FDA Executive Summary

Prepared for the
July 14, 2006, meeting of the
Ophthalmic Devices Panel

P050034
VisionCare Ophthalmic Technologies, Inc.
Implantable Miniature Telescope (IMT)

1. PROPOSED INDICATIONS FOR USE

The Implantable Miniature Telescope (IMT) is indicated for use in adult subjects with bilateral, stable, untreatable moderate to profound central vision impairment due to macular degeneration. Subjects selected for implantation should meet the following criteria:

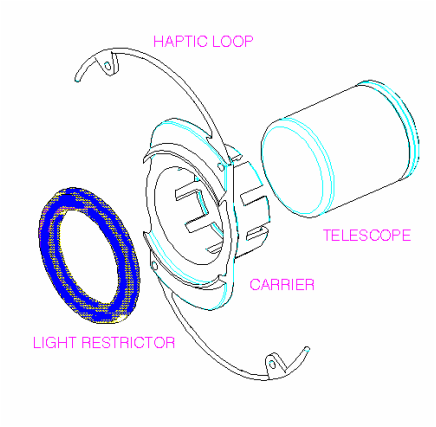
- 55 years of age or older with bilateral, stable central vision disorders resulting from age-related macular degeneration (AMD) as determined by fluorescein angiography, and evidence of cataract.
- Distance BCVA (best corrected visual acuity) between 20/80 and 20/800, and adequate peripheral vision in one eye (the non-targeted eye) to allow for orientation and mobility.
- Achieve at least a five-letter improvement on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart in the eye scheduled for surgery using an external telescope.
- Show interest in participating in a postoperative visual rehabilitation program.

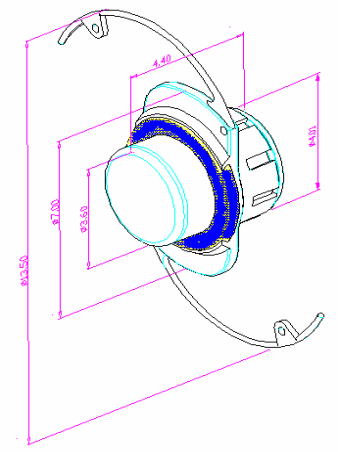
2. DEVICE DESCRIPTION

VisionCare's IMT is a visual prosthetic device which, when combined with the cornea, constitutes a telephoto lens for improvement of visual acuity in subjects with bilateral moderate to profound macular degeneration. The IMT device is surgically implanted in the posterior chamber of the eye, in place of the eye's crystalline lens and is held in position by haptic loops.

The IMT device contains two micro lenses, which magnify objects in the central visual field, allowing the patient to see without the need for external low-vision aids. A magnified image is projected by the IMT implant onto the retina, enabling the patient to recognize and identify objects that could not otherwise be seen. The IMT device is

available in two models: Wide Angle (WA) 2.2X, and Wide Angle (WA) 3.0X, which provide nominal magnification of x2.2 and x2.7, respectively.





Both models are designed predominantly for the restoration of intermediate to far vision (increasing the ability to view objects several meters away from the patient). The addition of conventional spectacles provides correction for near vision activities.

The IMT device is implanted in one eye only. The implanted eye provides central vision, while the fellow eye continues to be used for peripheral vision.

The IMT implant is composed of three primary components; a fused silica capsule that contains optical elements, a clear polymethylmethacrylate (PMMA) carrier, and a blue PMMA light restrictor. The optical component is snap-fitted into the carrier. One of the internal components (not in contact with body fluids or tissue) of the IMT implant contains stainless steel, which may interfere with the safe use of Magnetic Resonance Imaging (MRI). Until MRI compatibility of the IMT implant has been established, the use of MRI is contraindicated, as stated in the proposed labeling.

3. PRE-CLINICAL STUDIES

a. Biocompatibility – Biological testing (M050004, Module 1)

A summary of the biocompatibility testing that the sponsor performed to support the safe use of the IMT is provided in the table below. The sponsor has conducted all testing in conformance with the relevant sections of International Organization for Standardization (ISO) 10993 and ISO 11979. Additionally, the sponsor has conducted all testing in conformance with Good Laboratory Practices (GLP) regulations. Testing was performed on ethylene oxide (EO) sterilized finished IMTs or a “mock device” that is a replica of the original product.

Test	Method	Extract(s)
Cytotoxicity	ISO Agarose Overlay	"Solid"
		Saline
		YAG Laser extract (saline)
	Inhibition of Cell Growth (1 point)	Water for Injection
	MEM Elution	Minimum Essential Medium
Systemic	USP and ISO Systemic Toxicity	Saline, sesame oil
Implantation	ISO Muscle Implantation Study (30 days and 12 weeks)	N/A
	Rabbit Ocular Implantation (6 months)	N/A
Genotoxicity	Ames Test	Ethanol, saline
	In Vitro Chromosomal Aberration Study	McCoy's 5A Medium
	Mouse Bone Marrow Micronucleus Study	Saline, sesame oil
Irritation, Sensitization	ISO Ocular Irritation	Saline
	Murine Local Lymph Node Assay	Saline, DMSO

Note: The cytotoxicity test on the YAG laser extract and the six month animal implantation tests were conducted on finished devices rather than "mock IMTs."

An in vivo intraocular implantation study was conducted in rabbits for a six month period. The control device was a PMA approved PMMA intraocular lens (IOL). The test and control lenses were surgically implanted in the posterior chamber of 10 rabbits following phacoemulsification of the natural lens (test lens in one eye, PMMA lens in contralateral eye). The eyes were evaluated by slit lamp examination according to a modified McDonald-Shadduck scoring system, and slit lamp exams were conducted preoperatively, on days 1, 3, 7, weeks 2 through 4, and biweekly until 6 months postop. At 6 months postop, the rabbits were euthanized and the eyes were enucleated and submitted for histopathological examination.

Macroscopic examinations revealed no ocular irritation trends that would be considered clinically significant effects from the test article. Microscopic evaluations of the ocular tissue sections revealed no adverse effects directly related to the test article. The changes in the lens capsules and the presence of regenerative and degenerative lenticular fibers were present for both test and control eyes and are related to the animal model used rather than a treatment effect. There were no significant differences between the eyes that received the test versus the control article.

FDA has no remaining concerns.

b. Biocompatibility - Physico-chemical testing (M050004, Module 1)

The sponsor performed the following physico-chemical testing as described in the ISO biocompatibility standard 11979-5.

i. Extractables – The extraction was performed in purified water and then in chloroform at 37 degrees C for 72 hours. The sponsor has summarized the results as follows: High Performance Liquid Chromatography (HPLC) analysis showed no hydroxyethylmethacrylate (HEMA) detected in the purified water blank or test extract solutions (the chloroform blank and test extract solutions were analyzed but had peaks that interfered with the detection of HEMA and other compounds); GC/MS (Gas Chromatography/Mass Spectrometry)analysis showed no semi-volatile organic compounds in the blank or test extract solutions; Inductively Coupled Plasma (ICP) analysis showed that the metals/elements analyzed were all below the detectable level with the exception of Boron and Silicon (the concentrations were 1.86 ppm and 1.41 ppm, respectively); Ultraviolet (UV) spectroscopy identified no extractable substances in the purified water extract, gravimetric determination showed that the change in mass following the purified water and chloroform extractions was 0.00016g and 0.22353g, respectively. This study is acceptable and demonstrates that the levels of extractables are very low.

ii. Hydrolytic stability – This study looks for the degradation products due to hydrolysis. The testing was performed at 37^{o} C and 50^{o} C for 30 and 90 days. The sponsor has summarized the results as follows: HPLC analysis showed no HEMA detected; GC/MS analysis showed no semi-volatile organic compounds; ICP analysis showed that the metals/elements analyzed were all below the detectable level; UV spectroscopy identified no extractable substances, gravimetric determination showed that the change in mass following each extraction was <0.00041 g. This study is acceptable and demonstrates that this device is hydrolytically stable.

iii. Exhaustive extraction – This testing was performed using hexane to determine the total amount of extractable material from the device. The sponsor has summarized the results as follows: The analysis of the hexane extracts showed the percentage of material extracted from the test material was 0.02%. This test is acceptable and demonstrates that the total extractables in the device are very low.

iv. Photostability –The sponsor has performed the photostability testing in conformance with the procedures described in ISO 11979-5. No evidence of instability in the absorbance properties or release of toxic compounds was observed.

v. Nd:YAG testing – The devices were placed in vials with 2 ml of saline and were subjected to laser damage at a power of 5.1 mJ for 50 hits on the periphery of the test article. The sponsor noted that the laser beam did not pass through the glass portion of the test article. The sponsor has summarized the results as follows: HPLC analysis showed no HEMA detected; GC/MS analysis showed no semi-volatile organic compounds; ICP analysis showed that the metals/elements analyzed were all below the detectable level with the exception of Boron and Silicon (the concentrations were 4.4 ppm and 5.4 ppm, respectively); and UV spectroscopy identified no extractable substances. The study demonstrates that the

Nd:YAG does not damage the periphery of the IMT. The sponsor is recommending that the laser not be focused through the central portion of the IMT as this would cause damage to the device. Therefore, no evaluation was performed to determine if the laser could be focused through the optical portion of the IMT.

FDA has no remaining concern.

c. Sterilization, Packaging and Shelf Life (M050004, Module 2)

The IMT is packaged in a protective case with cap, and then placed into a blister pack with a Tyvek lid, and ethylene oxide sterilized for a sterility assurance level calculated to 10^{-6}. FDA has no remaining concerns regarding the sterilization of the IMT – all issues were resolved in PMA P050034.

The sponsor has proposed a 24 month shelf life for the IMT. FDA has no remaining issues regarding the shelf life at 24 months - all issues were resolved in PMA P050034.

d. Manufacturing (M050004, Module 3)

FDA has no remaining concerns. This module was accepted and closed September 12, 2005.

4. CLINICAL STUDIES

The sponsor conducted a prospective multi-center clinical trial utilizing twenty-eight (28) clinical sites and enrolling a total of 218 consecutive subjects.

a. Safety/ Effectiveness Endpoints

Primary Effectiveness Endpoint for this study was defined as an improvement of 2 lines or greater in either near or distance best corrected acuity in 50% of the implanted eyes at 12 months post-implantation.

Quality of Life surveys (Activities of Daily Living (ADL) and National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)) were secondary measurements of efficacy.

The primary Safety Endpoint for this study was the mean percentage endothelial cell density (ECD) loss less than or equal to 17% at one year post IMT implantation.

An average loss of 10-17% within one year after large incision surgery was noted from the sponsor's review of the literature. The sponsor's objective was to demonstrate that the mean percentage of cell loss could be demonstrated with statistical confidence to be no more than 17%. The statistical power used for the sponsor's sample size calculations was

80% at the expected mean loss of 13.5% (mean of 10% to 17%). The standard deviation of percentage loss in the ECD was assumed to be 0.175 (17.5%), which was estimated based on the feasibility clinical study.

Secondary safety endpoint was preservation of best corrected visual acuity. Specifically, no more than 10% of implanted eyes were to experience a loss of more than 2 lines of either near or distance BCVA without a corresponding improvement in BCVA (gain of 2 lines or more). For example, a gain of 2 or more lines of near BCVA (BCNVA – best corrected near visual acuity) in eyes with loss of more than 2 lines distance BCVA (BCDVA – best corrected distance visual acuity), and vice versa.

Adverse events and complications were collected as additional safety endpoints.

b. Inclusion/Exclusion Criteria

Key inclusion criteria included a BCDVA (best corrected distance visual acuity) between 20/80 and 20/800, and adequate peripheral vision in one eye (the non-implanted eye) to allow navigation. Prospective study subjects needed to demonstrate improvement with an external telescope of at least five letters on the ETDRS chart in the eye scheduled for surgery. Subjects selected to enroll in this study had to be at least 55 years of age, and have an anterior chamber depth of ≥2.5 mm and have the need for cataract surgery.

