

**FDA OPHTHALMIC DEVICES ADVISORY PANEL
INFORMATION PACKAGE FOR MARCH 27, 2009
REVIEW OF P050034**

**VISIONCARE OPHTHALMIC TECHNOLOGIES
IMPLANTABLE MINIATURE TELESCOPE
(IMT™ BY DR. ISAAC LIPSHITZ)**

VOLUME I OF III

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1.0 BACKGROUND AND INTRODUCTION

End-stage age-related macular degeneration (AMD) is a growing public health problem. No pharmacotherapeutic interventions are available to treat this irreversible stage of AMD (AREDS, 2003; Owen et al, 2003; Evans et al, 2004, Augood et al, 2006). In the most advanced stage of AMD, bilateral scotomas and geographic atrophy cause severe visual impairment. Bi-lateral end-stage AMD affects approximately 60,000 to 80,000 people in the United States each year, most of them elderly (AREDS No. 11, 2003; Schein et al, 2005; Wang et al, 1998). These severe decreases in visual acuity cause reductions in quality of life, increased dependency, and depression (Jager et al, 2008; Williams et al, 1998; Casten et al, 2004; Brown et al, 2000).

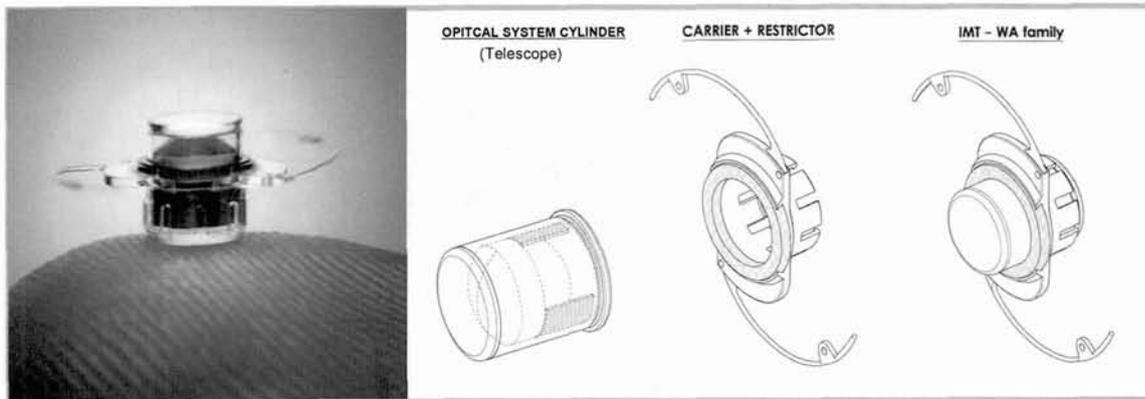
The only interventions currently available to patients with geographic atrophy or disciform scar AMD are vision aids such as special spectacles and external head-mounted or hand-held telescopes. Although these aids are widely available, adoption is limited because they are difficult to use, bulky, uncomfortable, and unattractive. External telescopes require suppression of natural eye movements such that the wearer must learn to scan the visual field by moving the entire head. People who do not properly adapt to this behavioral change requirement may experience a conflict between the visual and vestibular systems resulting in nausea. A Veterans Administration review of visual rehabilitation appliances found no convincing evidence to document the benefits of such appliances (Adams et al, 2003).

VisionCare Ophthalmic Technologies, Inc. has developed the Implantable Miniature Telescope or IMT, to improve vision in patients with moderate (20/80) to profound (20/800) vision impairment due to bilateral end-stage age-related macular degeneration. The device enlarges the retinal image of the central field to reduce the impact of the vision-impairing central scotoma.

The IMT, which is shown in Figure 1, is 4.4 mm long, 3.6 mm in diameter, and has an overall (haptic-to-haptic) diameter of 13.5 mm; the weight of the IMT is 115 mg in air and 60 mg in aqueous humor. The device has three primary elements: the optical system cylinder, the carrier, and a blue light restrictor ring. Materials contacting the aqueous humor are quartz glass (optical cylinder) and PMMA (carrier and light restrictor ring).

There are 2 models of the IMT, the WA (wide-angle) 2.2X and the WA 3.0X (nominally 2.7X). Both models are designed to restore intermediate vision, increasing the ability to view objects several meters away from the patient.

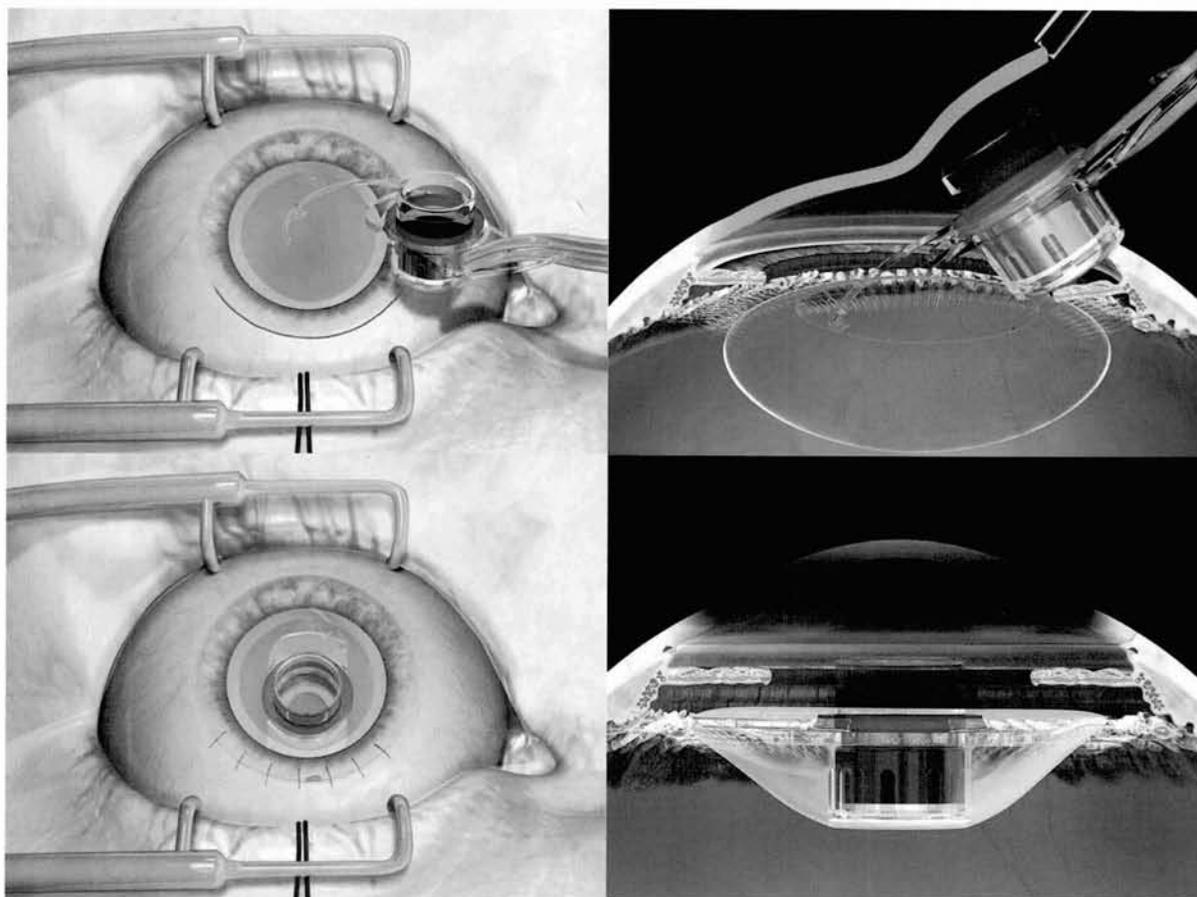
FIGURE 1: IMPLANTABLE TELESCOPE AND COMPONENTS
A013, VOL 1, PAGE 2, FIGURE 1



The IMT is implanted monocularly in the anterior segment for central vision. The fellow eye provides peripheral vision for orientation and mobility. Implantation of the device allows patients to participate in both static and dynamic activities at near, intermediate and distance vision ranges, day or night, indoors or outdoors, without mounted or hand-held appliances.

