: BCDVA Over Time in VisAbility Study

	Pre-op N=708	1 Month Exam N=698	3 Month Exam N=689	6 Month Exam N=686	12 Month Exam N=687	24 Month Exam N=668
n (Reported)	708	696	688	684	687	668
20/16 or better	449 (63.4%)	442 (63.5%)	533 (77.5%)	544 (79.5%)	581 (84.6%)	552 (82.6%)
20/20 or better	**708 (100.0%)**	**676 (97.1%)**	**684 (99.4%)**	**682 (99.7%)**	**683 (99.4%)**	**665 (99.6%)**
20/25 or better	708 (100.0%)	696 (100.0%)	687 (99.9%)	684 (100.0%)	687 (100.0%)	668 (100.0%)
20/32 or better	708 (100.0%)	696 (100.0%)	687 (99.9%)	684 (100.0%)	687 (100.0%)	668 (100.0%)
20/40 or better	708 (100.0%)	696 (100.0%)	687 (99.9%)	684 (100.0%)	687 (100.0%)	668 (100.0%)
20/50 or better	708 (100.0%)	696 (100.0%)	688 (100.0%)	684 (100.0%)	687 (100.0%)	668 (100.0%)

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

Post-operatively, 98.0% of implanted eyes had no change or at least one line of improvement in BCDVA at the 12 month exam after baseline (**Table 9**).

Ten eyes in 9 patients had a decrease in BCDVA ≥ 10 letters up to 3 lines lost at 3 months or later (**Table 9** and **Figure 20**). Per protocol, these events were reported as AEs (note: some of these decreases in BCDVA occurred at unscheduled visits and are therefore not reflected in **Table 9**). Five of these eyes had a transient decrease in BCDVA associated with ocular surface findings that resolved following treatment. One eye showed a temporary 2 line decrease of unknown etiology from 20/12.5 at baseline to 20/20 at 6 months, which then resolved at 12 months. Other causes of BCDVA decrease included cataract (2), corneal abrasion (1), and non-arteritic ischemic optic neuropathy secondary to systemic hypertension (1).

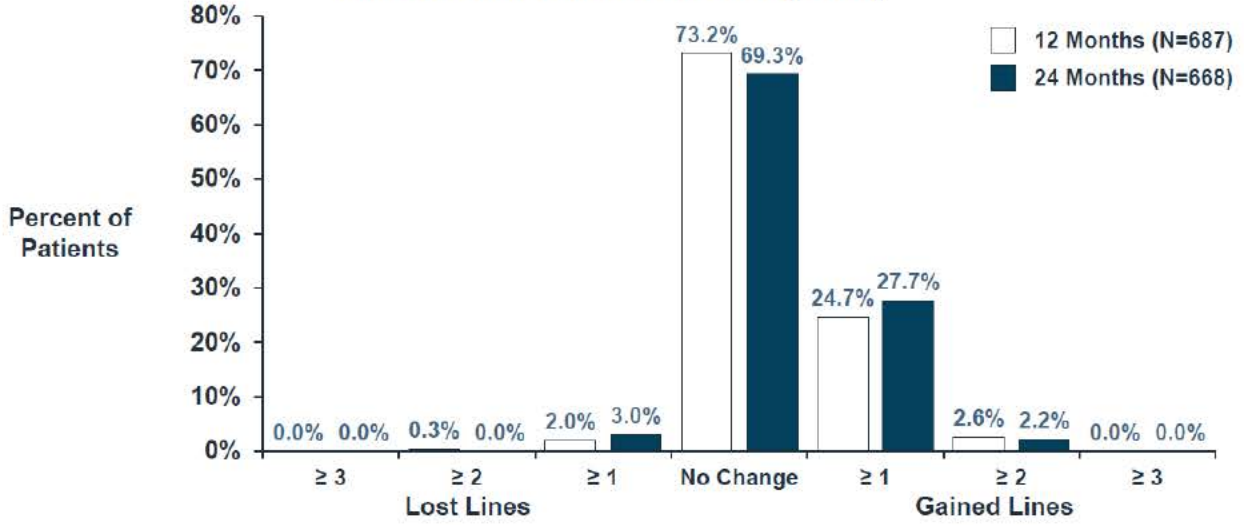
Loss of BCDVA resolved in all cases by the next study visit interval. By 24 months, there were no losses of BCDVA greater than 1 line (5 letters) reported.