Evidence of active CNV (choroidal neovascularization) on fluorescein angiography or treatment for CNV within the past six months constituted an exclusion from enrollment. If the fellow eye demonstrated an anticipated need for cataract extraction and intraocular lens implantation during the first 12 months following IMT implantation, they were not selected for enrollment. If cataract extraction was anticipated, it had to be performed at least 30 days prior to enrollment in the clinical study. Ophthalmic related surgery within the 30 days preceding implantation of the IMT was an exclusion criterion. The following conditions in the designated operative eye were also cause for exclusion: myopia > 6.0 D; hyperopia > 4.0 D; axial length < 21 mm; ECD < 1600 cells/mm^2; narrow angle, i.e., less than Shaffer grade 2; cornea stromal or endothelial dystrophies or disorders; inflammatory ocular disease; zonular weakness or instability of the crystalline lens; pseudoexfoliation; diabetic retinopathy; untreated retinal tears; retinal vascular disease; optic nerve disease; history of retinal detachment; and retinitis pigmentosa. Additional exclusions included the presence of any intraocular tumor and medical or ophthalmic condition that in the opinion of the investigator rendered the subject unsuitable for participation in the study. Any ophthalmic pathology that compromised the patient's peripheral vision in the fellow eye or any ocular condition that predisposed the patient to eye rubbing was also causes for exclusion.

Subjects with significant communication impairments or severe neurological disorders that would interfere with the study requirements were deemed unsuitable. Additionally, a history of previous intraocular or corneal surgery of any kind in the operative eye(s), whether refractive or therapeutic prohibited enrollment. If an individual had a known sensitivity to planned study concomitant medications, they could not participate in the

study. Typically, in order for a patient to be suitable for enrollment in this clinical trial, they could not be participating in any other clinical trials, even if not ophthalmic. And finally, a history of steroid-responsive rises in intraocular pressure, uncontrolled glaucoma, or preoperative (pre-op) intraocular pressure (IOP) >22 mm Hg deemed a patient unsuitable for enrollment.

Once selected to participate in the clinical trial, a specific procedure was followed to select the operative eye. Visual acuity was assessed with a hand-held external telescope utilizing ETDRS charts. The sponsor provided two or more sets of 2.2X and 3.0X Galilean external telescopes with reading caps to each site for use in the trial. These Galilean telescopes were used for all in-office testing and a 2.2X Galilean external telescope was given to potential subjects to try at home for a period of at least three days. Subjects were assigned either a 2.2X or 3.0X telescope based on their need for magnification and their responsiveness to magnification. Subjects who did not notice any improvement with a 2.2X were then tested with a 3.0X. If they responded to the 3.0X, then they were given a 3.0X. Subjects had to achieve at least a five-letter improvement (minimal one line) on the ETDRS chart in the proposed operative eye with at least one of the external telescopes in order to proceed with the surgery. Subjects who did not meet this criterion were excluded from the trial.

If the patient had BCDVA better than 20/200 in either eye, the eye with worse visual acuity was chosen for implantation. If BCDVA was equal to or worse than 20/200, or the same in both eyes, the physician and patient decided which eye would be implanted.

Subjects experiencing improvement in visual acuity with the external telescope(s), were further evaluated for eligibility based on distance and near best spectacle corrected visual acuity; manifest refraction; IOP by applanation tonometry; slit lamp evaluation; dilated fundus examination and photography; flurorescein angiography; specular microscopy; pachymetry; and, A-scan.

c. Operative Procedures

In preparation for surgery, the subjects were anesthetized via either retrobulbar or peribulbar injection. The IMT was implanted after phacoemulsification had been performed through either a limbal insertion technique or a scleral tunneling procedure. Limbal incisions were 10 mm – 11 mm at 120º to 160º degrees arc length. The scleral tunnel incisions were 10mm in length and placed from the 10 o'clock to the 2 o'clock positions approximately 2.5 mm – 3 mm posterior to the limbus. Both the limbal and scleral tunnel incisions methods utilized a 6.5 mm continuous curvilinear capsulorhexis. With both techniques, placement was in the capsular bag along with the haptics and utilized a peripheral iridectomy.

d. Post-operative Evaluation and Examination Schedule

Postoperatively, one drop of a topical ophthalmic antibiotic solution was to be administered following surgery, and then continued per product labeling for at least two days. One drop of Voltaren Ophthalmic (diclofenac sodium 0.1%, CIBA Vision Ophthalmics) or equivalent was to be administered following surgery, and then continued per product labeling for at least two days. Prednisolone acetate (1%) or equivalent was to be administered every 2 waking hours for the first two weeks post-implantation, followed by administration every 4 waking hours for 2-4 weeks. The prednisolone acetate (1%) was to be gradually tapered over the next 4 to 6 weeks for a total duration of postoperative steroid treatment of approximately 3 months. Homatropine 5% or a similar drug was to be administered twice daily for 4 to 6 weeks postoperatively. If homatropine was inadequate to maintain cycloplegia, the use of atropine was allowed. The Investigator exercised clinical judgment in deciding if a more moderate or rapid tapering of the topical steroid regimen was indicated for some subjects, particularly in eyes with signs of medicamentosa.

FDA had concerns about the aggressive postoperative regimen of ophthalmic steroids. The sponsor was asked to provide FDA with information regarding the presence or absence of medicamentosa and/or any other complications resulting from such an intense postoperative medication regimen. The sponsor responded to this issue in Amendment #2 by stating that there were no cases of medicamentosa and no other complications related to the post-operative medication regimen reported in the clinical trial. The recommendation for intense post-operative regimen will be reflected in the labeling.

Subjects were followed and evaluated according to the following schedule:

Preoperative Evaluation	Day -90 to Day 0
Operative Evaluation	Day 0
Day 1	24 to 36 hours postoperative
Day 7	4 to 10 days postoperative
1 month	2 to 6 weeks postoperative
3 months	6 to 18 weeks postoperative
Vision training	Week 1, 2, 4, 6, 10 and 12, +/- 4 days
6 months	18 to 32 weeks postoperative
9 months	32 to 44 weeks postoperative
12 months	44 to 56 weeks postoperative
18 months	66 to 78 weeks postoperative
24 months	84 to 102 weeks postoperative

Specular microscopy was performed preoperatively and at the Month 3, 6, 9, 12, 18 and 24 examinations in the treated and fellow eyes with the non-contact Konan or Topcon Specular Microscope. Three images were obtained at each visit. Specular micrographs were sent to a central reading center (B. McCarey, Ph.D., Emory University) for analysis and the mean density from all three images was used for statistical analyses.

Sites were instructed to take three acceptable images at each visit. The mean density from the three images was used for the analysis. A central reading center performed the analyses and conducted the cell counts according to a preordained methodology.

e. Clinical study results

A total of 218 consecutive subjects were enrolled at 28 U.S. clinical sites. Twelve (12) of the 218 enrolled eyes were excluded from further analyses, resulting in a study population of 206 eyes of 206 enrolled subjects. Of the 12 excluded subjects, one subject canceled surgery, in 5 eyes the IMT was not implanted due to surgical complications, and in 6 eyes the IMT was removed at the time of surgery. Of the 206 eyes comprising study population, 115 eyes were implanted with the WA 2.2X and 91 eyes were implanted with the WA 3.0X.

At the time of database lock, 194 eyes had reached the 12-month follow-up, 180 eyes had reached the 18-month follow-up examination and 148 eyes had reached 24-month follow-up. Based on statistical modeling, (generalized estimating equation [GEE] and regression methods), a determination was made by FDA that the PMA could be submitted with these numbers of subjects at the corresponding follow-up periods.

i. Accountability

Accountability for this study was $\geq$ 98.5% for visits through 6 months, 97.0% (196/202) at 9 months, 97.5% (194/199) at 12 months, 91.4% (180/197) at 18 months, and 95.5% (148/155) at 24 months. A total of 16 subjects have been discontinued from the study, including 10 subjects who died during the course of follow-up and 6 subjects who discontinued following removal of the IMT prior to study completion. A total of 8 subjects had the IMT explanted postoperatively. Six (6) of these 8 subjects were discontinued from the study before completing required follow-up.

ii. Demographics

Demographically, 108 (52.4%) subjects were male and 98 (47.6%) were female. The mean age was 75.4 years (standard deviation (S.D.) 7.2, range 55 – 93 years). The majority of subjects were Caucasian (198/206 or 96.1%); 1.9% of the study population was Hispanic, 1.5% was black and 0.5% was Asian. The left eye has undergone IMT implantation more frequently than the right eye (52.4% versus 47.6%).

iii. Pre-operative/ Operative Parameters

Preoperative clinical analysis shows that the average anterior chamber depth (ACD) was 3.15 mm (S.D. 0.37 mm, range 2.48 - 4.74 mm). Preoperative axial length, determined by A-scan, was 23.74 mm (S.D. 0.93, range 21.53 – 26.14 mm). The major form of AMD represented was described as disciform scar only (n=91 or 44.2%), or geographic atrophy only (n=78 or 37.9%). Cataract type was specified as

nuclear in the vast majority of eyes (n=203 or 98.5%). At baseline, mean BCDVA was 20/312, mean BCNVA at 8 inches was 20/315 and mean BCNVA at 16 inches was 20/262.

The operative characteristics of the study cohort show that a limbal insertion was performed in 63.6% (131/206) of the study subjects, and the remaining eyes (36.4% or 75/206) underwent scleral tunneling. In 100% of eyes (206/206) the crystalline lens was extracted via conventional phacoemulsification techniques. In 87 eyes (87/206 or 42.2%), Healon V alone or in combination with another viscoelastic was used during the procedure. Mean capsulorhexis size was 6.6 mm (S.D. 0.59 mm; range 5.0 – 8.5 mm). In most eyes (203/206 or 98.5%) the iris position was flat following IMT implantation. The superior loop of the haptic was reported to be in the bag in 96.1% (198/206) of eyes and the inferior loop of the haptic was in the bag in 97.6% (201/206). The IMT position was reportedly centered in 99.5% (205/206) of eyes. As required in the study protocol, iridectomy was performed in all but 4 (1.9%) study eyes. Other surgical procedures performed at the time of IMT implantation consisted of pupil stretch and lysis of peripheral anterior synechiae.

iv. Effectiveness outcomes

Improvement of 2 lines or greater in either near or distance best corrected acuity was reported for 89.1% of eyes at 6 months, 89.7% at 9 months, and 90.1% at 12 months, 87.2% at 18 months and 85.7% at 24 months.

Eyes with profound visual impairment (pre-op BCDVA worse than 20/400) showed a significantly higher success rate at 12 and 18 months than eyes with moderate impairment (pre-op BCDVA 20/80 to 20/160) at baseline. This trend continued at 24 months.

SUMMARY OF VISUAL ACUITY EFFECTIVENESS ENDPOINTS

BCVA Endpoints	6 Months n (%) % CI	9 Months n (%) % CI	12 Months n (%) % CI	18 Months n (%) % CI	24 Months n (%) % CI
Effectiveness (N=)	201	195	192	179	147
Overall Effectiveness Endpoint ≥2 lines gain of BCDVA or BCNVA*	***179 (89.1%) 84.7%, 92.5%***	***175 (89.7%) 85.4%, 93.1%***	***173 (90.1%) 85.8%, 93.4%***	***156 (87.2%) 82.3%, 91.1%***	***126 (85.7%) 80.1%, 90.2%***
Binomial exact p-value for Ha: > 50%	***<.0001***	***<.0001***	***<.0001***	***<.0001***	***<.0001***
≥2 lines gain of BCDVA and BCNVA*	138 (68.7%) 62.8%, 74.1%	134 (68.7%) 62.8%, 74.2%	141 (73.4%) 67.7%, 78.6%	127 (70.9%) 64.9%, 76.5%	99 (67.3%) 60.4%, 73.7%
Not reported/IMT removal	1	1	2	1	1
Total	202	196	194	180	148

Best Corrected Distance Visual Acuity (BCDVA)

At 6 months 156/201 (77.6%) eyes gained at least two lines of BCDVA, 126/201 (62.7%) gained at least three lines of BCDVA, 79/201 (39.3%) gained at least four lines of BCDVA, 40/201 (19.9%) gained at least five lines of BCDVA, and 14/201 (7.0%) gained at least six lines of BCDVA. At 12 months, 155/193 (80.3%) eyes gained at least two lines, 128/193 (66.3%) eyes gained at least three lines, 87/193 (45.1%) eyes gained at least four lines, 49/193 (25.4%) eyes gained at least five lines, and 21/193 (10.9%) gained at least 6 lines of BCDVA. Similar outcomes were reported at 18 and 24 months, with approximately 75% of eyes gaining at least 2 lines, over 60% gaining at least 3 lines, over 40% gaining $\geq$ 4 lines, about 20% with a gain of $\geq$ 5 lines and approximately 10% with a gain of at least 6 lines of BCDVA. The mean increase in lines of BCDVA was 3.3 lines (S.D. 2.1) at 6 months, 3.3 lines (S.D. 2.3) at 9 months, 3.4 lines (S.D. 2.3) at 12 months, 3.3 lines (S.D. 2.2) at 18 months, and 3.1 lines (S.D. 2.2) at 24 months. These gains in BCDVA were both statistically and clinically significant.