The IMT is implanted by ophthalmic surgeons in an outpatient procedure under local anesthetics. Utilizing a 12 mm limbal incision, dispersive and cohesive viscoelastics, a 7 mm capsulorrhexis, and cataract extraction by phacoemulsification, the implantable telescope is surgically positioned within the capsular bag. The IMT typically protrudes through the pupil, with clearance of approximately 2.5 mm between the device and the corneal endothelium (Figure 2).

FIGURE 2: SURGICAL PROCEDURE AND DEVICE POSITION
A013, VOL 1, PAGE 3, FIGURE 2

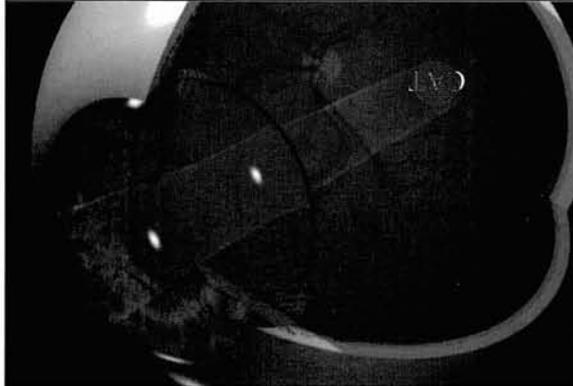


Once implanted, the optical system of the IMT, in conjunction with the cornea, functions as a fixed focus telephoto system that enlarges the object in the patient's central visual field. The IMT projects a magnified image onto a large area of the retina, approximately 54° (Figure 3). The high-resolution images and relatively large viewable central visual field resulting from the device's intraocular placement and wide-angle design, allow patients to recognize and identify objects that they could not otherwise see with their natural lens or an intraocular lens (IOL).

FIGURE 3: IMAGE ON SCARRED MACULA AND IMAGE ON IMT IMPLANTED EYE RETINA
A013, VOL 1, PAGE 4, FIGURE 3

Scarred Macula

Central Visual Field Projection with Natural Lens/IOL



Wide-Angle Implantable Telescope

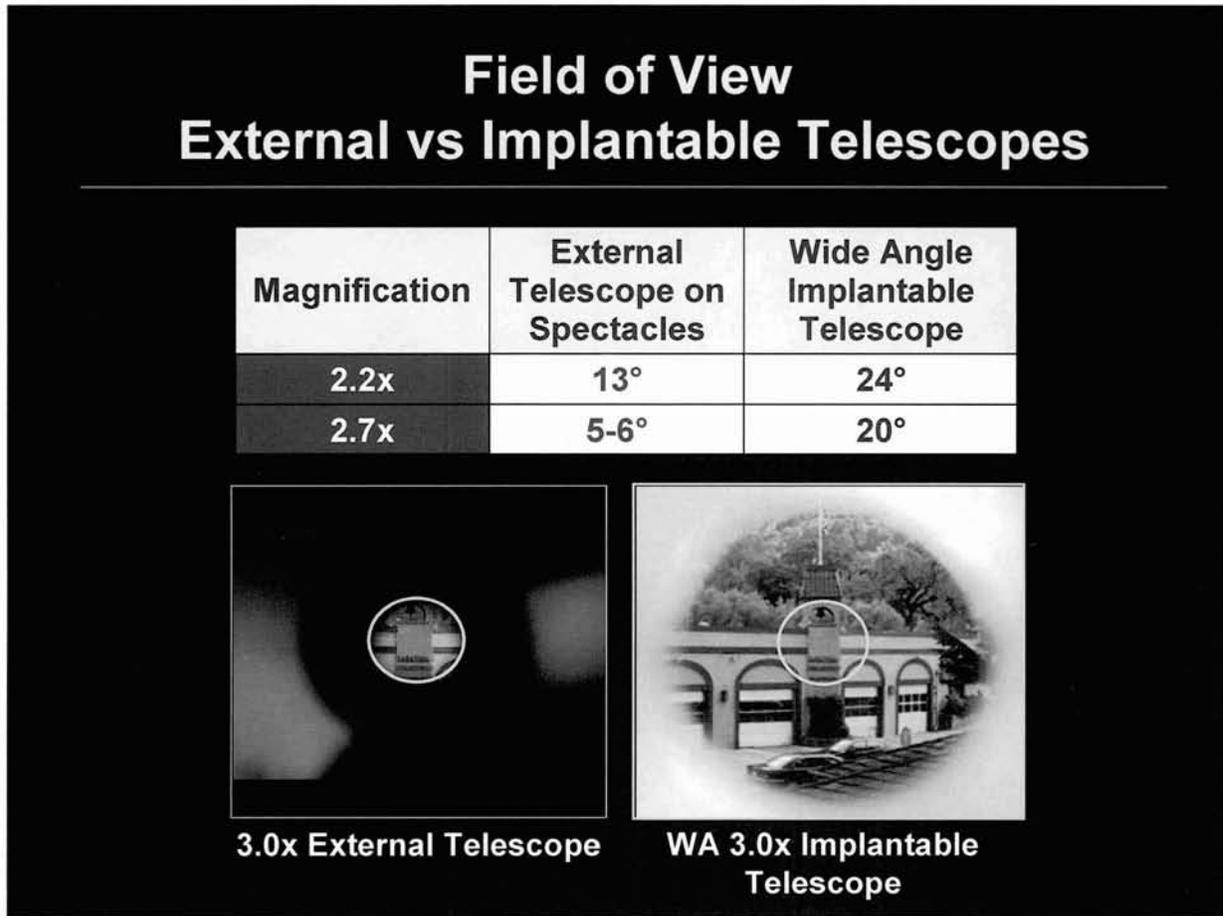
Central Visual Field Projection



The WA 3.0X and WA 2.2X IMT devices provide a 20° and 24° forward field of view, respectively. The forward fields of view provided by both models of the IMT are appreciably greater than those provided by conventional external hand-held or spectacle-mounted low vision telescopes, typically 9° and 14° for 3.0X and 2.2X telescopes. These values do not take into account the substantial reduction in the field of view due to vertex distance from the cornea as indicated in the data provided in Figure 4.

Depth of focus is maintained from 1.5 m up to 10 m which is ideal for intermediate distance visual activities. Standard prescription spectacles are dispensed for distance and near vision correction to enhance the focus of the enlarged retinal image for distance and near activities. External magnifiers can provide additional magnification.

FIGURE 4: FIELD OF VIEW WITH EXTERNAL TELESCOPE VS IMT
A013, VOL 1, PAGE 5, FIGURE 4



The IMT restricts the peripheral field of an IMT-implanted eye, beyond the forward field of view provided by the IMT. However, the IMT allows scanning of reading materials and other images using natural eye movements, rather than head movements thus also providing a wide effective-field of view in the implanted eye. Unlike hand-held or hand-operated magnifiers, IMT implants allow patients to have both hands available to perform activities of daily living. Since there is no relative movement between the eye and the telescope, there are no induced optical aberrations. The placement of the magnifying device entirely inside the eye eliminates the problems encountered with external low vision telescopes such as vertex distance to cornea, the perception of increased speed of motion, and vestibular conflict that scanning with head motions can cause.

2.0 PMA P050034 HISTORY

PMA P050034 was originally submitted to FDA in September 2005, and was reviewed by the Ophthalmic Devices Advisory Panel in July 2006. At the time of Advisory Panel review, Protocol IMT-002 had been completed through 12 months, allowing analysis of the primary effectiveness and safety outcomes at 12 months as planned in the study protocol. Data were also presented through 18 and 24 months for endothelial cell density (ECD) and other ocular safety findings for the majority of study subjects.