Table 9: Change in BCDVA from Baseline in VisAbility Study

	1 Week N=702	1 Month Exam N=698	3 Month Exam N=689	6 Month Exam N=686	12 Month Exam N=687	24 Month Exam N=668
n (Reported)	702	696	688	684	687	668
Gained 3 lines	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%)	8 (1.2%)	9 (1.3%)	18 (2.6%)	15 (2.2%)
Gained ≥ 1 line	44 (6.3%)	57 (8.2%)	109 (15.8%)	125 (18.3%)	170 (24.7%)	185 (27.7%)
No change	510 (72.6%)	565 (81.2%)	553 (80.4%)	540 (78.9%)	503 (73.2%)	463 (69.3%)
Lost ≥ 1 line	148 (21.1%)	74 (10.6%)	26 (3.8%)	19 (2.8%)	14 (2.0%)	20 (3.0%)
Lost ≥ 2 lines	40 (5.7%)	15 (2.2%)	2 (0.3%)	3 (0.4%)	2 (0.3%)	0 (0.0%)
Lost ≥ 3 lines	10 (1.4%)	0 (0.0%)	1 (0.1%)	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%)
Lost ≥ 5 lines	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not reported	0	2	1	2	0	0

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

Figure 20: Change in BCDVA Lines Gained or Lost from Baseline at the 12 Month and 24 Month Exam in VisAbility Study



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

6.2.3 Surgical Complications

Fifteen surgical complications were observed in 13 eyes of 13 patients, or 1.8% (13/708) of all 708 implanted eyes (**Table 10**). Ten of these events were reported as AEs, with the remaining 5 complications resolving by Day 1. The AEs included 8 scleral perforations and 2 explants resulting from failure to achieve adequate pupil response within the first 6 hours following surgery. Each of the AEs was managed appropriately and resolved within the first 8 days postoperative.

Perforation of the sclera during VisAbility Micro Insert implantation was an intraoperative complication of clinical significance and is covered in more detail in Section 6.4.2.

The VisAbility Micro Insert removals in 2 patients on the day of surgery were due to Grade 2 ASI, which is covered in more detail in Section 6.4.1.

The remaining 5 complications resolved by Day 1, and included:

- One patient experiencing nausea and vomiting that resolved by Day 1. This was deemed to be a reaction to anesthesia.
- Two patients with shallow tunnels in 1 quadrant that were recut with a new Scleratome and successfully implanted without complication.
- Two patients who were visually observed to have decreased intraocular pressure associated with scleral perforations; both eyes had normal pressures on Day 1.

Table 10: Surgical Complications in VisAbility Study

Events	Number of Events	% of Patients (N=360)		% of Eyes (N=708)	
		n	%	n	%
Eyes reported with any surgical complications*	15	13	3.6%	13	1.8%
Intraoperative ocular events					
Scleral perforation	8	8	2.2%	8	1.1%
Decreased IOP	2	2	0.6%	2	0.3%
Shallow implant tunnel	2	2	0.6%	2	0.3%
Postoperative ocular events					
Pupil abnormalities	2	2	0.6%	2	0.3%
Allergic reaction (to medication, sutures, or anesthetic)	1	1	0.3%	1	0.1%

*An eye could be reported with multiple surgical complications.
Note: there were no events of choroidal effusion; increased IOP; intraocular bleeding, malpositioned implants; vitritis; or iridodialysis.

6.3 Serious Ocular Adverse Events

There were no serious ocular events or deaths in this study.

6.4 Adverse Events of Clinical Interest

6.4.1 Anterior Segment Ischemia

As a recognized complication following compromise of the anterior ciliary circulation, ASI was mitigated in this clinical trial through surgical training and postoperative pupillometry, with timely explantation if criteria were not met. ASI is an acute, self-limited event that occurs only in the immediate postoperative period and does not occur later nor recur during the postoperative course. ASI resolves spontaneously over time (Saunders et al. 1994).

Although published literature reports that "[l]eft untreated, the most severe cases [of ASI] can result in phthisis bulbi" (Pineles et al. 2018), the onset of ASI can be easily recognized by decreased pupillary response (Olver and Lee 1992), and once collateral circulation is established ASI resolves spontaneously over time (Saunders et al. 1994). Moreover, Refocus is aware of just one case of phthisis bulbi coinciding with ASI that has been reported in published literature, a case which occurred approximately 60 years ago (Girard and Beltranena 1960). In this case, ASI occurred following scleral buckling surgery with disinsertion of all 4 rectus muscles, which was complicated by hyphema and a persistent intraocular pressure elevation to 60 mmHg requiring secondary surgical intervention. It is likely that in this case the hyphema and resulting ocular hypertension played a significant role in the development of phthisis. Ultimately, ASI most often involves a self-limited response, which resolves without sequelae and with no detrimental effect on vision even in severe cases because of the extensive collateral circulation of the anterior segment of the eye.