Stratification by age at implant or gender did not affect the improvement in BCDVA. When BCDVA was stratified by the two IMT models, i.e., WA 3.0X and WA 2.2X, better visual outcomes were observed in subjects implanted with the WA 3.0X at 12 and 18 months

At 12 months, 20.0% of subjects with moderate impairment gained three or more lines of BCDVA. Sixty-one and eight tenths percent (61.8%) of subjects with severe impairment (pre-op BCDVA 20/161 to 20/400) gained three or more lines of BCDVA and 88.9% of subjects with profound impairment gained two or more lines of BCDVA. This difference was statistically significant ($p < 0.001$). At 18 months postop, 26.3% of subjects with moderate impairment and 77.6% of those with profound impairment gained at least three lines of BCDVA. At 24 months, 23.5% of subjects with moderate impairment, 55.4% of eyes with severe impairment, and 76.6% of eyes with profound impairment gained at least three lines of BCDVA. Thus, subjects with profound impairment gained considerably more lines of BCDVA than subjects with moderate impairment at 12, 18 and 24 months.

Best Corrected Near Visual Acuity (BCNVA)

BCNVA was evaluated at both eight (8) and sixteen (16) inches for all of the near measurements (in this section, unless specific distance is indicated, BCNVA refers to both distances). Near visual acuity assessments were based on M values, not on the number of letters correctly read. If only 1 or 2 letters could be read correctly at the 8.0M line, which is the worst line on the reading card used in this study, a visual acuity of 10.0M was recorded. If none of the letters could be read correctly, a visual acuity of 12.5M was recorded.

At 8 inches, a gain of at least 2 lines of BCNVA was reported for 137/201 (68.2%) eyes, a gain of $\geq$ 3 lines of BCNVA was reported for 98/201 (48.8%), a gain of $\geq$ 4

lines of BCNVA was reported for 61/201 (30.3%) eyes, a gain of ≥ 5 lines of BCNVA was reported for 38/201 (18.9%), and a gain of ≥ 6 lines of BCNVA was reported for 18/201 (9.0%) at 6 months. At 12, 18 and 24 months, 70% of eyes had a gain of ≥ 2 lines of BCNVA. A gain of ≥ 3 lines was reported for approximately 50%, a gain of ≥ 4 lines of BCNVA in 35% to 40% of eyes, a gain of ≥ 5 lines in close to 20% of eyes, and a gain of ≥ 6 lines of BCNVA at 8 inches in fewer than 10% of eyes at each of these visits. The mean line increase in BCNVA at 8 inches was stable over time with a gain of 2.3 lines (S.D. 2.6) at 6 months, 2.3 lines (S.D. 2.8) at 9 months, 2.4 lines (S.D. 2.9) at 12 months, 2.4 lines (S.D. 2.7) at 18 months, and 2.3 lines (S.D. 3.0) at 24 months.

At 24 months, subjects with profound impairment gained considerably more lines of BCNVA at 8" than subjects with moderate impairment. The mean line increase in BCNVA at 16 inches was 2.1 lines (S.D. 2.4) at 6 months, 2.4 lines (S.D. 2.4) at 9 months, 2.4 lines (S.D. 2.5) at 12 months, 2.3 lines (S.D. 2.4) at 18 months, and 2.3 lines (S.D. 2.6) at 24 months. A gain of ≥ 2 lines of BCNVA at 16 inches was reported for 136/201 (67.7%) eyes. One hundred four (104) of these eyes (51.7%) gained at least three lines, 55 (27.4%) gained at least four lines, 19 (9.5%) gained at least five lines, and 8/201 (4.0%) eyes gained at least six lines of BCNVA at 16 inches. These eyes remained generally stable at 9 months, 12 month, 18 months and 24 months with respect to their gain in lines of acuity. On the average, a third of the implanted eyes gained ≥ 4 lines of BCNVA across the various examination intervals within the investigation. Of particular note is that 10% to 15% of eyes in the study cohort gained 5 or more lines of BCNVA at the 16 inch near testing distance. A gain of 3 or more lines was generally consistent when best corrected near acuity was measured at 8 inches or at 16 inches. The impact of stratification factors was observed at 18 months only. Those eyes implanted with WA 3.0X and eyes with profound impairment gained significantly more lines of BCNVA at 16 inches than eyes implanted with WA 2.0X or moderate impairment respectively.

Improvement in BCDVA and BCNVA

To demonstrate that the IMT can improve both distance and near visual acuity, the improvement in BCNVA at 8 or 16 inches was correlated with the improvement in BCDVA for all eyes at 12 months. Data was available for BCDVA and BCNVA at 12 months for 193 eyes. 83.4% of subjects (161/193) experienced a gain of both best corrected distance and near acuity at 12 months.

At 12 months, a gain of ≥ 2 lines or more in both best corrected distance and near visual acuity was achieved by 73.1% (141/193) of eyes and a gain of or ≥ 3 lines was reported for 52.8% (102/193) of subjects, respectively.

At 18 months, 70.9% (127/179) gained ≥ 2 lines of BCNVA as well as > 2 lines BCDVA. Close to 50% of eyes (89/179) gained ≥ 3 lines of BCDVA and ≥ 3 lines of BCNVA.

At 24 months, 67.3% (99/147) gained ≥ 2 lines of BCNVA with a gain of ≥ 2 lines BCDVA. At 24 months, 51.0% of eyes (75/147) had a gain of ≥ 3 lines of BCDVA with a gain of ≥ 3 lines of BCNVA.

Effect of Pre-operative Parameters on Effectiveness Outcomes

A GEE analysis was performed on the primary effectiveness target for 12 to 24 months. Age at implant, postoperative visit and gender were found to have an effect on the improvement in BCDVA. The moderate impairment group had the lowest success rate among the three preoperative BCDVA groups, with more severely impaired eyes achieving the most significant improvement in vision. Acuity increased from the youngest age group to the oldest age group for subjects with a 2.2X IMT implant. For subjects with a 3.0X IMT implant the improvement in visual acuity among the three younger age groups were similar., but the oldest age group had the lowest success rate among the four age groups. The improvement in visual acuity at 12 months was slightly higher for female subjects than for males. However, the proportion of eyes in female subjects with improvement in visual acuity decreased about 7% at 18 and 24 months, while for males subjects the proportion of eyes achieving an improvement in visual acuity remained relatively constant between 12 and 24 months.

Quality of Life Assessment

The sponsor administered the National Eye Institute Visual Function (NEI-VFQ) and Activities of Daily Living (ADL) Questionnaires.

The VFQ-25 subscales of general vision, near activities, and distance activities have been described as particularly important in demonstrating the difficulty individuals with bilateral severe AMD have in performing daily activities. At 12 months these respective subscales improved by 14.0 points, 11.2 points, and 7.9 points. Additionally, clinically significant improvements across all vision specific subscales (social functioning, mental health, role difficulties, and dependency) were observed. In subscales where no improvement or a decline in performance was expected (color vision, driving and peripheral vision), performance was stable or declined.

The most significant point change in the quality of vision subscales was reported for general vision, followed by near vision activities and distance vision activities. While there was a small decrease in the point change for general vision over the 12 month follow-up period for this instrument, the point change remained relatively stable for near vision activities. Improvement in the vision specific activities subscales of the VFQ-25 was most substantial at 3 and 6 months, perhaps reflecting the noticeable change from baseline in best corrected acuity experienced by the majority of study subjects. There was a slight decrease in the point change for social functioning and mental health at 9 months. However, for the most part, the reported values remained relatively stable over time for all four subscales. When the factors of age, gender, IMT model, preoperative BCDVA and 12-month visual acuity improvement were

analyzed, no effect was found for any of these baseline characteristics on the improvement in the VFQ composite score ($p>0.05$). The sponsor provided a data listing of subjects (n=7) whose overall VFQ-25 composite score worsened by more than 15 points at the last available visit. Of these 7 subjects, 5 experienced improvement in at least one measure of acuity, and the remaining 2 subjects had no change in acuity.

The sponsor presented the mean scores and mean changes in scores for both the NEI-VFQ and ADL Questionnaires. FDA requested that the sponsor provide FDA with the frequency analyses for each rating within each category assessed in the NEI-VFQ and ADL questionnaires for both the scores and change in score analyses. The sponsor did comply with this request and furnished a stratification of each question and the frequency of each response within each category in Amendment #2.

Some questions on items 5, 6, 7, 8, and 9 on the VFQ-25 specifically identify visual activities that are related to the IMT population. For example, with improved visual acuity, one would expect to have an increase in independent mobility, reading street signs and names of stores, and reading ordinary print in newspapers. Subjects reporting extreme difficulty with the items pertaining to visual function generally showed a lessening of this difficulty by one year postop. The number of subjects reporting little and moderate levels of difficulty increased at one year**.** It was unclear from the data reported whether some of the subjects who initially reported extreme difficulty subsequently reported moderate difficulty. FDA requested that the sponsor evaluate pertinent items to determine if the subjects reporting a particular level of difficulty in task performance remained in the same category throughout the first 12 months. The sponsor, however, has not adequately addressed this issue.

Analysis of the ADL outcomes showed improvement from 41.4 (S.D. 15.6) at baseline to 60.2 (S.D. 17.5) at 3 months, 58.6 (S.D. 18.8) at 6 months, 57.3 (S.D. 19.0) at 9 months, and 55.9 (S.D. 19.6) at 12 months. At 12 months, the mean improvement from baseline was 14.1 points. For the subcategory of mobility, the mean score improved from 53.8 (S.D. 19.1) at baseline to 69.7 (S.D. 18.3) at 3 months, 68.0 (S.D. 19.8) at 6 months, 66.8 (S.D. 20.0) at 9 months, and 66.0 (S.D. 20.2) at 12 months. The mobility subscale improved by 12.0 points at 12 months versus baseline. For the subcategory of distance activities, the mean ADL score improved from 43.7 (S.D. 15.5) at baseline to 61.3 (S.D. 18.3) at 3 months, 59.2 (S.D. 19.0) at 6 months, 59.0 (S.D. 19.6) at 9 months, and 57.3 (S.D. 20.2) at 12 months. The distance activities subscale improved by 13.4 points at 12 month versus baseline. The mean score for the subcategory of near activities improved from 30.9 (S.D. 18.6) at baseline to 53.2 (S.D. 20.1) at 3 months, 52.2 (S.D. 22.3) at 6 months, 49.6 (S.D. 22.2) at 9 months, and 48.5 (S.D. 22.8) at 12 months. The scores for near activities improved by 17.0 points at 12 months versus baseline. For all three ADL constructs (mobility, distance activities and near activities) there was a substantial improvement, the largest being for near activities.

During the July 14, 2006 meeting, the Ophthalmic Devices Panel will be asked to discuss the implications, if any, of the Quality of Life Assessment outcomes for the approval of IMT device.

v. Safety outcomes

The proportion of eyes with >2 lines loss of BCDVA and no change/loss of BCNVA, or >2 lines loss of BCNVA and no change/loss of BCDVA, was 4.5% (9/201) at 6 months, 4.6% (9/195) at 9 months, 5.2% (10/193) at 12 months, 4.5% (8/179) at 18 months, and 6.1% (9/147) at 24 months. Loss >2 lines of both BCDVA and BCNVA occurred in 1.0% of eyes at 6 months, 2.1% at 9 months, 1.0% at 12 months, 1.1% at 18 months and 1.4% at 24 months. The proportion of eyes with >2 lines loss of BCDVA and no change of BCNVA was 0.5% at 6 months, 1.0% at 9 months, 0.5% at 12 months, 0.6% at 18 months and 0.0% at 24 months. Finally, the proportion of eyes with >2 lines loss in BCNVA and no change in BCDVA was 3.0% at 6 months, 1.5% at 9 months, 3.6% at 12 months, 2.8% at 18 months and 4.8% at 24 months. Only 3 eyes (3/201 or 1.5%) were reported to have a loss of >2 lines of BCDVA at 6 months. The percentage of eyes with this loss of BCDVA remained relatively stable over the course of follow-up, with 3.1% (6/195) at 9 months, 2.1% (4/193) at 12 months, 2.2% (4/179) at 18 months, and 1.4% (2/147) at 24 months.