The Panel did not recommend approval, and in September 2006, the Division of Ophthalmic Devices identified the measures necessary to make the PMA approvable.

Since then, Vision Care has followed the study subjects for an additional two years, and the PMA now includes safety and effectiveness data of the IMT through four years. Together with suggested changes in the labeling, these data demonstrate that the IMT is safe and effective for the conditions of use prescribed, suggested, or recommended in the labeling.

The details of the suggested labeling are provided in Section 7.0 of this Executive Summary. To facilitate review, a guide to the location in this Executive Summary of data, analyses, and information provided in response to issues raised at the July 2006 meeting of the Ophthalmic Devices Advisory Panel may be found in Appendix 1.

3.0 IMT CLINICAL TRIALS

With this amendment, P050034 for the Implantable Miniature Telescope includes results of a completed 2-year clinical trial (Protocol IMT-002) and 4-year data from an extension study (Protocol IMT-002-LTM) planned for 5 years of follow-up after implantation of the IMT.

3.1 PROTOCOL IMT-002

Protocol IMT-002 was a prospective multicenter clinical trial conducted to evaluate safety and effectiveness of the IMT for the improvement of visual acuity in subjects with bilateral, stable, untreatable moderate (20/80) to profound (20/800) central vision impairment due to age-related macular degeneration or Stargardt's macular dystrophy. The protocol was submitted to FDA and approved in 2002. A copy of the study protocol and list of the clinical investigators are provided in Appendices 7 and 8 of this document.

STUDY ENDPOINTS

Study outcomes were defined as follows:

EFFECTIVENESS

- The primary effectiveness endpoint was an improvement at 12 months of 2 lines or more in either near or distance best-corrected acuity in 50% of the implanted eyes.
- The secondary effectiveness endpoints were improvements in visual function quality of life questionnaires (VFQ-25 and ADL).

SAFETY

The safety endpoints were:

- Preservation of best corrected visual acuity, defined as no more than 10% of subjects having a loss of greater than 2 lines in either near or distance BCVA without a corresponding gain of 2 or more lines in the other.
- Mean endothelial cell density less than or equal to 17% at 12 months post-implantation.
- Adverse events and complications.

PATIENT POPULATION

The study enrolled consecutive subjects who provided informed consent and satisfied the following inclusion and exclusion criteria:

INCLUSION CRITERIA

- Bilateral, stable, untreatable central vision disorders (untreatable AMD or Stargardt's macular dystrophy) as determined by fluorescein angiography.
- Cataract.

- Distance BCVA between 20/80 and 20/800, and adequate peripheral vision in one eye (the non-implanted eye) to allow navigation.
- Achievement of at least a five-letter improvement on the ETDRS chart with an external telescope in the eye scheduled for surgery, with the external telescope.
- Anterior chamber depth of ≥ 2.5 mm in the operative eye.
- Available for the study duration of approximately 24 months and willing to return for all visits for training and evaluation.
- Alert, mentally competent, and able to understand and comply with the requirements of the clinical trial, and personally motivated to abide by the requirements and restrictions of the clinical trial.
- At least 55 years of age.

EXCLUSION CRITERIA

- Evidence of active CNV on fluorescein angiography or treatment for CNV within the past six months.
- Anticipated need for cataract extraction and intraocular lens implantation during the first 12 months following IMT implantation in the fellow eye. Any anticipated cataract extraction 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.
- Any of the following conditions in the operative eye:
 - Myopia > 6.0 D
 - Hyperopia > 4.0 D
 - Axial length < 21 mm
 - Endothelial cell density < 1600 cells/mm²
 - Narrow angle, i.e., less than Shaffer grade 2
 - Cornea stromal or endothelial dystrophies or disorders
 - Inflammatory ocular disease
 - Zonular weakness/instability of crystalline lens
 - Pseudoexfoliation
 - Diabetic retinopathy
 - Untreated retinal tears
 - Retinal vascular disease
 - Optic nerve disease
 - History of retinal detachment
 - Retinitis pigmentosa
 - 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.

- Any ocular condition that predisposed the patient to eye rubbing.
- Significant communication impairments or severe neurological disorders that prevented or interfered with the study requirements.
- Previous intraocular or corneal surgery of any kind in the operative eye(s), including any type of surgery for either refractive or therapeutic purposes.
- History of steroid-responsive rise in intraocular pressure, uncontrolled glaucoma, or preoperative IOP >22 mm Hg.
- Known sensitivity to planned study concomitant medications.
- Participation in any other ophthalmic drug or device clinical trial during the time of this clinical investigation.

STUDY PROCEDURES

Consented subjects underwent a baseline evaluation to determine eligibility for the study. A component of the baseline evaluation consisted of evaluation with a 2.2X and 3.0X external telescope. Both telescopes were used by the study site to evaluate subjects' vision improvement with the external telescope. A 2.2X external telescope was given to potential subjects to utilize at home for a period of at least three days to provide a simulation of visual acuity that may be achieved with the IMT while attempting routine daily tasks.

Subjects underwent IMT implantation performed using either a limbal insertion technique or a scleral tunneling procedure. Anesthesia was induced by retrobulbar or peribulbar injection, and mydriatic agents were administered to ensure adequate pupil dilation during surgery. Limbal IMT insertion was performed through a 10 to 12 mm incision made at 120° to 160° arc length. For scleral tunnel insertion, an incision at least 10 mm in length was performed 2.5 to 3 mm posterior to the limbus. A tunnel was then created which opened into the anterior chamber at the limbus. A paracentesis was performed, and viscoelastic was injected into the anterior chamber. A continuous curvilinear capsulorhexis of approximately 6.5 mm was made in the lens capsule. Additional viscoelastic was injected into the anterior chamber and the capsular bag, and used to coat the IMT. The IMT was implanted by placing both loops inside the capsular bag, suturing the cornea and rotating the loops of the IMT to the 12:6 o'clock position. The viscoelastic was removed, the pupil was constricted, a peripheral iridectomy was performed and the incision was tested for leakage.

A sub-Tenon's injection of betamethasone depot (or appropriate substitute) was administered at the end of surgery. Additionally, a standardized course of topical antibiotic and nonsteroidal anti-inflammatory was administered at the end of surgery and continued per product labeling for at least 2 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, tapering 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.

Study investigators were directed to exercise clinical judgment in determining whether a more moderate or rapid tapering of the topical steroid regimen was indicated for some subjects, particularly in eyes with signs of medicamentosa.

Postoperatively, study subjects were examined and evaluated according to the following schedule of visits:

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
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	90 to 102 weeks postoperative

Study subjects were scheduled for vision training at Weeks 1, 2, 4, 6, 10 and 12.

The clinical parameters evaluated at study examinations were:

- Fundus examination (under dilation) and photography (baseline only)
- Fluorescein angiography (baseline only)
- Best spectacle-corrected distance acuity (ETDRS)
- Best spectacle-corrected near visual acuity (MN charts)
- Intraocular pressure (applanation)
- Slit lamp examination
- Pachymetry
- Specular microscopy of the central cornea
- Complications, adverse events and device malfunctions.
- VFQ-25 questionnaire & Activities of Daily Life (ADL) (through 12 months).

Postoperative visual examinations were performed by the investigator or a designee such as ophthalmic technicians, optometrists, and/or ophthalmologists under the supervision of the investigator using methods described in the study protocol. All preoperative and postoperative examinations were performed using similar pieces of equipment at each site.

Specular microscopy was performed preoperatively and at the Month 3, 6, 9, 12, 18 and 24 examinations in both the operated and fellow eyes using non-contact Konan or Topcon Specular Microscope; three images, OD and OS, were obtained at each visit. Images were transmitted to and analyzed by a central reading center at Emory University Department of Ophthalmology, under the

direction of H. Edelhauser, Ph.D. and B. McCarey, Ph.D. In addition to endothelial cell counts using the center method for counting, morphometric and morphologic analyses were performed to evaluate the percentage of hexagonal cells and the coefficient of variation.