Because pupillary dysfunction constitutes the earliest functional sign of ASI, sensitive and precise measurement of the pupillary response in the immediate postoperative period represents the only proven indicator of the risk of disease progression. Digital infrared dynamic pupillometry is the optimal indicator of iris neuromuscular function relative to iris vascular perfusion. Measurement of the dynamic response of the pupil to standardized illumination is the most sensitive means to assess the eye's recovery from surgery because pupillary abnormalities represent the earliest functional sign of ASI. The purpose of pupillometry in the immediate postoperative period in this study was to allow for timely removal of scleral implants and prevent the development of potential sequelae.

A total of 5 ASI related events occurred during this study (**Table 11**); all occurred in the early postoperative period with outcomes in line with the type and expected resolution of signs and symptoms reported in the literature (Saunders et al. 1994). Two eyes of 2 patients developed Grade 2 ASI on the day of the surgery, were explanted the same day, and experienced a complete recovery without sequelae in 1 week. One patient developed Grade 3 ASI involving anterior chamber reaction and pupil changes which resolved fully by 6 months postoperative without sequelae. One patient developed Grade 4 ASI on Day 1 involving corneal edema, anterior chamber

reaction and pupil changes. This eye recovered fully without sequelae by 6 months postoperative. Finally, 1 patient exhibited a mildly irregular pupil that resolved by 24 months with sequelae limited to 1–2 clock hours of stable iris transillumination.

To mitigate the risk of ASI, mandatory surgeon training and certification in the surgical technique will be required. As part of this training, surgeons will be taught that eyes not meeting protocol-defined pupil constriction criteria must undergo explantation within 6 hours of surgery to mitigate the risk.

Table 11: Postoperative Anterior Segment Ischemia Adverse Events in VisAbility Study

Grade	Signs	Disposition
Grade 2 (2 pts. – 2 eyes)	• Decreased pupillary response	• Explanted; recovered without sequelae
	• Decreased pupillary response	• Explanted; recovered without sequelae
Grade 3 (1 pt. – 1 eye)	• Slow but adequate pupillary response • Peaked pupil • Anterior chamber reaction	• Recovered without sequelae
Grade 4 (1 pt. – 1 eye)	• Decreased pupillary response • Anterior chamber reaction • Corneal edema	• Recovered without sequelae
Persistent pupillary abnormality (1 pt. – 1 eye)	• Pupil abnormality	• Recovered with 1–2 clock hours iris transillumination

6.4.2 Scleral Perforations

Scleral perforation, in the setting of VisAbility Micro Insert surgery, is a micro-perforation which occurs at the level of the scleral tunnel. These intraoperative events occurred in 1.1 % (8/708) of eyes; each of these perforations resolved (**Table 12**). Three cases (0.4% of all implanted eyes) resulted in sequelae which included 1 inadvertent bleb, 1 posterior vitreous detachment with retinal hemorrhage that resolved within 1 month, and 1 case of residual inflammation leading to posterior synechiae that were treated with a mydriatic agent and resolved within 2 weeks. The remaining 5 cases resulted in no postoperative sequelae; the clinical course of these eyes was routine. Six of the 8 eyes had DCNVA of 20/40 or better, and all 8 had BCDVA of 20/20 or better at 24 months.

Table 12: Overview of Scleral Perforations in VisAbility Study

Case	Sequelae	DCNVA		BCDVA
		Baseline	24 months	24 months
1	Inadvertent bleb, low IOP, cataract removal Multifocal IOL at 6 months	20/50	20/25*	20/20*
2	ST Quadrant not implanted, Day 1 anterior chamber cell/flare. hypotony/IOP 5 mmHg, Posterior vitreous detachment, retinal hemorrhage Resolved within one month	20/63	20/63	20/12.5
3	Residual inflammation, posterior iris synechiae post-op, Day 6 and 7 Resolved Day 11	20/50	20/20	20/16
4	None	20/80	20/25	20/16
5	None	20/63	20/40	20/16
6	None	20/63	20/20	20/16
7	None	20/63	20/32	20/12.5
8	None	20/50	20/25	20/12.5