SUMMARY OF SAFETY ENDPOINTS

Safety (N=)	201	195	193	179	147
Overall Safety Rate >2 lines loss of BCDVA and no change/loss of BCNVA or >2 lines loss of BCNVA and no change/loss of BCDVA†	***9 (4.5%) 2.4%, 7.7%***	***9 (4.6%) 2.4%, 7.9%***	***10 (5.2%) 2.8%, 8.6%***	***8 (4.5%) 2.2%, 7.9%***	***9 (6.1%) 3.2%, 10.4%***
Binomial exact p-value for Ha: safety rate < 10%	***0.0033***	***0.0048***	***0.0120***	***0.0055***	***0.0696***
>2 lines loss of BCDVA and BCNVA‡	2 (1.0%) 0.2%, 3.1%	4 (2.1%) 0.7%, 4.6%	2 (1.0%) 0.2%, 3.2%	2 (1.1%) 0.2%, 3.5%	2 (1.4%) 0.2%, 4.2%
>2 lines loss of BCDVA and no change in BCNVA§	1 (0.5%) 0.0%, 2.3%	2 (1.0%) 0.2%, 3.2%	1 (0.5%) 0.0%, 2.4%	1 (0.6%) 0.0%, 2.6%	0 (0.0%) 0.0%, 2.0%
>2 lines loss of BCNVA and no change of BCDVA§	6 (3.0%) 1.3%, 5.8%	3 (1.5%) 0.4%, 3.9%	7 (3.6%) 1.7%, 6.7%	5 (2.8%) 1.1%, 5.8%	7 (4.8%) 2.3%, 8.8%
Not reported/IMT removal	1	1	1	1	1
Total	202	196	194	180	148

At 12 months, two eyes (2/193 or 1.0%) experienced a loss of more than 2 lines of both BCDVA and BCNVA at 8 inches *or* 16 inches. The loss of BCNVA at 8 or 16 inches was correlated with the loss of BCDVA at 12 months (n=193) in order to

determine the number of eyes with a loss of more than 2 lines of both BCDVA and BCNVA. The same analysis was conducted for all eyes treated at 18 months. One hundred seventy-nine (179) eyes had both BCDVA and BCNVA measurements at 18 months. Of these 179 eyes, two (1.1%) experienced a loss of more than 2 lines of both BCDVA and BCNVA at 8 inches or 16 inches at 18 months. At 24 months, 2 eyes (4%) of the 147 eyes with BCDVA and BCNVA measurements experienced a loss of more than 2 lines of both best corrected distance and near acuity at 8 inches or 16 inches. Only 5 study eyes lost more than 2 lines of both BCDVA and BCNVA during the course of the study.

Summary of Adverse Events and Complications

Adverse events are tabulated in Attachment A. There were two cases of corneal decompensation resulting in two corneal transplants. Operatively, there were 2 (1.0%) adverse events. These adverse events consisted of an IMT with condensation on the device and an IMT with a broken haptic, both of which required replacement. These are further described in section 18.7, Device Failures.

There were 8 IMT explants. Four subjects (008-207, 008-208, 010-206, 012-210) requested removal of the IMT since they were dissatisfied with the device. In 2 of these 4 eyes, visual acuity was improved from baseline and in the other 2 eyes, visual acuity had decreased from baseline. The IMT was removed from two eyes (013-202, 023-217) due to condensation of the telescope portion of the IMT (see Section 18.7: Device Failure). Removal of the IMT was also performed in the eyes (013-209, 031-203) that underwent corneal transplantation as a result of corneal decompensation.

The most prevalent complication reported (see Attachment B) for the study population consisted of increased IOP requiring treatment within the first week after surgery, with 50 cases (24.3%) reported at Day 1 and 14 cases (6.8%) reported at Day 7. Reports of increased IOP requiring treatment occurring beyond 7 days were classified as adverse events. The sponsor believes that the increase in IOP is related to the use of high molecular weight viscoelastic material (Healon V) used in the eye and to coat the IMT.

Posterior Capsular Opacification

Posterior capsule opacification (PCO) was reported in a single eye (1/174 or 0.6%) at 18 months and in two eyes (2/147 or 1.4%) at 24 months. Both cases were graded "moderate." No Nd:YAG capsulotomies were performed during the study. Nd:YAG laser was used to re-open the peripheral iridectomy in seven eyes.

While the clinical trial did not report any severe occurrences of PCO, the sponsor was asked to provide FDA with a treatment approach for visually significant PCO. Specifically, the sponsor was asked if a YAG capsulotomy can be performed. If a YAG cannot be performed, how can the issue of posterior capsule opacification (PCO) be clinically addressed? Additionally, the sponsor was asked to explain why

they believe that IMT may inhibit the development of PCO. The sponsor responded to these issues in Amendment #2 as follows:

"The clinical trial report presented a rate of PCO development of 0.5% (1/206) as a complication in Table A46 of the PMA application. This case was graded as mild by the investigator and did not require any interventional strategies… Categorized as slit lamp findings, there were 32 other eyes reported as having PCO most of which were described as minimal (30/32; 93.8%). Of these 32 eyes, two (2) were graded as moderate. At the last available visit, 24 of the 32 eyes did not show any PCO. This indicates that there was significant discrepancy in reporting. This leaves eight (8) eyes remaining with PCO --- 6 were minimal and 2 were considered moderate. In these eight (8) cases, there were no visual sequelae."

FDA asked for clarification as to why 2 eyes with moderate PCO reported as a slit lamp finding were not included with the one case of PCO reported as a complication. This was addressed by the sponsor in a subsequent amendment as follows:

"The reason for inclusion of only this single case as a complication is that the other cases of PCO were not identified by the study investigators as complications on the case report forms, and were therefore tabulated separately based on the slit lamp findings (M4, Volume 2, page 156, Table A24F --- Posterior Capsular Opacification). The case report form for the IMT-002 clinical study provided a grading scale of none, minimal, moderate, or severe for grading of posterior capsule opacification. Based on this grading scale, and FDA's request, the rate of PCO has been revised to include all slit lamp findings of PCO graded as minimal or higher that persisted. Thus, Table 46 (Ocular Complications) has been revised to include the 8 study eyes with PCO (6 minimal and 2 moderate) that were present at the last available visit…"

With regard to the IMT's affect on PCO, the sponsor points to the physical design of the IMT. The sponsor claims that they utilized specific design objectives to minimize the occurrence of PCO. The primary elements included the biocompatibility of the material used, the geometry of the device, its alignment with the capsular bag in order to minimize cell migration, and surgeon related factors. Based on these factors, the IMT was designed using fused silica quartz and a tight radius edge design on the posterior aspect of the IMT which is in contact with the capsular bag. The IMT has a loop configuration and angulation producing wide contact with the capsular bag and keeping it taut and in contact with the tight radius edge posterior window. Additionally, surgeons were trained in implantation of the IMT. Careful cleaning and polishing of the capsular bag, along with meticulous removal of viscoelastic was stressed. Surgeons were also taught not to fire Nd:YAG laser through the optics of the telescope because they would damage it.

With respect to treatment of PCO, should it develop, the sponsor provided the following response:

"YAG capsulotomy has not been performed on any IMT implanted subjects as of the writing of this report. However, the feasibility of performing YAG laser capsulotomy and/or iridectomy has been examined in a rabbit study. YAG capsulotomy was successfully performed in 8 rabbit eyes implanted with the IMT. The results of this study were reported in the Journal of Cataract and Refractive Surgery (2003). The YAG capsulotomy can be performed by focusing the laser beam on the posterior capsule, and aiming and firing the laser through the periphery of the telescope but making sure that the beam does not pass through the optical components of the telescope. The actual procedure for performing the YAG in this manner has been developed. The following method is proposed:

- Maximally dilate the pupil.
- Ensure that there are no adhesions between the pupillary margin of the iris and the telescope apparatus. If adhesions are present, carefully dissect the adhesions with the laser.
- Aim the laser and the posterior capsule and fire the laser around the periphery of the telescope.
- Avoid contact between the laser and optical glass elements of the telescope.
- Do not aim and fire the laser through the optical telescope member of the IMT. (The laser can be aimed through and fired through the PMMA carrier plate and haptics.)
- Needling may be required to complete dislodgement of the membrane from the posterior aspect of the IMT. If needling is utilized, special care should be taken to minimize any force or scratching on the posterior window which could result in damage to the posterior window. Needling may also be used to remove a secondary cataract, either alone or in conjunction with a YAG procedure. "

During the course of the IMT study, needling was utilized in 2 subjects with visually significant PCO. One patient had completed Phase I and the other completed the study through Phase II. The first patient successfully underwent the needling procedure. The second patient who completed the entire 24 month protocol underwent needling with a pars plana approach two months following completion of the study. FDA informed the sponsor that 2 events of needling should have been reported in the original list of adverse events and secondary surgical interventions necessary for management of PCO. The sponsor has revised the Professional Use Information to include a description of cases of visually significant PCO requiring the needling procedure.

The sponsor plans on modifying the patient labeling in the following manner so as to properly inform subjects of the potential for PCO and how it will be managed should it develop:

"A laser may be used to make an opening in the membrane behind the implant, which may improve vision. This laser procedure is usually performed in the office. The procedure takes only a short time and does not require anesthetic. This procedure is

known as YAG capsulotomy. Your physician may decide the cloudy membrane is not suitable for laser treatment and may perform an outpatient surgical procedure using conventional surgical instruments that requires local anesthetic."

During the July 14, 2006 meeting, the Ophthalmic Devices Panel will be asked to discuss the implications of developing of PCO secondary to IMT implantation.

Endothelial Cell Density

The mean decrease in ECD for the total population of study eyes was 25.3% at 1 year which is higher than the target endpoint of ≤ 17%. The mean change from baseline to 3 months was 20.0% (S.D. 21.1%), increasing slightly to 22.4% (S.D. 20.9%) at 6 months and to 24.4% (S.D. 20.5%) at 9 months. The percent change in ECD from baseline to 12 months was 25.3% (S.D. 21.3%), from baseline to 18 months was 25.2% (S.D. 22.2%), and from baseline to 24 months was 28.2% (S.D. 22.5%).

PERCENTAGE CHANGE IN ECD FROM BASELINE (MEAN, SD)
ALL EYES IMPLANTED WITH IMT

ECD % Change from Baseline	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	192	198	190	186	180	144
Mean	-20.0%	-22.4%	-24.4%	-25.3%	-25.2%	-28.2%
Standard Deviation	21.1%	20.9%	20.5%	21.3%	22.2%	22.5%
90% confidence interval for mean	-22.5%, -17.5%	-24.8%, -19.9%	-26.9%, -22.0%	-27.9%, -22.7%	-28.0%, -22.5%	-31.3%, -25.1%
Median	-13.0%	-17.0%	-19.2%	-20.9%	-21.3%	-24.2%
Range	-85.1%, 18.0%	-84.4%, 30.9%	-87.5%, 13.5%	-87.6%, 12.7%	-87.9%, 25.1%	-80.9%, 28.1%
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Decrease >40%	34 (17.7%)	36 (18.2%)	37 (19.5%)	40 (21.5%)	36 (20.0%)	37 (25.7%)
Decrease 30.01% to 40%	17 (8.9%)	21 (10.6%)	24 (12.6%)	26 (14.0%)	27 (15.0%)	19 (13.2%)
Decrease 20.01% to 30%	25 (13.0%)	28 (14.1%)	31 (16.3%)	30 (16.1%)	30 (16.7%)	28 (19.4%)
Decrease 10.01% to 20%	36 (18.8%)	48 (24.2%)	45 (23.7%)	41 (22.0%)	32 (17.8%)	26 (18.1%)
Decrease 0.01% to 10%	55 (28.6%)	53 (26.8%)	42 (22.1%)	38 (20.4%)	44 (24.4%)	27 (18.8%)
Increase 0.0% to 10%	20 (10.4%)	8 (4.0%)	8 (4.2%)	10 (5.4%)	8 (4.4%)	5 (3.5%)
Increase 10.01% to 20%	5 (2.6%)	3 (1.5%)	3 (1.6%)	1 (0.5%)	2 (1.1%)	1 (0.7%)
Increase 20.01% to 30%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.7%)
Increase 30.01% to 40%	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase >40%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N = number of successful IMT implanted eyes returned for the visit with non-missing ECD change from baseline.
Percentage change in ECD from baseline = (postop - baseline) ÷baseline ×100.
% = n ÷N ×100