STATISTICAL METHODS

This section briefly describes the sample size calculations for the trial and the planned analyses for:

- Primary effectiveness outcome, i.e., the proportion of patients with improvement of at least 2 lines in either distance or near BCVA at 12 months postoperatively; the target for determining effectiveness was 50% of eyes;
- VFQ-25 and ADL scores, and
- Percent loss in endothelial cell density (ECD) from baseline to 12 months postoperatively.

Analyses of other outcomes are described in the sections summarizing the data.

The calculated sample size of approximately 200 eyes gave 80 percent power to detect a proportion of eyes that improved at least 2 lines and considerably more than 80 percent power to exclude a mean percentage loss in ECD of at least 17%. Calculations were based on the following criteria and assumptions: Type I error rates of 0.05; a 60% expected proportion of 2-line improvement as seen in VisionCare's feasibility study; a 13.5% mean loss in ECD with a standard deviation of 17.5% as seen in the feasibility study; and a 20% loss to follow-up or noncompliance. A review of the literature had shown an average ECD loss of 10% to 20% within one year of large incision surgery, extra capsular cataract extraction. The figure of 13.5% used in the power calculations for mean loss in ECD was selected because it was the midpoint of the observed range.

An exact binomial statistic was used to test the primary effectiveness outcome. A 90% Clopper-Pearson 90% confidence interval was calculated. Some analyses of this outcome were performed by age category, gender, preoperative visual acuity status, and IMT model. Analyses were not performed within clinical site because most sites had few patients.

Both BCDVA and BCNVA were calculated using LogMAR values. The change in the best corrected distance visual acuity (BCDVA) was calculated for each eye by subtracting the baseline LogMAR value from the postoperative LogMAR value. A difference in the LogMAR value of -0.1 and +0.1 represents a one-line improvement and a one-line decrease in visual acuity, respectively. A LogMAR value of 1.7 was assigned to subjects who could not read any letters on the ETDRS chart. The change in the best corrected near visual acuity (BCNVA) was calculated for each eye based on the M-value. M-values were converted to the corresponding LogMAR value. The change in BCNVA for each eye was then calculated in the same way as the change in BCDVA. If the M-value was not assigned but the number of letters read correctly was not zero, an M-value of 10.0M was assumed. Otherwise an M-value of 12.5M was assumed for subjects who could not read any ETDRS letters.

VFQ-25 and ADL scores were analyzed using published scoring methods (Mangione et al, 2001; Clemons et al, 2003; Mangione et al, 1998; Globe et al, 2004; Mangione et al, 1992; Mangione et al, 1995; Martin et al, 2004; Cahill et al, 2005). Changes from baseline were calculated.

For predicting long-term ECD loss rates, VisionCare previously presented a piecewise regression model with breakpoints at 3 and 9 months. This model was discussed at the July 2006 Ophthalmic Devices Panel when only partial 24 month ECD information was available. While the piecewise regression model accounted for the fact that loss of ECD is not linear over time, with substantial ECD loss occurring in the immediate postoperative period followed decreasing rates of ECD loss, because of questions raised by the Panel and then CDRH regarding this model, VisionCare sought a more appropriate model. The biexponential model described by Armitage, Dick and Bourne (Armitage et al, 2003) and by Patel, Hodge and Bourne (Patel et al, 2004) was identified as a more relevant model for ECD loss.

The actual rate of ECD loss for the period from baseline to 4 years following implantation has been analyzed using the data from IMT-002 and IMT-002-LTM studies.

3.2 PROTOCOL IMT-002-LTM (LONG-TERM MONITORING)

Protocol IMT-002-LTM was intended to serve as a post-approval study designed to provide long-term follow-up on subjects implanted with the IMT in Protocol IMT-002. This protocol was submitted to FDA in February 2006, approved in May 2006 and the first subject enrolled in June 2006. Subjects in Protocol IMT-002 were asked to consent to an additional 3 years of follow-up in Protocol IMT-002-LTM. Under Protocol IMT-002-LTM, subjects were asked to return for examination at 30, 36, 42, 48, 54, and 60 months after surgery. Examinations at each study visit consisted of slit lamp exam, measurement of intraocular pressure, best corrected distance vision, endothelial cell density, pachymetry, complications, and adverse events. At the time of protocol and local IRB approvals, the majority of subjects participating in IMT-002-LTM had passed the 30 month visit window. Examination of baseline characteristics, efficacy, and ECD performance showed no difference between the cohort of subjects participating and the cohort not participating in IMT-002-LTM except for a higher mean ECD level reported at 12 months for subjects not participating in the study. A copy of Protocol IMT-002-LTM, a list of study investigators, and a complete set of analyses are provided in Appendices 9, 10 and 2, respectively.

4.0 DEMOGRAPHIC, BASELINE, AND ACCOUNTABILITY INFORMATION

Protocol IMT-002 enrolled 218 subjects at 28 clinical sites. One subject cancelled surgery, resulting in a cohort of 217 operated eyes.

As seen in Table 1, 52% of the group was male, the mean age was approximately 76 years, and nearly 96% were Caucasian. Mean baseline anterior chamber depth was 3.15 mm and mean baseline BCDVA was 20/312. The type of AMD was described as disciform scar only (43%) or geographic atrophy only (39%). Three eyes were identified as presenting with drusen only; however, a review of the medical records for these 3 subjects, following closure of the database, revealed that all 3 eyes had presented with GA and drusen.

TABLE 1
DEMOGRAPHIC AND BASELINE CHARACTERISTICS
OPERATED SUBJECTS (N=217) IMT-002
A013, VOL 1, PAGE 13, TABLE 1

217 Eyes of 217 Operated Subjects			
		Number	Percentage
Gender			
Female		103	47.5%
Male		114	52.5%
Race			
Caucasian		208	95.9%
Black		3	1.4%
Hispanic		5	2.3%
Asian		1	0.5%
Age (In Years)			
Mean (SD)		75.6 (7.3)	
Minimum		55	
Maximum		93	
Anterior Chamber Depth			
Mean (SD)		3.15 (0.38)	
Minimum		2.48	
Maximum		4.74	
Type of AMD			
Geographic atrophy (GA)		85	39.2%
Disciform scar		93	42.9%
GA & Drusen		11	5.1%
GA & Disciform scar		8	3.7%
Drusen & Disciform scar		13	6.0%
GA & Drusen & Disciform scar		7	3.2%
Best-corrected Visual Acuity			
Mean BCDVA		20/312	
(Range)		(20/873, 20/80)	
Mean BCNVA @8"		20/315	
(Range)		(20/1262, 20/50)	
Mean BCNVA @16"		20/260	
(Range)		(20/632, 20/63)	

Surgical complications resulted in 11 subjects not being implanted with the IMT, leaving a cohort of 206 IMT-implanted subjects.

Of the 11 subjects not successfully implanted, in 5 eyes the IMT was not implanted because of surgical complications and in 6 eyes implantation of the IMT was attempted but the device was removed at the time of surgery, also as a result of surgical complications (Table 2). A standard intraocular lens was placed in these 11 eyes.

Detailed information on this cohort of eyes is provided in Appendix 3 of this submission.

TABLE 2
OPERATED EYES WITHOUT IMT PLACEMENT
IMT-002
A013, VOL 1, PAGE 14, TABLE 2

Number of Eyes	Surgical Complication
Cases with Intraoperative Contraindications for IMT Implantation	
3	Posterior Capsule Tear
2	Choroidal Detachment
Cases with IMT Placed and Removed Intraoperatively	
4	Posterior Capsular Tear
1	Zonular Dehiscence
1	Choroidal Hemorrhage

Limbal insertion of the IMT was performed in 64% of the study eyes; the remaining eyes (36%) underwent scleral tunneling. The crystalline lens was extracted by conventional phacoemulsification techniques, with mean capsulorrhexis size of 7 mm. The study protocol specified iridectomy, which was performed in all but 4 (2%) study eyes. Other surgical procedures performed at the time of IMT implantation consisted of pupil stretch and lysis of peripheral anterior synechiae.