*denotes visual acuity with Multifocal IOL in place

6.4.3 Removals Through 24 Months

In addition to the 2 eyes that were explanted in connection with the 2 cases of Grade 2 ASI identified above, an additional 11 eyes were explanted for the following primary reasons: 3 eyes due to redness/cosmesis, 4 eyes due to foreign body sensation, 2 eyes due to perceived lack of effect, and 2 eyes due to residual refractive error (**Table 13**). Including these 11 cases as well as the 2 cases of Grade 2 ASI, explants were performed in a total of 1.8% of implanted eyes (13/708) in 8 patients though 24 months (**Table 15**). There was no impact on distance visual acuity in explanted eyes, and all eyes returned to baseline. There were no sequelae.

6.4.4 Removals after 24 Months

Following the 24 month IDE study, an additional 7 subjects/14 eyes had all Micro Inserts removed during the interim period between the 24 month study exit and enrollment in the VIS-2014-5YR long term study (**Table 14**). The eyes were explanted for the following primary reasons: 4 eyes due to foreign body sensation, 8 eyes were explanted due to a combination of dry eye, cosmesis or perceived lack of effect and 2 eyes of 1 subject was explanted secondary to a systemic health issue. During the 5 year study, 1 subject was explanted during the 4th year due to lid margin disease, and one subject was explanted during the 5th year due to redness (**Table 14**). All eyes achieved BCDVA of 20/20 or better, post explant.

A cumulative explant rate through 5 years of follow-up is presented in **Table 15.**

Table 13: Reasons for Removals at 2 Years of Follow-up and BCDVA at Baseline and Post-Explant

Explants	Explant Year	Patient	Reasons for Explant	Baseline BCDVA	Last Available (post-explant) BCDVA
1	1	1	Inadequate pupil response DOS	20/20	20/20
2	1	2	Inadequate pupil response DOS	20/16	20/16
3	1	3	Cosmesis	20/20	20/16
4 5	1	4	Residual refractive error; Perceived lack of effect	20/16 20/16	20/12.5 20/16
6 7	2	5	Cosmesis; Perceived lack of effect	20/16 20/16	20/20 20/16
8 9	2	6	Perceived lack of effect; Ocular surface dryness	20/20 20/16	20/16 20/16
10 11	2	7	Foreign body sensation; Redness/Cosmesis	20/16 20/16	20/16 20/16
12 13	2	8	Foreign body sensation; Ocular surface dryness	20/16 20/16	20/12.5 20/12.5

DOS = Day of Surgery

Table 14: Reasons for Removals after 2 Years of Follow-up and BCDVA at Baseline and Post-Explant

Explants	Explant Year	Patient	Reasons for Explant	Baseline BCDVA	Last Available (post-explant) BCDVA
Post 24 Month - Prior to VIS-2014 5YR					
14 15	3	9	Foreign body sensation	20/12.5 20/16	20/16 20/16
16 17	3	10	Dryness	20/16 20/16	20/20 20/16
18 19	3	11	Systemic disease	20/20 20/20	20/16 20/16
20 21	3	12	Cosmesis	20/16 20/12.5	20/16 20/16
22 23	3	13	Foreign body sensation	20/12.5 20/12.5	20/12.5 20/16
24 25	3	14	Perceived lack of effect	20/16 20/16	20/16 20/16
26 27	3	15	Perceived lack of effect	20/16 20/16	20/20 20/20
VIS-2014 5YR					
28 29	4	16	Lid margin disease	20/16 20/16	20/16 20/16
30 31	5	17	Redness	20/20 20/20	20/20* 20/20*

*UCDVA (BCDVA was not collected post-explant)

Table 15: Device Explantation Through 5 Years of Follow-up

	Number of Device Explants (Eyes) by Year	Number of Patients by Year
Year 1	5	4
Year 2	8	4
Year 3	14	7
Year 4	2	1
Year 5	2	1
Total*	31	17

* VIS-2014 enrolled 708 eyes. VIS-2014-5YR follow up study enrolled 556 of the 708 eyes as of 15Jul2020 and enrollment is ongoing.