PERCENTAGE CHANGE IN ECD FROM BASELINE (MEAN, SD)
24-MONTH CONSISTENT COHORT OF EYES IMPLANTED WITH IMT

ECD % Change from Baseline	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	130	130	130	130	130	130
Mean	-19.6%	-22.4%	-24.5%	-26.4%	-25.9%	-28.2%
Standard Deviation	21.5%	21.8%	21.6%	22.2%	23.0%	22.7%
90% confidence interval for mean	-22.7%, -16.5%	-25.6%, -19.2%	-27.6%, -21.3%	-29.6%, -23.1%	-29.2%, -22.5%	-31.5%, -24.9%
Median	-12.4%	-15.8%	-18.9%	-22.2%	-22.0%	-24.2%
Range	-74.9%, 12.8%	-82.5%, 30.9%	-87.5%, 11.6%	-87.4%, 12.7%	-80.5%, 25.1%	-80.9%, 28.1%
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Decrease >40%	26 (20.0%)	26 (20.0%)	29 (22.3%)	32 (24.6%)	28 (21.5%)	33 (25.4%)
Decrease 30.01% to 40%	9 (6.9%)	13 (10.0%)	11 (8.5%)	16 (12.3%)	21 (16.2%)	17 (13.1%)
Decrease 20.01% to 30%	13 (10.0%)	17 (13.1%)	20 (15.4%)	24 (18.5%)	21 (16.2%)	26 (20.0%)
Decrease 10.01% to 20%	25 (19.2%)	30 (23.1%)	30 (23.1%)	23 (17.7%)	19 (14.6%)	24 (18.5%)
Decrease 0.01% to 10%	37 (28.5%)	34 (26.2%)	32 (24.6%)	26 (20.0%)	30 (23.1%)	23 (17.7%)
Increase 0.0% to 10%	16 (12.3%)	6 (4.6%)	6 (4.6%)	8 (6.2%)	8 (6.2%)	5 (3.8%)
Increase 10.01% to 20%	4 (3.1%)	3 (2.3%)	2 (1.5%)	1 (0.8%)	2 (1.5%)	1 (0.8%)
Increase 20.01% to 30%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)
Increase 30.01% to 40%	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase >40%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N = number of successful IMT implanted eyes with ECD change from baseline at all visits.
Percentage change in ECD from baseline = (postop - baseline) ÷baseline ×100.
% = n ÷N ×100

Corneal edema at Day 1 postop, and surgical order/experience were identified as major factors that appeared to be associated with the immediate postoperative ECD losses. These analyses in the original submission prompted further statistical investigation. FDA requested more sophisticated analysis from the sponsor. See the Statistics section on endothelial cell loss (§6.d & e) for a more complete discussion of factors that were related to cell loss.

ECD loss increased substantially with increasing corneal edema on postoperative day 1; based on the ANOVA (analysis of variance) this observation proved to be statistically significant at 3 months ($p<0.0001$), 6 months ($p<0.0001$), and 9 months ($p=0.0001$). Group wise comparisons also showed a statistical difference in normal vs. 2+ edema, and 1+ edema vs. 2+ edema at 3, 6 and 9 months.

Stratification of ECD by incision type was also performed, by comparing mean ECD following limbal insertion to scleral tunneling. While no statistically significant differences were found, reduction in ECD was lower in eyes with limbal incisions at 9 months. Interestingly, anecdotal comments have been made by a number of the study surgeons that limbal incisions may be safer and less traumatic to the corneal endothelium, since less manipulation of the endothelium is likely to occur due to the geometry of the incision. Incision size was also stratified into two groups --- <12mm and ≥12mm. In this analysis (incision size) significance was demonstrated at 3, 6 and 9 months postop ($p<.0442$, 0.0417, 0.0499 respectively). The larger incision sizes produced greater losses from baseline as compared to smaller incision sizes (<12mm).

Comparison of mean changes in ECD from baseline stratified by ACD reveals a clinically significant trend for all post-op intervals. In the table below, constructed by FDA, eyes with ACDs of >3.5mm as compared to eyes with less than 3.0mm have clinically significant less ECD loss (from 3.8% to 7.7%). Eyes with ACDs >3.0mm - 3.50mm showed clinically significant less ECD loss as compared to ACDs of ≤3.0 mm (ranging from 2.0% to 6.3% with the exception of 18 months, where the difference was only 0.6%).

Postop Interval	**Anterior Chamber Depth**		
	≤3.00mm **Mean ECD loss (SD)** *90% C.I.*	**>3.00-3.50mm** **Difference in Mean ECD loss**	**>3.50mm** **Difference in Mean ECD loss**
3 months	-22.1% (21.9%) -26.2%, -18.1%	**2.8% less ECD loss**	**5.2% less ECD loss**
6 months	-26.3% (22.9%) -30.5%, -22.0%	**6.3% less ECD loss**	**7.5% less ECD loss**
12 months	-26.1% (21.6%) -30.2%, -22.0%	**2.0% less ECD loss**	**5.0 less ECD loss**
18 months	-27.0% (24.0%) -30.6%, -21.1%	**0.6% less ECD loss**	**3.8% less ECD loss**
24 months	-31.7% (25.5%) -37.5%, -25.8%	**2.5% less ECD loss**	**7.7% less ECD loss**

In the April 26th Amendment (p. 29), the sponsor provided a regression analysis modeling percent ECD loss as a function of ACD. The relationship between ACD and ECD loss was found to be highly significant.

The major safety concern is the ongoing loss of ECD and its impact on the corneal integrity and subsequently, the vision of those implanted with the IMT. Those results are presented in Section 6, Statistics.

Due to the potential corneal decompensation, ECD < 1,000 cells/mm^2 was of a particular concern to FDA. Sponsor reported ECD < 1,000 cells/mm^2 in a total of 29 IMT-implanted eyes at any postoperative visit (Table 27 of August 2005 submission below), with 18 eyes having this ECD at 24 months.. The majority of eyes with ECD < 1000 cells/mm^2 (65.5% or 19/29) had Day 1 edema of grade 2+ or more, as compared to only 18.6% (33/177) of eyes with ECD greater than 1,000 cells/mm.^{2}

ENDOTHELIAL CELL DENSITY (MEAN, SD)
ALL EYES IMPLANTED WITH IMT

ECD	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	206	192	198	190	186	180	144
Mean	2496.13	1996.87	1936.83	1890.82	1871.29	1878.11	1786.36
Standard Deviation	354.33	585.92	579.73	572.29	592.09	618.22	602.61
Median	2510.0	2026.3	2017.8	1938.8	1929.5	1977.5	1860.0
Range	1695.0, 3356.0	432.3, 3125.7	385.3, 2935.7	309.0, 3008.0	310.7, 2959.0	351.0, 2900.0	385.7, 2930.0
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥3000	13 (6.3%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2500 to <3000	92 (44.7%)	44 (22.9%)	35 (17.7%)	27 (14.2%)	29 (15.6%)	31 (17.2%)	17 (11.8%)
2000 to <2500	80 (38.8%)	55 (28.6%)	66 (33.3%)	61 (32.1%)	56 (30.1%)	57 (31.7%)	43 (29.9%)
1500 to <2000	21 (10.2%)	59 (30.7%)	56 (28.3%)	59 (31.1%)	57 (30.6%)	46 (25.6%)	46 (31.9%)
1000 to <1500	0 (0.0%)	17 (8.9%)	24 (12.1%)	26 (13.7%)	23 (12.4%)	25 (13.9%)	20 (13.9%)
<1000	0 (0.0%)	16 (8.3%)	17 (8.6%)	16 (8.4%)	21 (11.3%)	21 (11.7%)	18(12.5%)
95% CI for % of eyes with ECD<1000	0.0%, 1.8%	4.8%, 13.2%	5.1%, 13.4%	4.9%, 13.3%	7.1%, 16.7%	7.4%, 17.3%	7.6%, 19.0%

N = number of successful IMT implanted eyes returned for the visit with non-missing ECD.
% = n ÷N ×100
95% CI was calculated based on Clopper Pearson method.

During the July 14, 2006 meeting, the Ophthalmic Devices Panel will be asked to discuss the impact of ECD losses on the demonstration of the safety of IMT device in the intended population.

vi. Postoperative Vision Rehabilitation

The sponsor's goals for the vision rehabilitation program were to facilitate adjustment to the IMT expeditiously while optimizing function. Traditionally, the professionals direct the rehabilitation. In the IMT trial, the patient was responsible for implementing the rehabilitation program with assistance from the family. The family verified that training was performed and that the home environment (lighting and contrast) was modified to optimize rehabilitation. No validated methods of measuring the outcome of training were utilized in this trial to verify subjects' improvement in their ability to function at home, work, and elsewhere. Therefore, there is no reliable evidence that the vision rehabilitation program as designed and implemented by the sponsor has had any improvement on functional visual performance for subjects in the IMT clinical trial. FDA believes that an effective postoperative rehabilitation program should be focused upon the patient's targeted related to visual function.

The sponsor's training program did not include the use of any of the following professionals to conduct baseline functional abilities: rehabilitation teachers; occupational therapists; rehabilitation counselors; social workers and orientation and mobility specialists. FDA informed the sponsor that state associations and other agencies for the blind and visually impaired are located in almost every state and are resources for providing rehabilitation services. The sponsor believes that there is

limited availability of rehabilitation professionals and that physicians may not be able to comply should labeling require Vision Rehabilitation by professionals. The sponsor, however, does agree that the benefits of the IMT may be maximized by training and has proposed the following labeling: "Low vision rehabilitation services are recommended to maximize the potential for successful use of the IMT."

FDA is concerned about patient adaptation to the increased magnification and the potential associated proprioceptive changes. These effects are known to alter judgment of localization of objects in the visual space, the ability to walk, negotiate curbs and steps, and to read. Therefore, FDA recommended that the labeling should specify that professional vision rehabilitation services should include orientation and mobility as well as reading training.

During the July 14, 2006 meeting, the Ophthalmic Devices Panel will be asked to consider a vision training rehabilitation program as a requirement for IMT implantation.

5. VISION SCIENCE

a. Visual acuity criterion for success

Two IMT versions were implanted: a 2.2-power device that expands the central 24° of field to 54.8° on the retina; a 2.7-power device that expands the central 20° of field to 54° on the retina. These nominal magnification factors predict respective visual acuity improvements of 3.4 lines (0.34 logMAR), and 4.3 lines (0.43 logMAR) from optical considerations alone. In response to FDA's deficiency, the sponsor argued that less than the theoretical improvement should be expected clinically because of the reduced central vision in the study subjects. However, they also provided the following table showing that about 50% of IMT eyes achieved at least the predicted improvement, consistent with the optical magnification.

Table Q17
Improvement of BCDVA or BCNVA of at Least 3.4 Lines for 2.2X Model and Improvement of BCDVA or BCNVA of at Least 4.3 Lines for 3.0X Model
All Eyes Implanted with IMT

	1 Month n/N %	3 Months n/N %	6 Months n/N %	9 Months n/N %	12 Months n/N %	18 Months n/N %	24 Months n/N %
WA 2.2 X, Improved at least 3.4 lines							
BCDVA	29/114 25.4%	48/112 42.9%	50/112 44.6%	50/108 46.3%	57/110 51.8%	48/100 48.0%	37/ 82 45.1%
BCNVA	26/112 23.2%	43/112 38.4%	44/112 39.3%	45/108 41.7%	47/109 43.1%	41/100 41.0%	38/ 82 46.3%
BCDVA or BCNVA	44/114 38.6%	64/112 57.1%	65/112 58.0%	66/108 61.1%	72/110 65.5%	59/100 59.0%	50/ 82 61.0%
WA 3.0 X, Improved at least 4.3 lines							
BCDVA	17/ 91 18.7%	36/ 89 40.4%	38/ 90 42.2%	36/ 88 40.9%	42/ 83 50.6%	35/ 79 44.3%	23/ 65 35.4%
BCNVA	10/ 90 11.1%	22/ 89 24.7%	23/ 90 25.6%	26/ 88 29.5%	24/ 83 28.9%	21/ 79 26.6%	21/ 65 32.3%
BCDVA or BCNVA	23/ 91 25.3%	43/ 89 48.3%	48/ 90 53.3%	48/ 88 54.5%	49/ 83 59.0%	42/ 79 53.2%	31/ 65 47.7%

N = number of treated eyes returned for the visit with a non-missing VA change. % = n ÷N ×100.

The sponsor has proposed safety and effectiveness criteria for visual acuity that are based on the unadjusted preoperative acuity rather than on the acuity predicted from the magnified postoperative retinal image.