Subject availability and accountability for Protocol IMT-002 are summarized in Table 3. At Month 12, 90% of the study subjects were available for analysis; at Month 24, 80% were available. Information on the subjects who missed the 24 month visit is provided in Appendix 3.

Patient availability and accountability for Protocol IMT-002-LTM are presented in Table 4.

TABLE 3
AVAILABILITY AND ACCOUNTABILITY
OPERATED SUBJECTS (N = 217)
IMT-002
A013, VOL 1, PAGE 15, TABLE 3

		1 Month	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Available for Analysis	n/N (%)	217/217 (100.0%)	207/217 (95.4%)	204/217 (94.0%)	196/217 (90.3%)	196/217 (90.3%)	180/217 (82.9%)	174/217 (80.2%)
Discontinued	n/N (%)	0/217 (0.0%)	7/217 (3.2%)	11/217 (5.1%)	13/217 (6.0%)	16/217 (7.4%)	20/217 (9.2%)	29/217 (13.4%)
Deceased		0/217 (0.0%)	1/217 (0.5%)	3/217 (1.4%)	3/217 (1.4%)	5/217 (2.3%)	7/217 (3.2%)	10/217 (4.6%)
IMT removed postoperatively		0/217 (0.0%)	1/217 (0.5%)	1/217 (0.5%)	1/217 (0.5%)	2/217 (0.9%)	2/217 (0.9%)	8/217 (3.7%)
Lost to Follow-up	n/N (%)	0/217 (0.0%)	0/217 (0.0%)	0/217 (0.0%)	1/217 (0.5%)	2/217 (0.9%)	8/217 (3.7%)	13/217 (6.0%)
Missed Visit	n/N (%)	0/217 (0.0%)	3/217 (1.4%)	2/217 (0.9%)	7/217 (3.2%)	3/217 (1.4%)	9/217 (4.1%)	1/217 (0.5%)
% Accountability = Available for Analysis ÷ (Enrolled - Discontinued)		217/217 (100.0%)	207/210 (98.6%)	204/206 (99.0%)	196/204 (96.1%)	196/201 (97.5%)	180/197 (91.4%)	174/188 (92.6%)

TABLE 4
AVAILABILITY AND ACCOUNTABILITY
OPERATED SUBJECTS
IMT-002 -LTM
A013, VOL 1, PAGE 15, TABLE 4

	30 Months	36 Months	42 Months	48 Months
Available for analysis	3/3 (100%)	84/85 (99%)	113/125 (90%)	106/129 (82%)
Discontinued (cumulative)			4/125 (3%)	6/129 (5%)
Deceased			3/125 (2%)	5/129 (3%)
IMT removed postoperatively			1/125 (1%)	1/129 (1%)
Lost to Follow-up			3/125 (2%)	10/129 (8%)
Missed Visit		1 /85 (1%)	5/125 (4%)	7/129 (5%)
% Accountability = Available for Analysis / (Enrolled - Discontinued)	3/3 100%	84/85 99%	113/121 93%	106/123 86%

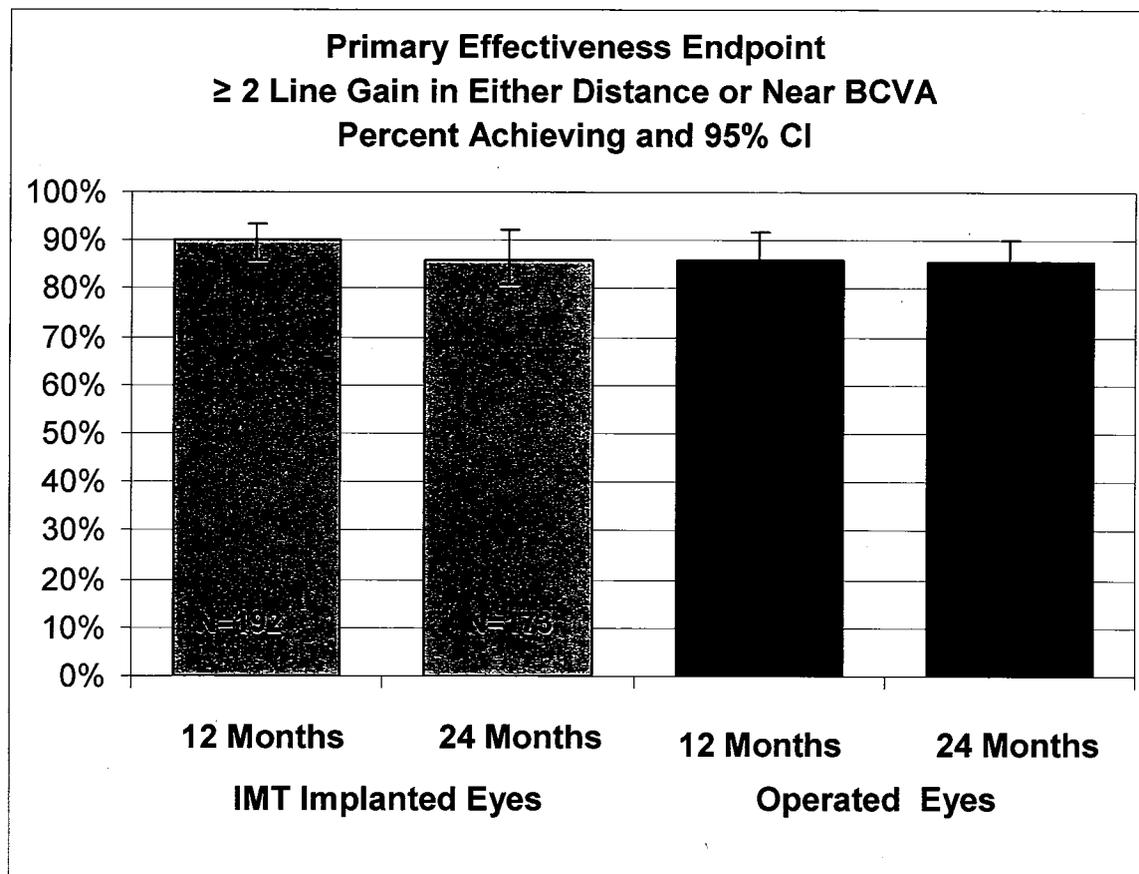
5.0 EFFECTIVENESS

The IMT improved visual acuity and quality of life in subjects with end-stage AMD. The primary effectiveness endpoint, a 2-line or greater gain in either distance or near BCVA at 12 months in at least 50% of study subjects, was met and exceeded. The secondary effectiveness endpoint, improvement in quality of life, was also achieved.

5.1 VISUAL ACUITY

Ninety percent of IMT-implanted eyes achieved at least a 2-line or greater gain in either distance or near BCVA at 12 months, thus exceeding the 50% criterion specified for the primary endpoint. This improvement was maintained at 24 months (Figure 5).

FIGURE 5
A014, VOL 1, PAGE 16, FIGURE 5



Additional insights into the effectiveness of the IMT are provided in the following analyses.

Mean BCDVA improved from 20/312 at baseline to 20/141 at 12 months and to 20/149 at 24 months (Table 5). Mean BCNVA at 8 inches improved from 20/315 at baseline to 20/181 at 12 months and to 20/190 at 24 months. Mean BCNVA at 16 inches improved from 20/262 at baseline to 20/149 at 12 months and to 20/157 at 24 months.