6.4.5 Secondary Surgical Interventions Other than Explant

Re-Approximation of the Conjunctiva Due to Exposed Implants and Conjunctival Retraction (Conjunctival Retractions Requiring Conjunctival Re-approximation)

Conjunctival retractions requiring secondary surgical intervention occurred in 15 eyes (2.1%) of 15 patients (4.2%). These included 5 eyes with exposure of one VisAbility Micro Insert segment and 10 eyes with no exposure. All events were limited to the early postoperative period between Day 1 to Week 1, with all resolved within 1–10 days without sequelae. There were no signs of infection in any of these cases; 1 eye developed a conjunctival cyst 6 weeks after implantation and Day 1 conjunctival re-approximation, however the cyst was 180 degrees from the area of resutured. Mitigation of this risk involves implementing the proper recommended suturing technique which will be ensured by surgeon training.

Laser Retinopexy for Retinal Hole/Tear

Laser retinopexy was conducted in 2 eyes of 2 patients. One case of an asymptomatic retinal hole which was an incidental finding observed during the 1 week dilated fundus exam, and 1 case of a retinal tear associated with a PVD was observed at 8 months. Both cases were treated and stabilized with uncomplicated laser retinopexy and resolved with normal findings at 24 months. Neither event was deemed to be related to implantation of the VisAbility Micro Insert segments, nor were these in eyes in which scleral perforation had occurred.

6.5 Safety Conclusions

The VisAbility Micro Insert System demonstrates a favorable safety profile. Post-operatively, 98% and 97% of implanted eyes showed no change (<1 line change) or an improvement in BCDVA from baseline at 12 months and 24 months, respectively. A majority of the ocular AEs were mild in nature and resolved by the next postoperative visit. Importantly, this procedure is performed outside the visual axis, and therefore involves no permanent compromise of distance vision, nor any optical side effects or aberrations.

7 FOLLOW-UP STUDY AND POST-MARKET ACTIVITIES

7.1 VIS-2014-5YR Study

VIS-2014-5YR A Prospective, Multicenter Clinical Trial Of The VisAbility™ Micro Insert System For The Improvement Of Near Visual Acuity In Presbyopic Subjects - Long-Term Follow-Up was approved by FDA on November 28, 2018, under (b) (4) [redacted].

The VIS-2014-5YR is a continuation, post approval study designed to demonstrate the long-term safety and effectiveness of the VisAbility Micro Insert in presbyopic subjects. 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. VIS-2014-5YR consists of extended follow-up of these subjects; no new subjects will be treated as part of this study. The aim of this multicenter, observational study is to obtain an additional 36 months of safety and effectiveness data.

Each subject who was implanted or explanted with the VisAbility™ Micro Insert in Protocol VIS-2014 will be invited to participate. Those subjects who agree to participate will be consented, enrolled, and will be examined at 36, 48, and 60 months post-operatively, with no planned interventions. Those who refuse consent/decline participation will be documented accordingly and will not be eligible for longer term follow-up.

Subjects who opt to have all implant segments bilaterally removed (explanted) after enrollment will be followed for 2 years post removal, up to a maximum of 5 years follow-up. Additional visits may include but are not limited to examination at day 1, week 1, month 1, and 2 annual visits, post removal.

The primary and secondary endpoints of the post-approval phase are safety. The effectiveness endpoint of the post-approval phase is the long-term reliability of the VisAbility implant. The specific endpoints are described below:

The primary safety outcomes will evaluate:

- Explantation 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)

The secondary safety outcomes will evaluate:

- 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)

The secondary effectiveness outcome will evaluate the 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).

Annual reports will be submitted when each 12 month follow-up interval has been completed.

7.2 Controlled Access

Following approval, Refocus will conduct a controlled introduction of the VisAbility Micro Insert System.

During the pivotal clinical trial and human factors testing, Refocus limited access to surgeons with a proven track record of surgical excellence and demonstrated commitment to the highest standards of patient care. Post-approval, the initial introduction of the VisAbility Micro Insert System during the first 3 to 6 months will be limited to those surgeons that were involved in the clinical study. Refocus 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 3 to 6 month introductory period, Refocus plans to launch the VisAbility Micro Insert System in 3 selected cities where experienced investigators are available to participate in training and mentoring of new surgeons. Refocus plans to train approximately 35–45 surgeons to offer the VisAbility Micro Insert procedure by the end of the first year. Surgeons will continue to enroll all eligible patients in a third-party data registry, which will allow monitoring of surgical outcomes as well as both timely and appropriate response if additional training is indicated. Surgeons will also have support and access to experienced clinical application specialists and a patient focused practice management team.