During the July 14, 2006 meeting, the Ophthalmic Devices Panel will be asked to consider this question:

- Is preoperative acuity acceptable as a baseline for safety and effectiveness evaluations of acuity, or should an adjusted baseline be used that takes into account the magnification of the retinal image?

b. Binocular visual performance considerations

The IMT was implanted in only one eye of each patient, ostensibly to provide expanded central vision in the implanted eye while allowing normal peripheral vision in the fellow eye. This configuration produces discordant visual input to the two eyes, e.g.: (a) extreme retinal image size differences; (b) unequal image motion from consensual eye movements; (c) permanent loss of patterned input to the peripheral retina of the implanted eye; and (d) permanent limitation of the binocular visual field. Such differences in binocular input are typically related to pronounced binocular rivalry and suppression effects.

The sponsor's strategy to mitigate problems with binocular rivalry, suppression, and magnification differences has been to recommend a self- and family-administered training program in which the subject is supposed to learn to suppress conflicting information in the implanted eye during orientation and mobility tasks, and to suppress conflicting information in the fellow eye during central vision tasks. This strategy depends critically on the assumption that subjects can learn to suppress either eye at will. The sponsor has provided no validation data to show how well IMT subjects learn to control suppression, either by direct measurements or by explicit questions, but argues instead that positive responses to general questionnaires and the lack of spontaneous reports of binocular problems adequately demonstrate the success of the training procedure.

During the July 14, 2006 meeting, the Ophthalmic Devices Panel will be asked to consider these questions:

- Are additional data and analyses needed to assess IMT subjects' ability to use their implanted eye for central vision tasks and their fellow eye for peripheral vision tasks?

6. STATISTICS

VisionCare conducted a prospective multi-center clinical trial IMT-002 under IDE G000115, in which a total of 218 consecutive subjects were enrolled and 206 subjects were implanted at 28 clinical sites and followed at 1 day, 1 week, 1 month, 3 months, 6

months, 9 months, 12 months, 18 months and 24 months postoperatively. Of the 206 eyes, 115 eyes were implanted with 2.2xWA and 91 eyes were implanted with the 3.0x WA device.

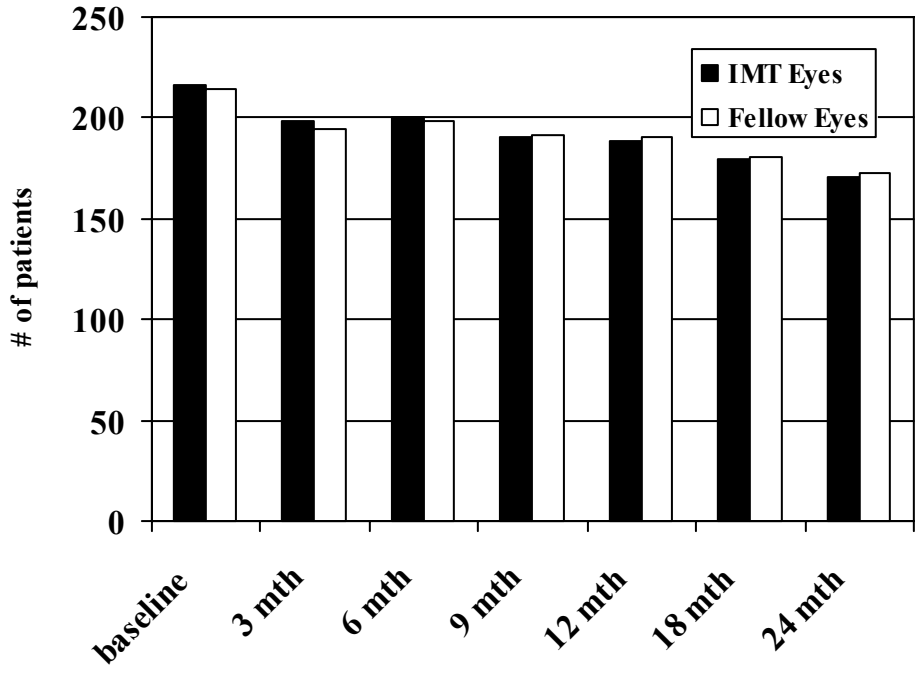
a. **Patient Accountability**

Sponsor's analysis for accountability is defined as the ratio of the number of subjects available for analysis to the number of total enrolled eyes minus discontinued and non-eligible. The result is listed below for each month;

1 month	206/206	=	100%
3 months	201/203	=	99%
6 months	202/202	=	100%
9 months	196/201	=	97.5%
12 months	194/197	=	98.5%
18 months	180/196	=	91.8%
24 months	148/155	=	95.5%.

The sponsor also provided a dataset for both IMT eyes and fellow eyes which have ECD measurements overtime. The accountability of ECD measurements is summarized by the FDA and shown on Figure 1.

FDA Figure 1. Subjects with ECD measurements in Study IMT-002



b. **Primary Effectiveness Endpoint**

Based on the sponsor's table (Table 9-4, Page 32, Volume I) titled "Summary of effectiveness and safety endpoints in visual acuity for all AMD device implanted eyes", the overall success ≥ 2 lines gain in BCDVA, was achieved by 89.1% of eyes at 6 months, by 89.7% at 9 months, 90.1% at 12 months, 87.2% at 18 months and 85.7% at 24 months.

The p-value from the Exact test for the null hypothesis (success rate ≤50%) was < 0.001 at each time point, indicating that the success rate is statistically significantly better than 50%. It indicates that the result significantly surpassed the effectiveness endpoint criterion defined in the protocol.

c. **Primary Safety Endpoint**

The rates of subjects who experienced a loss of more than 2 lines in either near or distance BCVA without a corresponding improvement [gain of 2 or more lines] in the other BCVA), for 6 months, 9 months, 12 months, 18 months and 24 months are 4.5%, 4.6%, 5.2%, 4.5% and 6.1%, respectively. All of these rates are less than the 10% as defined in the protocol.

The p-value from the Exact test for the null hypothesis (safety rate ≥ 10%) was less than 0.05 at the 6, 9, 12 and 18 month follow-up visits, but equal to 0.0696 at the 24 month visit.

The sponsor's results for effectiveness and safety are summarized in Table 9-4 of the submission as follow:

TABLE 9-4
SUMMARY OF EFFECTIVENESS AND SAFETY ENDPOINTS IN VISUAL ACUITY
ALL AMD DEVICE IMPLANTED EYES

BCVA Endpoints	6 Months n (%) % CI	9 Months n (%) % CI	12 Months n (%) % CI	18 Months n (%) % CI	24 Months n (%) % CI
Effectiveness (N=)	201	195	192	179	147
Overall Effectiveness Endpoint (Success Rate) ≥2 lines gain of BCDVA or BCNVA*	*179 (89.1%) 84.7%, 92.5%*	*175 (89.7%) 85.4%, 93.1%*	*173 (90.1%) 85.8%, 93.4%*	*156 (87.2%) 82.3%, 91.1%*	*126 (85.7%) 80.1%, 90.2%*
Binomial exact p-value for Ha: success rate > 50%	*<.0001*	*<.0001*	*<.0001*	*<.0001*	*<.0001*
≥2 lines gain of BCDVA and BCNVA*	138 (68.7%) 62.8%, 74.1%	134 (68.7%) 62.8%, 74.2%	141 (73.4%) 67.7%, 78.6%	127 (70.9%) 64.9%, 76.5%	99 (67.3%) 60.4%, 73.7%
Not reported/IMT removal	1	1	2	1	1
Total	202	196	194	180	148
Safety (N=)	201	195	193	179	147
Overall Safety Rate >2 lines loss of BCDVA and no change/loss of BCNVA or >2 lines loss of BCNVA and no change/loss of BCDVA†	*9 (4.5%) 2.4%, 7.7%*	*9 (4.6%) 2.4%, 7.9%*	*10 (5.2%) 2.8%, 8.6%*	*8 (4.5%) 2.2%, 7.9%*	*9 (6.1%) 3.2%, 10.4%*
Binomial exact p-value for Ha: safety rate < 10%	*0.0033*	*0.0048*	*0.0120*	*0.0055*	*0.0696*
>2 lines loss of BCDVA and BCNVA‡	2 (1.0%) 0.2%, 3.1%	4 (2.1%) 0.7%, 4.6%	2 (1.0%) 0.2%, 3.2%	2 (1.1%) 0.2%, 3.5%	2 (1.4%) 0.2%, 4.2%
>2 lines loss of BCDVA and no change in BCNVA§	1 (0.5%) 0.0%, 2.3%	2 (1.0%) 0.2%, 3.2%	1 (0.5%) 0.0%, 2.4%	1 (0.6%) 0.0%, 2.6%	0 (0.0%) 0.0%, 2.0%
>2 lines loss of BCNVA and no change of BCDVA§	6 (3.0%) 1.3%, 5.8%	3 (1.5%) 0.4%, 3.9%	7 (3.6%) 1.7%, 6.7%	5 (2.8%) 1.1%, 5.8%	7 (4.8%) 2.3%, 8.8%
Not reported/IMT removal	1	1	1	1	1
Total	202	196	194	180	148

For effectiveness, N = number of records with non-missing BCDVA and BCNVA changes from preop. The records with BCDVA gain ≥2 lines and BCNVA missing and the records with BCNVA gain ≥2 lines and BCDVA missing were counted as successful events.
For safety, N = number of records with non-missing BCDVA and BCNVA changes from preop. The records with BCDVA loss > 2 lines and BCNVA missing and the records with BCNVA loss > 2 lines and BCDVA missing were counted as safety events.
Not reported = number of records with missing BCDVA and/or BCNVA changes from preop.
IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately.
Total = number of treated eyes that returned for the visit.
% = n ÷N x100. %CI = 90% confidence interval for %. It was calculated based on Clopper Pearson method.

* BCNVA gain ≥2 lines means that either BCNVA at 8" or BCNVA at 16" gained ≥2 lines.

† No gain in BCNVA means that both BCNVA at 8" and BCNVA at 16" did not gain ≥2 lines. No gain in BCDVA means that BCDVA did not gain ≥2 lines.

‡ >2 lines loss in BCNVA means that one BCNVA (8" or 16" lost > 2 lines without the other BCNVA (8" or 16") gaining ≥2 lines.

§ No change = within a loss of 2 lines to a gain of <2 lines. For BCNVA, it means that both BCNVA at 8" and BCNVA at 16" are within a loss of 2 lines to a gain of <2 lines.

d. **Endothelial Cell Density**

The sponsor provided a series of descriptive statistics for ECD loss in the PMA and subsequent amendments. The results showed that ECD percentage has changed drastically from baseline to 12 months (a 25% decrease) and from baseline to 24 months (a 28.4% decreases) after IMT implantation. In addition, ECD changes from 3 month to 18 month ($p<0.0001$) and from 6 month to 18 month ($p=0.0012$) are statistically significant using a GEE model based comparison. In terms of annual loss, by using 3-24 months data, the annual loss rate is 5.4% with a 95% CI (2%, 8.8%).

The FDA review team requested the sponsor provide some additional analyses on ECD loss after reviewing the PMA submission. The sponsor submitted an amendment on April 25, 2006 to respond to the request. FDA's review of the key statistical issues is provided below:

i. ECD loss from baseline to 3, 12, 18 and 24 months

The percentiles of ECD percentage change from baseline to 3, 12, 18 and 24 months were computed in the reviewer's Table 1. Data were presented for the following groups: IMT eyes, all fellow eyes, fellow eyes pseudo-phakic or phakic eyes. It is noticed that for the IMT eyes at each time point, the percentiles of ECD percentage change is constantly larger than that of the fellow eyes, or pseudophakic or phakic fellow eyes.