TABLE 5
MEAN BCVA AT BASELINE, 12 MONTHS AND 24 MONTHS
IMT-IMPLANTED EYES
IMT-002

A013, VOL 1, PAGE 17, TABLE 5.1

	Baseline		12 Months		24 Months	
	N	Mean	N	Mean	N	Mean
Mean BCDVA 95% CI	206	20/312 (20/334, 20/291)	193	20/141 (20/152, 20/131)	173	20/149 (20/161, 20/138)
Mean BCNVA at 8" 95% CI	206	20/315 (20/341, 20/291)	192	20/181 (20/196, 20/167)	173	20/190 (20/207, 20/174)
Mean BCNVA at 16" 95% CI	206	20/262 (20/282, 20/244)	192	20/149 (20/161, 20/138)	173	20/157 (20/170, 20/145)

At 12 months, 73% of eyes improved two or more lines in both best corrected near and distance acuity, with 53% gaining 3 or more lines in both BCNVA and BCDVA. Forty-five percent or more and 25% or more subjects gained 4 or 5 lines of distance visual acuity. These data, along with the results at 24 months, are shown in Table 6.

TABLE 6
SUMMARY OF IMPROVEMENT IN VISUAL ACUITY
IMT-IMPLANTED EYES
IMT-002

A013, VOL 1, PAGE 18, TABLE 6

IMPROVEMENT IN VISUAL ACUITY	12 MONTHS % (n)	24 MONTHS % (n)
≥ 2 LINES GAIN OF BCDVA OR BCNVA	90.1% (173)	86.1% (149)
≥ 2 LINES GAIN OF BCDVA AND BCNVA	73.4% (141)	65.9% (114)
≥ 3 LINES GAIN OF BCDVA AND BCNVA	53.1% (102)	49.1% (85)
BCDVA LINES GAINED		
≥ 2 LINES GAIN OF BCDVA	80.3% (155)	74.6% (129)
≥ 3 LINES GAIN OF BCDVA	66.3% (128)	59.5% (103)
≥ 4 LINES GAIN OF BCDVA	45.1% (87)	42.8% (74)
≥ 5 LINES GAIN OF BCDVA	25.4% (49)	19.1% (33)
BCNVA LINES GAINED (8" OR 16")		
≥ 2 LINES GAIN OF BCNVA	82.8% (159)	77.5% (134)
≥ 3 LINES GAIN OF BCNVA	67.7% (130)	63.0% (109)
≥ 4 LINES GAIN OF BCNVA	49.0% (94)	43.9% (76)
≥ 5 LINES GAIN OF BCNVA	28.6% (55)	24.3% (42)

VISUAL ACUITY OUTCOMES BY BASELINE BCDVA GROUPS

Gain in lines of visual acuity at 12 and 24 months for each category of baseline distance vision is presented in Table 7

BCDVA and BCNVA improved both at 12 and 24 months in all three baseline distance vision groups (20/80 to 20/160+, 20/160 to 20/400+ and worse than 20/400). The effect was greatest in the subjects with the worst baseline distance vision.

TABLE 7
SUMMARY OF IMPROVEMENT IN VISUAL ACUITY
IMT-IMPLANTED EYES
STRATIFIED BY PREOPERATIVE BCDVA
IMT-002
A013, VOL 1, PAGE 19, TABLE 7.1

IMPROVEMENT IN VISUAL ACUITY	12 MONTHS			24 MONTHS		
	Baseline BCDVA 20/80 to 20/160+	Baseline BCDVA 20/160 to 20/400	Baseline BCDVA Worse than 20/400	Baseline BCDVA 20/80 to 20/160+	Baseline BCDVA 20/160 to 20/400	Baseline BCDVA Worse than 20/400
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
≥2 LINES GAIN OF BCDVA OR BCNVA	86.7% (13)	86.1% (99)	98.4% (61)	71.4% (10)	83.7% (87)	94.5% (52)
≥2 LINES GAIN OF BCDVA AND BCNVA	46.7% (7)	69.6% (80)	87.1% (54)	35.7% (5)	65.4% (68)	74.5% (41)
≥3 LINES GAIN OF BCDVA AND BCNVA	13.3% (2)	47.0% (54)	74.2% (46)	21.4% (3)	43.3% (45)	67.3% (37)
BCDVA LINES GAINED						
≥2 LINES GAIN OF BCDVA	53.3% (8)	74.8% (86)	96.8% (61)	42.9% (6)	71.2% (74)	89.1% (49)
≥3 LINES GAIN OF BCDVA	13.3% (2)	60.9% (70)	88.9% (56)	21.4% (3)	54.8% (57)	78.2% (43)
≥4 LINES GAIN OF BCDVA	0.0% (0)	39.1% (45)	66.7% (42)	7.1% (1)	37.5% (39)	61.8% (34)
≥5 LINES GAIN OF BCDVA	0.0% (0)	13.9% (16)	52.4% (33)	0.0% (0)	13.5% (14)	34.5% (19)
BCNVA LINES GAINED 8" OR 16"						
≥2 LINES GAIN OF BCNVA	80.0% (12)	80.9% (93)	87.1% (54)	64.3% (9)	77.9% (81)	80.0% (44)
≥3 LINES GAIN OF BCNVA	60.0% (9)	64.3% (74)	75.8% (47)	50.0% (7)	58.7% (61)	74.5% (41)
≥4 LINES GAIN OF BCNVA	40.0% (6)	43.5% (50)	61.3% (38)	28.6% (4)	41.3% (43)	52.7% (29)
≥5 LINES GAIN OF BCNVA	26.7% (4)	23.5% (27)	38.7% (24)	14.3% (2)	21.2% (22)	32.7% (18)

VISUAL ACUITY OUTCOMES FOR IMT MODELS

Improvements in BCDVA and BCNVA were achieved with both the IMT WA 2.2X and WA 3.0X implantable telescopes (Table 8). However the WA 3.0X provided somewhat superior results as compared to the WA 2.2X as would be expected given the higher magnification of this model.

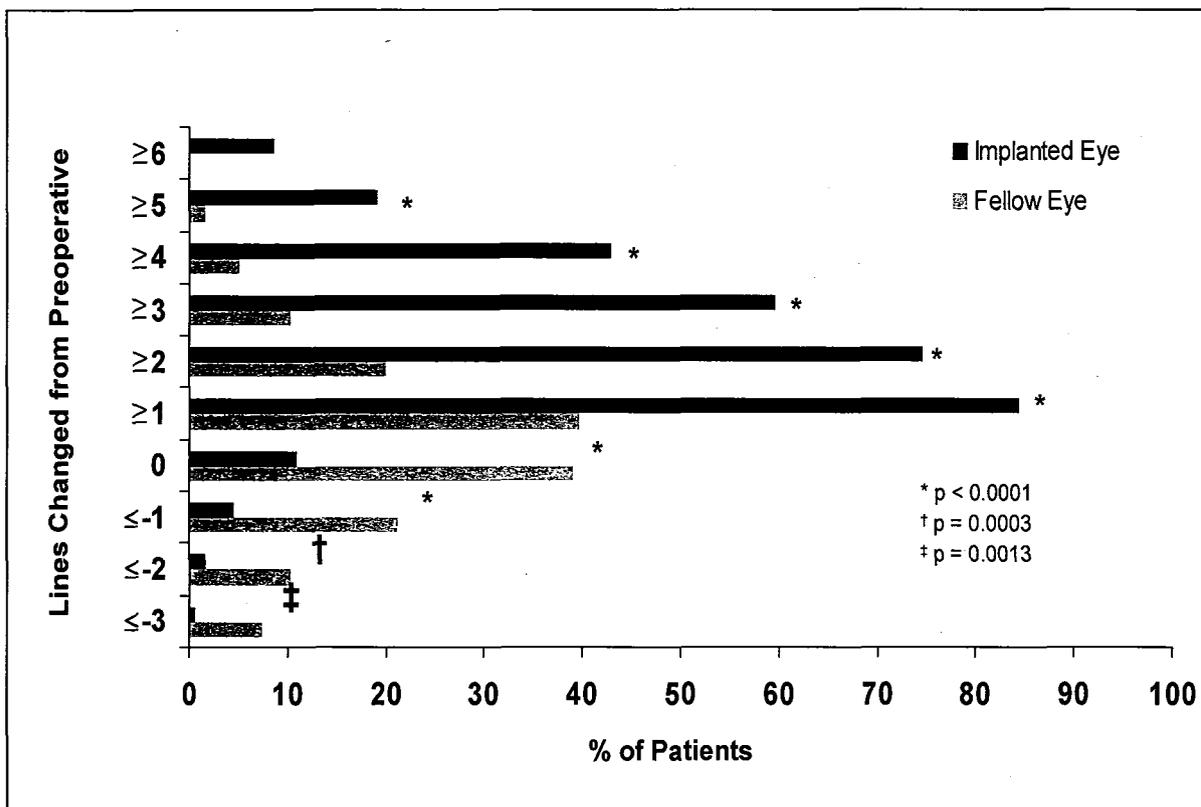
TABLE 8
SUMMARY OF IMPROVEMENT IN VISUAL ACUITY
IMT-IMPLANTED EYES
STRATIFIED BY IMT MODEL
IMT-002
A013, VOL 1, PAGE 20, TABLE 8