7.3 Training and Certification

Qualified surgeons are to be trained and certified in the selection of appropriate patients, performance of successful VisAbility Micro Insert surgery, and management of potential complications. This training and certification will continue to be a requirement prior to device receipt for all surgeons requesting the device post-market.

Prior to performing his or her first VisAbility Micro Insert System procedure, training and certification will require each surgeon to:

- Successfully complete the VisAbility Micro Insert System didactic training review course.
- Successfully complete the VisAbility Micro Insert System hands on wet lab course.
- Observe a VisAbility Micro Insert System surgical procedure at an experienced certified surgeon’s location.
- Successfully complete no fewer than 5 VisAbility Micro Insert System surgical procedures on 5 eyes under the observation of a Refocus Group designated proctor.
- Successfully complete a review of the postoperative results for the above proctored cases with a Refocus Group representative sometime in the first postoperative month.

Once verified by Refocus, the surgeon 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/or instrumentation updates, Refocus 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. To maintain certification status, these previously certified VisAbility Micro Insert System surgeons will be retrained by the Refocus representatives, with all training documented. Additionally, surgeons will be expected to review the updated materials, file the updated materials for ease of reference, and archive obsolete training materials.

Certified VisAbility Micro Insert System surgeons and their practices must agree, if requested, to participate in ongoing reporting of results in a manner consistent with Health Insurance Portability and Accountability Act (HIPAA) requirements, as part of the post-market approval study.

As shown in **Table 16**, this training and certification program differs from the training the physicians received in the VisAbility clinical trial. The investigators in the VisAbility Study were trained in a wet lab session using cadaveric animal eyes to learn the instrumentation. Refocus clinical specialists trained staff on the study protocol. Prior to surgery, a surgeon trainer did a review of the surgery steps and was present at initial surgeries. However, there was no formal didactic program with testing, as there will be for new surgeons' post-market.

Table 16: Investigator Training vs Post-Market Surgeon Training

Training	Clinical Study Investigators	Post-Market Surgeons
Formal Didactic with Testing		
Best Practices (Inclusion/Exclusion Criteria, Post-Operative care)		✓
Pearls to avoid complications		✓
Wet Lab Training		
Demonstration of proficiency	✓	✓
Surgery Review & Proctoring		
Minimum 5 eyes for proctoring	✓	✓
Post-Operative Support and Monitoring		
Clinical specialist monitoring		✓
Surgeon trainer "sign off" & Mentorship		✓
Reporting Requirements		✓
3rd Party Registry		✓

7.4 Proposed Post Approval Study VIS-2014-PAS

VIS-2014-PAS is a Prospective, Multicenter Post Approval Study of the VisAbility™ Micro Insert System in Presbyopic Subjects. The protocol for the proposed post-approval study, which has already been submitted to the FDA, describes data collection through 12 months postoperative including both safety and effectiveness outcomes.

This is a prospective, 1 year, multicenter, single-arm clinical study that will enroll up to 150 subjects ranging in age between 45 and 60 years of age with DCNVA and uncorrected near visual acuity (UCNVA) of 20/50 to 20/80 (inclusive). A controlled rollout will occur in 3 targeted markets and subjects will be enrolled at up to 15 clinical sites.
Subjects will be consented and screened based on medical history, ocular history, and visual acuity criteria. Subjects should satisfy specific inclusion and exclusion criteria to be eligible for surgery. Subjects will be implanted with the VisAbility Micro Insert in both eyes on the same day and subjects will be examined at one day, one week and at 1, 6, and 12 months, post-operatively.

Subjects who opt to have all implant segments bilaterally removed (explanted) after enrollment will receive additional follow-up, post removal.

Sample size for this study is based on a desire to further characterize the safety and effectiveness of the VisAbility™ Micro Insert System. A total of 150 subjects will provide a precision (i.e., 95% confidence interval half-width) of approximately 8% for binomial variables (based on an exact binomial interval). Similarly, this sample size will provide a precision of approximately 0.16 for continuous variables (based on a t-distribution, on the effect size scale, i.e., standard deviation units). Finally, the planned sample size will provide a greater than 90% probability of observing one or more events of interest for events that occur at a population rate of 1.5% or higher.