FDA Table 1. ECD% Change from Baseline

Change from baseline	3 months	12 months	18 months	24 months
IMT Eyes				
N	193	186	180	171
Worst 5% pts	-66.82%	-68.85%	-74.15%	-74.55%
Worst 10% pts	-51.97%	-57.72%	-59.55%	-58.92%
Median (50th percentile)	-13.50%	-20.90%	-21.32%	-24.00%
All fellow Eyes				
N	189	186	179	171
Worst 5%	-10.07%	-16.31%	-19.49%	-28.48%
Worst 10%	-7.53%	-10.56%	-12.27%	-15.65%
Median (50th percentile)	-0.63%	-1.31%	-1.17%	-2.70%
Pseudophakic Fellow Eyes				
N	33	34	33	30
Worst 5%	-17.65%	-33.78%	-28.75%	-33.03%
Worst 10%	-5.09%	-16.31%	-17.42%	-15.17%

Change from baseline	3 months	12 months	18 months	24 months
Median (50th percentile)	-2.66%	-5.53%	-3.41%	-4.88%
Phakic Fellow Eyes				
N	156	152	146	141
Worst 5%	-9.58%	-13.10%	-13.71%	-26.12%
Worst 10%	-4.48%	-5.15%	-6.47%	-6.39%
Median (50th percentile)	-0.29%	-0.69%	-0.78%	-2.11%

ii. Modeling ECD loss over time

The sponsor provided a mixed model to analyze chronic ECD loss from 3 to 24 months, from 6 to 24 months, and from 9 to 24 months, respectively. ACD and surgeon experience (surgical order) were included as covariates in the models. The results based on these analyses demonstrated that:

- Chronic ECD loss (from 3-24 months, or 6-24 months, or 9-24 months) is statistically significant ($p<0.001$).
- For those who underwent surgery by less experienced surgeon (surgical order $\leq 3^{rd}$), subjects with pre-operative ACD ≤ 3.00 mm had more ECD loss than subjects with pre-operative ACD > 3.0 mm. This effect was not found for subjects in group of surgical order $\geq 4^{th}$.

There is a statistically significant difference in ECD loss between the IMT-implanted eyes and phakic fellow eyes ($p=0.0003$ for 3 to 24 months, $p=0.0132$ for 6 to 24 months and $p=0.186$ for 9 to 24 months). The comparison between the IMT-implanted eyes and the pseudophakic fellow eyes did not show statistically significant differences ($p>0.05$ for all time interval comparisons). However, there are a very limited number of subjects with pseudophakic eyes.

The sponsor also provided prediction results based on their statistical model. The results showed that at 24 months, 20 subjects had ECD less than 1000.

Sponsor's Table: Percentage of subjects with predicted ECD ≤ 1000 for IMT eyes

Baseline Group		3-24 months	6-24 moths	9-24 months
At 2 years	**ECD < Q1**	23 (45.1%)	20 (40.8%)	20 (40.0%)
	ECD in Q1 ~ median	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ECD in Median ~ Q3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ECD > Q3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ECD < Q1	28 (54.9%)	25 (51.0%)	24 (48.0%)

Baseline Group		3-24 months	6-24 moths	9-24 months
3 years	ECD in Q1 ~ median	1 (2.0%)	0 (0.0%)	0 (0.0%)
	ECD in Median ~ Q3	0 (0.0%)	0 (0.0%)	0 (0.0%)
	ECD > Q3	0 (0.0%)	0 (0.0%)	0 (0.0%)
4 years	ECD < Q1	33 (64.7%)	27 (55.1%)	28 (56.0%)
	ECD in Q1 ~ median	3 (6.0%)	0 (0.0%)	0 (0.0%)
	ECD in Median ~ Q3	1 (2.0%)	0 (0.0%)	1 (0.0%)
	ECD > Q3	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note: 3-month groups were based on the quartiles of the predicted 3-month ECD values;
6-month groups were based on the quartiles of the predicted 6-month ECD values;
9-month groups were based on the quartiles of the predicted 9-month ECD values.

However, the sponsor's analyses have the follow limitations:

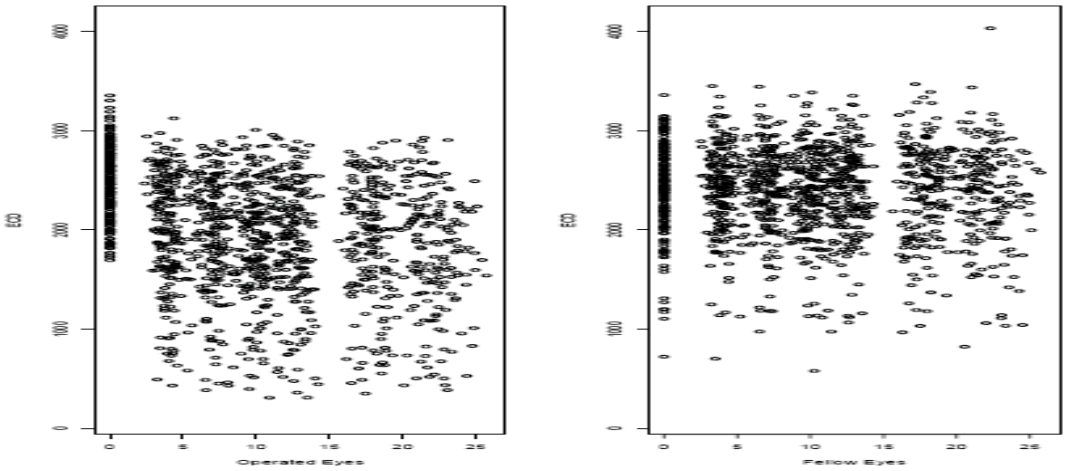
- Analyses on ECD change over time have excluded all baseline ECD values. This exclusion affects the evaluation of the impact of baseline ECD on the total ECD loss.
- Separate analyses on different study periods such as baseline to 3 months and 3 months to 24 months ignore the association (correlation) of these periods. The sponsor had run separate models on operated eyes and fellow eyes.
- There are variations in actual follow-up times vs. nominal visits specified by the study protocol. Actual visit time is preferable in the model to the use of the nominal visit time.

iii. FDA's analyses

In the FDA analysis, all ECD data was included in one model to fully evaluate ECD change over the study period. A mixed effect model was fitted to analyze the ECD data. Using this model, we were able to estimate the rate of ECD change in acute and chronic periods separately. The rates of ECD change between IMT eyes and fellow eyes in different periods can be also compared.

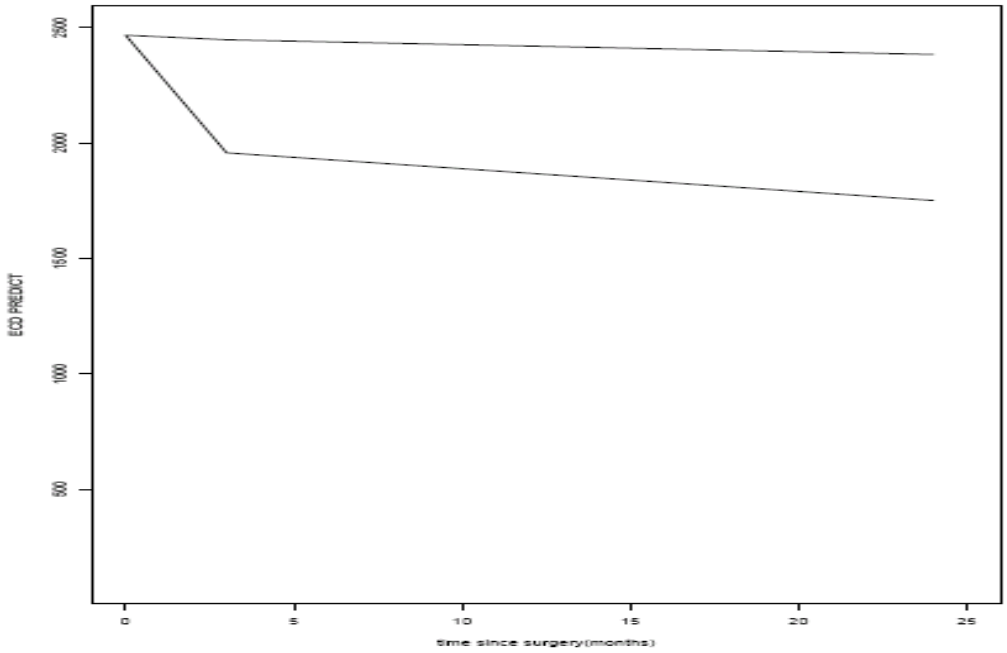
The plots below (Figure 2) describe ECD observations of each subject at each follow-up visit. The left panel is for IMT eyes and the right for fellow eyes.

FDA Figure 2: Observed ECDs for All Eyes



Using a mixed effect model similar to the sponsor's but including the baseline to 3 month data, and assuming two piecewise linear trend in ECD from baseline to 3 months and from 3 to 24 months for both IMT and fellow eyes, we have the fitted model as in Figure 3.

FDA Figure 3: Fitted Model



FDA Table 2. Results of Fitted ECD Model

	Estimate	Estimate	Standard Error	2-sided p-value
Operated Eyes	**Intercept**	2466.89	19.75	<0.0001
	Acute monthly change	-169.81	14.28	<0.0001
	Chronic monthly change	-9.83	1.38	<0.0001
Fellow Eyes	**Acute monthly change**	-6.59	4.61	0.1532
	Chronic monthly change	-3.03	1.05	0.0039

For the group of IMT eyes, there is a significant monthly decrease of 170 cells in ECD from baseline to 3 months ($p<0.0001$, Table 2). And ECD continues to decrease by 9.83 cells per month ($p<0.0001$, Table 2).

FDA Table 3. Comparison of ECD change rates

	2-sided p-value
Acute ECD slopes between Operated & Fellow eyes	<0.0001
Chronic ECD slopes between Operated & Fellow eyes	<0.0001
Operated eyes: acute vs. chronic	<0.0001
Fellow eyes: acute vs. chronic	0.4863

By comparing the rates of ECD change between IMT and fellow eyes (Table 3), it is found that:

- For the group of IMT eyes, rate of acute ECD loss (0-3 months) and rate of chronic ECD loss (3-24 months) are statistically significantly different ($P<0.0001$). However, for the fellow eyes, there is no statistically significant difference between the two periods ($p=0.4863$).
- During the acute period (baseline to 3 months), rates of ECD loss are significantly different between IMT and fellow eyes ($p<0.0001$).
- During the chronic period (3 to 24 months), rates of ECD are still significantly different between IMT and fellow eyes.

The FDA understands that it is always a questionable exercise to extrapolate beyond the range of available data and the prediction results are highly dependent on the model and assumptions. However, some type of extrapolation is necessary to weigh long-term effects. For this purpose, based on the estimates from the

fitted model, Table 4 summarizes the estimated number and percentage of subjects with predicted ECD ≤ 1000 at the end of year 2, 3 and 4.

FDA Table 4: Percentage of subjects with predicted ECD ≤ 1000

Group		Operated eyes (n=216)	Fellow eyes (n=216)
2 years	Overall	24/216 (11.1%)	1/216 (0.5%)
	Baseline ECD < Q1	11/54 (20.4%)	1/54 (1.9%)
	Baseline ECD in Q1 ~ median	4/54 (7.4%)	0
	Baseline ECD in Median ~ Q3	5/54 (9.3%)	0
	Baseline ECD > Q3	4/54 (7.4%)	0
3 years	Overall	38/216 (17.6%)	2/216 (0.9%)
	Baseline ECD < Q1	17/54 (31.5%)	2/54 (3.7%)
	Baseline ECD in Q1 ~ median	8/54 (14.8%)	0
	Baseline ECD in Median ~ Q3	9/54 (16.7%)	0
	Baseline ECD > Q3	4/54 (7.4%)	0
4 years	Overall	49/216 (22.7%)	3/216 (1.4%)
	Baseline ECD < Q1	21/54 (38.9%)	2/54 (3.7%)
	Baseline ECD in Q1 ~ median	12/54 (22.2%)	0
	Baseline ECD in Median ~ Q3	11/54 (20.4%)	1/53 (1.9%)
	Baseline ECD > Q3	5/54 (9.3%)	0

Note: The groups are based on baseline ECD quartiles of IMT and fellow eye groups.

By the end of the study (24 months), 11.1% of the IMT eyes would have ECD ≤ 1000; while the proportion in the fellow eye group would be 0.5%.