IMPROVEMENT IN VISUAL ACUITY	12 MONTHS		24 MONTHS	
	WA 2.2X	WA 3.0X	WA 2.2X	WA 3.0X
	% (n)	% (n)	% (n)	% (n)
≥2 LINES GAIN OF BCDVA OR BCNVA	89.0% (97)	91.6% (76)	84.5% (82)	88.2% (67)
≥2 LINES GAIN OF BCDVA AND BCNVA	67.0% (73)	81.9% (68)	60.8% (59)	72.4% (55)
≥3 LINES GAIN OF BCDVA AND BCNVA	46.8% (51)	61.4% (51)	40.2% (39)	60.5% (46)
BCDVA LINES GAINED				
≥2 LINES GAIN OF BCDVA	74.5% (82)	88.0% (73)	69.1% (67)	81.6% (62)
≥3 LINES GAIN OF BCDVA	60.0% (66)	74.7% (62)	52.6% (51)	68.4% (52)
≥4 LINES GAIN OF BCDVA	36.4% (40)	56.6% (47)	36.1% (35)	51.3% (39)
≥5 LINES GAIN OF BCDVA	16.4% (18)	37.3% (31)	14.4% (14)	25.0% (19)
BCNVA LINES GAINED 8" OR 16"				
≥2 LINES GAIN OF BCNVA	80.7% (88)	85.5% (71)	76.3% (74)	78.9% (60)
≥3 LINES GAIN OF BCNVA	64.2% (70)	72.3% (60)	58.8% (57)	68.4% (52)
≥4 LINES GAIN OF BCNVA	43.1% (47)	56.6% (47)	41.2% (40)	47.4% (36)
≥5 LINES GAIN OF BCNVA	28.4% (31)	28.9% (24)	20.6% (20)	28.9% (22)

VISUAL ACUITY FOR IMT-IMPLANTED EYES AND FELLOW EYES

The foregoing discussion of improvements in visual acuity utilized comparisons of IMT-implanted eyes to preoperative levels of visual acuity for the IMT-002 study. A comparison of IMT-implanted eyes to fellow eyes of IMT implanted eyes provides further information on improvement in visual acuity with the IMT. As shown in Figure 6, at 24 months after IMT implantation, the proportion of IMT-implanted eyes achieving improved BCDVA at all levels of line change was significantly greater the fellow eyes.

FIGURE 6
CUMULATIVE DISTRIBUTION OF CHANGE IN BCDVA AT 24 MONTHS FROM
BASELINE IMT-IMPLANTED EYES AND FELLOW EYES OF IMT-IMPLANTED EYES
 A013, VOL 1, PAGE 21, FIGURE 6



During the IMT-002-LTM trial, subjects maintained clinically significant improvements in BCDVA (Table 9) compared to baseline levels. At 36 and 48 month after IMT implant, approximately 70% of IMT-002-LTM subjects had a 2-line or greater improvement in BCDVA and approximately 50% had a 3-line improvement in BCDVA.

TABLE 9
CUMULATIVE BCDVA IMPROVEMENT FROM BASELINE
IMT-IMPLANTED EYES
IMT-002-LTM
A013, VOL 1, PAGE 22, TABLE 9.1

	36 Months	48 Months
	n (%)	n (%)
N	74	96
Gain ≥ 3 lines	39 (53%)	46 (48%)
Gain ≥ 2 lines	51 (69%)	65 (68%)
Gain ≥ 1 lines	63 (85%)	75 (78%)

Mean BCDVA improvements were generally retained at 36 and 48 months in IMT implanted eyes (Table 9). There was a slight decline in BCDVA at 48 months.

TABLE 10
MEAN BCDVA AT BASELINE, 36 MONTHS AND 48 MONTHS
IMT-IMPLANTED EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 22, TABLE 9.2

BCDVA	Baseline	36 Months	48 Months
IMT-Implanted Eyes			
N	206	74	96
Mean	20/312	20/156	20/171
95% CI	(20/334, 20/291)	(20/175, 20/139)	(20/191, 20/152)

The improvements in visual acuity produced by the IMT provide clinically meaningful benefits.

In the real world, people with 20/100 vision can watch TV, follow the program, and learn from and enjoy it. Improvement in vision to 20/100 with the IMT will provide the same result, as the acuity is the same. To achieve this specific goal, this means the patient can start with preoperative visual acuity in the 20/200 to 20/300 range based on the IMT-002 results. (This 20/100 case is just one example.) Individuals with 20/200 VA are considered to have form vision. Even visual acuity worse than 20/200 allows object perception. The functional benefit a person receives from the improvement afforded by the IMT depends where the individual is on the visual acuity spectrum – irrespective of whether the individual’s acuity is 20/80, 20/160, or 20/800, improved vision provides functional benefits. In Eleanor Faye’s book (E. D. Faye, Clinical Low Vision. Little, Brown and Co., 1976), she states “A person with distance acuity from 20/50 to and including

20/200 may move about with little difficulty. Acuity of 20/300 or 20/400 is usually considered adequate for gross object perception, but not for seeing fine details. Clearly, seeing fine detail is better than gross object perception and having gross object perception is better than no object perception." IMT-002 outcomes confirm that improvement in vision across a broad range of baseline acuity (20/80 to 20/800) affords benefits in both psychosocial as well as functional task aspects of quality of life.

Vision gain or loss has implications. If a patient with visual acuity of 20/250 loses 3 lines of acuity, this change results in a shift from the World Health Organization (WHO) and ICD-9 and 10 "low vision" category to each classification system's "blindness" category. In terms of ICD-9-CM definitions, this patient moves from "severe" to "profound" visual impairment. Alternatively, if a patient with visual acuity of 20/500 experiences an improvement of 3 lines vision, as was experienced by the majority of subjects in the IMT-002 clinical trial, he or she shifts categories in a positive direction and has less visual acuity impairment. Simply stated, these subjects have the benefit of better visual acuity, thus they are less impaired.

Improvement in visual acuity, the primary outcome measure of the IMT-002 clinical trial, and change in quality of life, the secondary efficacy outcome measure for the IMT-002 trial establish the clinical utility of the IMT across the range of baseline acuities. In the IMT-002 clinical trial, improvement in vision was observed in the overall study population and in the subgroups of moderate, severe, and profound vision impairment, with the primary efficacy endpoint of a 2 line gain in either distance or near acuity.

IMPROVEMENT IN VISUAL ACUITY ASSOCIATED WITH CATARACT REMOVAL AND IOL IMPLANTATION

The question has been raised whether removal of the cataract as part of the procedure in which IMTs are implanted accounted for the improvements in visual acuity seen in study subjects. As discussed in this section, removal of the cataract did not have a significant role in the reported improvement in visual acuity in IMT implanted subjects.