This sample size is appropriate since data from a subset of the first 360 subjects who have chosen to be enrolled in the VIS-2014-5YR study will also be used to further validate the long-term safety of patients who have received the VisAbility™ Micro Insert for the treatment of presbyopia.

DATA ANALYSES

Descriptive statistics and summaries will be provided for all eyes for the following:

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
- Explantation (full or partial)

Primary effectiveness outcomes:

- Change in DCNVA from baseline

CLINICAL PARAMETERS

The following clinical parameters will be measured:

- Near visual acuity (uncorrected, distance corrected)
- Distance visual acuity (best corrected)
- Minimum add to 20/20 (preoperative only)
- Dynamic pupillometry
- Manifest refraction
- IOP
- Slit lamp biomicroscopy
- Funduscopic examination

STATISTICAL ANALYSIS

Due to the observational nature of this study, the statistical analysis will be based on informal comparisons to the pre-approval data without formal statistical hypothesis tests. While there is interest in understanding the post-approval study data relative to the pre-approval data, informal comparisons without statistical hypothesis tests are appropriate as the study will not be protected by randomization, the post-approval study will be disjointed in time from the pre-approval data, and the study will include investigators who did not participate in the pre-approval study.

Analyses described in this section will be based solely on data from the current post-approval study.

Summary statistics will be provided for all primary and secondary outcomes (listed above in Section 2.4) for primary and all eyes.

Long-term safety and effectiveness will be evaluated through 1 year, which is sufficient to capture the safety events of interest, including anterior segment ischemia (ASI), scleral perforations and secondary surgical interventions. The study will also evaluate DCNVA and UCNVA as key effectiveness endpoints. This study will only prospectively enroll subjects under the Intended Use (IU) Population, thereby satisfying the specific objective of evaluating the device in this population.

To evaluate real-world performance of the device and surgeon experience, safety events of interest and key effectiveness endpoints will also be presented stratified by surgeon experience. For example, stratification defined by surgeon experience (newly trained surgeon vs. experienced surgeon) and/or case number (e.g., cases 1-10, 11-20, etc.).

No formal hypothesis tests are planned for comparison of either 1) the pre vs. post-market, or 2) surgeon experience.

8 BENEFIT-RISK ANALYSIS

Presbyopia is the most prevalent of all visual deficiencies,. Presbyopia is characterized by a progressive, age-related loss of accommodation and inability to see clearly at near distances. Uncorrected presbyopia is associated with reduced health-related quality of life, and presbyopia corrected with glasses is associated with a nominal decrease in quality of life, similar to that of treated systemic hypertension (Lord et al. 2002; Luo et al. 2008; McDonnell et al. 2003).

The VisAbility Study has demonstrated that the VisAbility Micro Insert System improves near vision in the presbyopic population without compromising distance vision. The VisAbility Micro Insert System has the capability of reversing the harmful effects of presbyopia and has shown clinically significant benefits that outweigh the risks.

The primary effectiveness endpoint criteria, achievement of DCNVA of Snellen equivalent 20/40 or better and at least 10 letters improvement in DCNVA in the primary eye, were successfully met at 24 months. At 12 and 24 months, 79.1% and 84.0% of patients achieved this threshold, respectively. The VisAbility Micro Insert met its intended use by providing a clinically significant improvement in near visual acuity in presbyopic patients.

Clinical data from the VisAbility Study also demonstrated that the VisAbility Micro Insert System can be safely implanted with no deleterious impact on vision. There was no permanent loss of lines of BCDVA, and the majority of AEs were generally mild in nature and resolved by the next postoperative visit. Unlike alternative surgical treatments, the VisAbility Micro Insert System is less invasive because it is implanted outside of the visual axis, with the corneal shape and integrity remaining unaffected. Additionally, the VisAbility Micro Insert System does not compromise the integrity of the cornea and lens, which is often the source of unwanted optical side effects such as glare, halos, starbursts, ghost images, or double vision.

In the clinical study, the mitigation and management of safety events related to the VisAbility Micro Insert System allowed for rapid resolution of AEs, supporting a favorable safety profile for the device. Of importance, the VisAbility Micro Insert System includes a marketing plan that consists of controlled access to the device in the introductory 3 to 6 months, as well as mandatory training and certification, thus continuing to ensure the safety of the VisAbility Micro Insert System.

Overall, the effectiveness and safety data generated through the clinical program have demonstrated that the VisAbility Micro Insert System has a favorable benefit-risk profile for use in presbyopic patients.

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