Analyses indicate that ECD experienced a drastic decrease from baseline to 3 months. Both the sponsor's and FDA's models found that chronic ECD loss from 3 to 24 months was also significant. It was found that by the end of the study (24 months), some IMT eyes had ECD lower than 1000. This is especially true for those with the worst ECD at baseline (>20%).

e. **Evaluation of the Effect of Anterior Chamber Depth (ACD) on ECD loss**

The sponsor provided a set of regression analyses using ECD percent changes from baseline to 3 months, 3 to 24 months, baseline to 24 months, 6 to 24 months and 9 to 24 months as dependent variables, separately. Independent variables included ACD, surgical order (<=3rd case and >= 4th case) and the interaction of ACD*surgical order. The results

showed that ACD had a linear effect on ECD percentage change from baseline to 3 months for the surgical order group of <= 3rd case (p=0.0081), but not for the surgical order group of >= 4th case (the interaction of ACD*surgical order was not statistically significant). Similar results were observed when ECD percentage change from baseline to 24 months was used as dependent variable (p=0.0304).

f. **Quality of Life**

Trained interviewers, who were not masked, administered the NEI-VFQ to each patient. Subjects were interviewed at baseline, 3 months, 6 months, 12 months and 24 months after enrollment. The NEI-VFQ was designed to be applicable to subjects with a number of different vision-limiting or vision threatening conditions. The results of the quality of life (QoL) analyses showed that the IMT may improve both vision and related QoL scores. The mean change in the general vision subscale at 12 months was 14.1 point improvement with a 95% confidence interval (CI) of 11.0-17.2. The overall composite score change at 12 months was 6.0 points with a 95% CI of 4.0-8.1.

7. POST-APPROVAL STUDIES

The epidemiology review of the VisionCare's PMA submission recommended that if the IMT is approved, a post-approval study should be conducted as a condition of approval for this first-of-a-kind device. The reviewer further recommended that the post market plan include the following two study components:

- continued follow-up of the pre-market clinical study cohort; and
- rigorous follow-up of patients who are implanted with the IMT after approval to address the deficiencies and concerns related to the safety and effectiveness of long-term use of the IMT.

The two post-approval study protocols should address the following elements: objectives, groups and outcomes of interest, study design, study size and representativeness, analysis plan, data collection and validation, patient follow-up, and reporting requirements (interim and final reports).

VisionCare's latest post-market plan is consistent with FDA's recommendations in proposing two follow-up studies of patients.

a. **Continued Follow-up of the Pre-market Clinical Study Cohort**

This continued follow-up study, already in progress, is a one arm, prospective, multi-center clinical study that will provide 3 additional years of follow-up of the 178 patients who participated in the 24-month pivotal study and who were also present at the 24-month follow-up visit. In the evaluation of ECD changes, fellow eyes serve as controls for the IMT implanted eyes. Study participants will be re-consented and examined at the

entry in the continued follow-up study and at months 30, 36, 42, 48, 54 and 60 post-implantation. Selected clinical parameters evaluated in the pivotal study will be evaluated at each visit, including best corrected distance acuity, intraocular pressure, slit lamp examination and specular microscopy, device failures, complications and adverse events. Quality of life will not be evaluated. Objectives of the continued follow-up study of the pivotal study cohort are:

- to determine whether the improvements in visual acuity achieved during the first 24 months of follow-up are sustained through the fifth post operative year, and
- whether there is a reasonable assurance that the effects of IMT implantation and chronic ECD loss do not result in decreases in ECD that fall below the threshold where corneal function is irreversibly compromised.

The sponsor's proposed study does not fully address the following issues:

- Omission of safety and effectiveness endpoints, criteria for success, and testable hypotheses.
- Whether the continued follow-up study has sufficient statistical power to assess long-term effects of IMT on ECD changes that would be clinically significant.
- Whether the ECD data generated by the continued follow-up will provide sufficient assurances about the long-term effects of IMT implantation on ECD under conditions of general use
- Definition of long-term effectiveness outcome in terms of BCDVA, and not in terms of both BCDVA and BCNVA (as defined in the PMA study).
- Use of inappropriate statistical techniques that neither account for the high correlation among repeated measures of ECD in the IMT implanted eye over time nor the high correlation between the IMT implanted eye and the fellow eye in analyses of ECD loss.

b. **Follow-up Patients Receiving the IMT Post Approval**

The second post approval study is designed to characterize the safety and effectiveness of the IMT among the first 500 consecutive patients who receive the IMT after marketing approval (if approved) by following them through the fifth postoperative year. Follow-up of this larger, more diverse patient population will allow the detection of rare and late occurring adverse events. Study participants will be examined at the study entry, day 1, week 1, month 1, 6, 12, 24, 36, 48, and 60. Telephone interviews of all study participants will be conducted at 6 month intervals between annual clinical examinations. The proposed post approval studies differ from the PMA clinical trial in two important ways. First, the sponsor proposes to omit the months 3 and 9 examinations, time points at which the sponsor reported significant changes in ECD. Second, the sponsor proposed not to perform the specular microscopy to assess ECD in the post approval study of new IMT recipients. This would be a serious omission given the concerns about the ECD loss associated with IMT implantation and the failure of the pivotal study to meet the pre-specified protocol criterion for safety (≤ 17% ECD loss at one year). There are no plans

to evaluate the effectiveness of the post implantation visual rehabilitation training designed to help patients with IMT implants to adjust to the IMT.

The sponsor's proposed study does not fully address the following issues:

- Omission of criteria for success for safety endpoints, and of a testable hypotheses for ECD changes
- Omission of study size calculations based on the ability to assess effects of IMT on ECD changes that would be clinically significant (as defined in the PMA study).
- Definition of long-term effectiveness outcome in terms of BCDVA, and not in terms of both BCDVA and BCNVA (as defined in the PMA study).
- Use of inappropriate statistical techniques that neither account for the high correlation among repeated measures of ECD in the IMT implanted eye over time nor the high correlation between the IMT implanted eye and the fellow eye in analyses of ECD loss.
- Lack of a procedure to ensure that all subjects screened for implantation and participation in the post approval study but not enrolled will be described.

ATTACHMENT A: REPORTED OCULAR ADVERSE EVENTS
ALL EYES IMPLANTED WITH IMT

Adverse Events*	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anterior chamber inflammation > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	3 (1.7%)	0 (0.0%)	3 (2.8%)	6 (2.9%)
Choroidal neovascularization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (1.0%)	1 (0.5%)	2 (1.1%)	2 (1.4%)	0 (0.0%)	5 (2.4%)
Conjunctivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	4 (1.9%)
Corneal edema > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	3 (2.0%)	2 (1.8%)	6 (2.9%)
Decrease in visual acuity	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.1%)	3 (2.0%)	2 (1.8%)	4 (1.9%)
Diplopia	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	1 (0.6%)	1 (0.7%)	2 (1.8%)	3 (1.5%)
Distorted pupil	0 (0.0%)	1 (0.5%)	3 (1.5%)	3 (1.5%)	3 (1.5%)	5 (2.5%)	4 (2.0%)	4 (2.1%)	4 (2.2%)	2 (1.4%)	3 (2.8%)	7 (3.4%)
Dry eye	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	6 (3.1%)	4 (2.1%)	3 (1.7%)	1 (0.7%)	4 (3.7%)	10 (4.9%)
Entropion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	3 (1.5%)
Exposed suture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	3 (1.5%)
Eye pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (1.0%)	1 (0.6%)	1 (0.7%)	3 (2.8%)	3 (1.5%)
Foreign body sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)	4 (2.0%)	4 (2.0%)	4 (2.1%)	4 (2.2%)	1 (0.7%)	7 (6.4%)	9 (4.4%)
Guttae	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	7 (3.5%)	8 (4.1%)	13 (6.7%)	11 (6.1%)	9 (6.1%)	3 (2.8%)	16 (7.8%)
IMT removal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.3%)	8 (3.9%)
Increased IOP requiring treatment > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.4%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	2 (1.4%)	3 (2.8%)	7 (3.4%)
Inflammatory deposits on IMT	0 (0.0%)	2 (1.0%)	9 (4.4%)	2 (1.0%)	5 (2.5%)	18 (8.9%)	21 (10.7%)	25 (12.9%)	24 (13.3%)	10 (6.8%)	6 (5.5%)	51 (24.8%)
Iridotomy > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.9%)	3 (1.5%)
Iris atrophy > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)	4 (2.0%)	4 (2.0%)	3 (1.5%)	6 (3.1%)	7 (3.9%)	7 (4.7%)	2 (1.8%)	7 (3.4%)
Iris transillumination defects > 21 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.4%)	9 (4.5%)	9 (4.5%)	9 (4.6%)	8 (4.1%)	8 (4.4%)	6 (4.1%)	2 (1.8%)	11 (5.3%)
Iritis > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	2 (1.0%)	1 (0.5%)	0 (0.0%)	4 (2.2%)	1 (0.7%)	7 (6.4%)	12 (5.8%)
Pigment deposits on IMT	0 (0.0%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	3 (1.5%)	4 (2.0%)	12 (6.1%)	12 (6.2%)	13 (7.2%)	7 (4.7%)	4 (3.7%)	23 (11.2%)
Posterior synechiae	0 (0.0%)	0 (0.0%)	4 (2.0%)	4 (1.9%)	7 (3.5%)	9 (4.5%)	8 (4.1%)	8 (4.1%)	7 (3.9%)	4 (2.7%)	4 (3.7%)	15 (7.3%)
Subconjunctival hemorrhage	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.5%)	9 (4.4%)
Subretinal hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.7%)	1 (0.9%)	3 (1.5%)
Vitreous hemorrhage > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (1.5%)
Vitreous in anterior chamber > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (1.9%)

% = n/N ×100.

The same adverse event could have been reported for a subject at multiple visits.

*The following complications occurred at a rate of ≤ 1.0%: Anterior ischemic optic neuropathy, Corneal decompensation > 7 days, Cyclitic membrane > 7 days, Cystoid macular edema, Device failure, Flat anterior chamber > 21 days, Floaters, Focal striae, IMT dislocation, IMT replacement

ATTACHMENT B: REPORTED OCULAR COMPLICATIONS
ALL EYES IMPLANTED WITH IMT

Complications*	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blepharitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.5%)	3 (1.5%)	2 (1.1%)	3 (2.0%)	2 (1.8%)	7 (3.4%)
Conjunctival injection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	1 (0.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (1.9%)
Corneal abrasion	0 (0.0%)	3 (1.5%)	4 (2.0%)	4 (1.9%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	11 (5.3%)
Corneal edema ≤ 30 days	0 (0.0%)	14 (6.8%)	7 (3.4%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (6.8%)
Corneal endothelial touch	2 (1.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Descemet's membrane separation	3 (1.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Dry eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	2 (1.4%)	0 (0.0%)	3 (1.5%)
Hyphema	0 (0.0%)	8 (3.9%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	10 (4.9%)
Increased IOP requiring treatment ≤ 7 days	0 (0.0%)	50 (24.3%)	14 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	57 (27.7%)
Increased IOP ≤ 15 days	0 (0.0%)	2 (1.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Iridotomy ≤ 7 days	2 (1.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Iris atrophy ≤ 7 days	0 (0.0%)	3 (1.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)
Iris damage	7 (3.4%)	5 (2.4%)	5 (2.4%)	5 (2.4%)	5 (2.5%)	5 (2.5%)	5 (2.6%)	4 (2.1%)	4 (2.2%)	3 (2.0%)	1 (0.9%)	7 (3.4%)
Iris prolapse	6 (2.9%)	3 (1.5%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	12 (5.8%)
Iris transillumination defects ≤ 21 days	0 (0.0%)	4 (1.9%)	6 (2.9%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (3.4%)
Posterior capsular rupture	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	3 (1.5%)
Posterior capsule opacification	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	0 (0.0%)	1 (0.5%)
Significant anterior chamber bleeding	3 (1.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Strabismus surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Suture rupture	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	4 (1.9%)
Vitreous in anterior chamber ≤ 7 days	0 (0.0%)	0 (0.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Watery eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (1.1%)	3 (2.0%)	1 (0.9%)	3 (1.5%)

% = n/N ×100.
The same complication could have been reported for a subject at multiple visits.

The following complications occurred at a rate of ≤ 1.0%: Anterior chamber hemorrhage, Anterior segment neovascularization, Anterior synechiae, Bleb, Blurred vision, Cataract, Cataract removal, Chalazion, Cortical remnants, Cyclitic membrane ≤ 7 days, Cyclodialysis cleft, Disc hemorrhage, Dry eyes, Ectropion, Endothelial folds, Flat anterior chamber ≤ 21 days, Folds in corneal graft, Glaucoma, Haze, Hypertony, Hypotony, Iris incarceration, Iritis ≤ 30 days, Keratitic precipitates on IMT, Ophthalmic migraine, Other, Peribulbar hemorrhage, Peripapillary hemorrhage, Phthisis, Superficial punctate keratitis, Surgical mydriasis, Uveitis, Vitreous bulge, Vitreous loss, Vitreous loss - vitrectomy required, Worsening cataract (fellow eye), Worsening of subretinal scarring, Wound leak