The potential contribution of cataract removal was evaluated by comparing improvements in visual acuity in the IMT-implanted eyes to:

1. Visual acuity in operated eyes that underwent cataract removal and implantation of an IOL rather than an IMT because of intraoperative complications
2. Visual acuity in a cohort of fellow eyes that underwent cataract removal and IOL implantation.
3. Visual acuity in eyes implanted with an IMT in which the IMT was explanted and an IOL implanted during the course of the study.

Preoperative cataract density was mild (2+) and visually insignificant in IMT-implanted eyes, in the eyes with aborted IMT implant, and in the fellow eyes of subjects who had cataract surgery during the study.

IMT implanted eyes gained an average of 3.4 lines of BCDVA at 12 months post implant. Removal of the cataract and implantation of an IOL in the 9 eyes with aborted IMT did not produce substantial gains in BCDVA; in this group the improvement in BCDVA from baseline was 0.38 lines. Similarly, in 22 fellow eyes with cataract surgery and implantation, BCDVA improved by 0.35 lines (Table 11). In the 6 eyes in which the IMT was explanted during the course of the study, when the IMT was removed and an IOL was implanted, these eyes lost an average of 2.2 lines after IMT removal (Table 12). Change in BCDVA from baseline for fellow eyes with cataract surgery during study, IMT eyes with aborted IMT implant and IOL implant, and IMT eyes with postoperative IMT removal and IOL implant was determined utilizing the last available BCDVA.

TABLE 11
CHANGE IN BCDVA FROM BASELINE
FOLLOWING CATARACT REMOVAL AND IOL IMPLANTATION
 A013, VOL 1, PAGE 25, TABLE 10

	All Eyes with Cataract Removal and IOL Implantation				IMT-Implanted Eyes at 12 Months
	Fellow Eyes of Subjects with Cataract Surgery During Study	IMT Eyes with Aborted IMT Implant & with IOL Implant	IMT Eyes with IMT Removal Postoperatively & with IOL Implant	Overall	
N	22	9	6	37	193
Mean Lines Change in BCDVA (95% CI)	0.35 (-0.60, 1.29)	0.38 (-0.32, 1.07)	-0.20 (-2.24, 1.84)	0.26 (-0.35, 0.88)	3.43 (3.10, 3.76)

TABLE 12
CHANGE IN BCDVA PRE-IOL IMPLANT
IMT EYES WITH IMT REMOVAL POSTOPERATIVELY & WITH IOL IMPLANT
 A013, VOL 1, PAGE 25, TABLE 11

	Change from Pre-IOL Implant
N	6
Mean Lines Change in BCDVA (95% CI)	-2.2 (-3.30, -1.10)

The proportions of eyes with gains of ≥ 2 lines and ≥ 3 lines of BCDVA is shown in Table 13 for the IMT-implanted cohort as compared to the fellow eyes that underwent cataract removal and IOL implantation. As shown, 91% of IMT-implanted eyes achieved a gain of 2 or more lines of BCDVA, and 73% gained 3 or more lines. In contrast, only 27% of the IOL-implanted fellow eyes gained 2 or more lines ($p < 0.001$), and just 9% gained 3 or more lines ($p < 0.0005$).

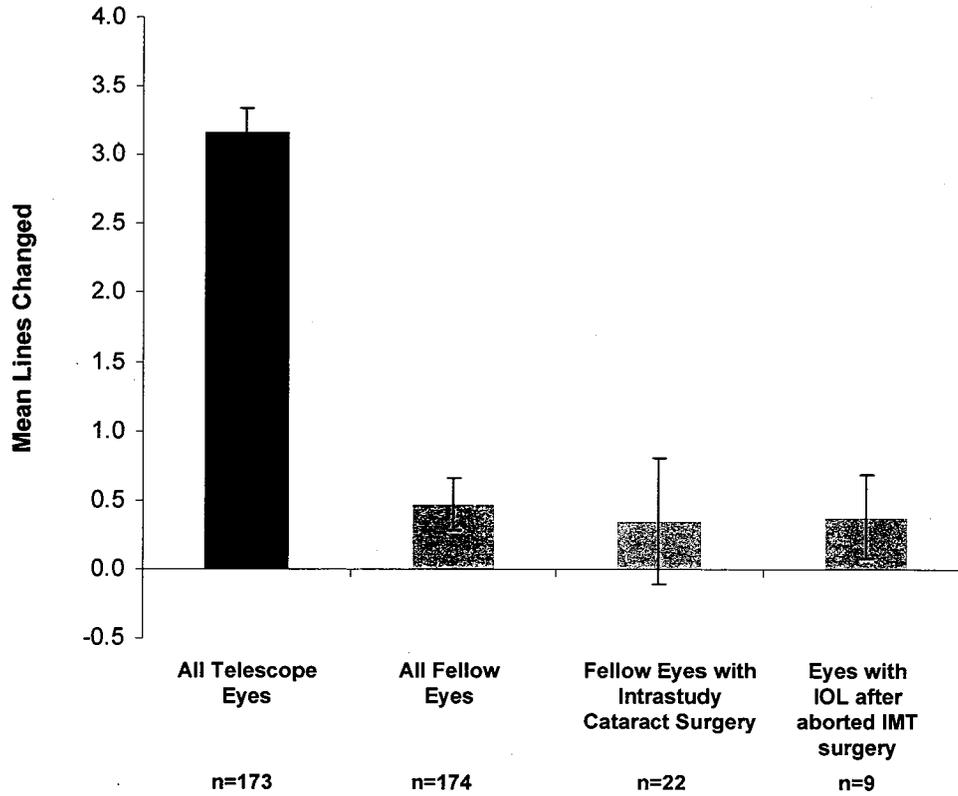
TABLE 13
BCDVA INCREASE ≥ 2 OR ≥ 3 LINES
FELLOW EYES WITH CATARACT SURGERY AND IOL IMPLANT DURING STUDY
AND CORRESPONDING IMT-IMPLANTED EYES
A013, VOL 1, PAGE 26, TABLE 12.1

BCDVA Increase	IMT Eyes N = 22 n (%)	Fellow Eyes N = 22 n (%)	McNemar P-value
≥ 2 Lines	20 (90.9%)	6 (27.3%)	0.0001
≥ 3 Lines	16 (72.7%)	2 (9.1%)	0.0005

BCDVA Change in Fellow Eyes = Change from study baseline to the last available BCDVA
BCDVA Change in IMT Eyes = Change from study baseline to 12-Month BCDVA

Fellow eyes that underwent cataract surgery and IOL placement during the IMT clinical trial experienced a change in BCDVA of 0.35 lines (Figure 7). This change was consistent with the change in BCDVA of 0.5 lines in the overall cohort of fellow eyes at 24 months. At 24 months, IMT-implanted eyes had an improvement in BCDVA of 3.2 lines (Figure 7).

FIGURE 7
CHANGE IN BCVA (MEAN, CI) FROM BASELINE TO 24 MONTHS
IMT-IMPLANTED EYES AND FELLOW EYES
 A017, PAGE 44 (HUDSON et al. AJO 2008; 146:664-673)



This finding of a limited effect of cataract removal on improvement in visual acuity is consistent with current clinical practice. In general and as confirmed in an informal survey of IMT-002 investigators, cataract removal and IOL implantation is not considered a standard of care in patients with bilateral central scotoma resulting from end-stage geographic atrophy or disciform scar with foveal involvement and moderate to profound vision impairment other than for patients complaining of glare disability from the presence of the cataract. In such cases, patients are generally informed that removal of the cataract and placement of an IOL is likely to resolve problems with glare, but with no improvement in visual acuity.

ACTUAL GAINS COMPARED TO THEORETICAL GAINS FOR EXTERNAL TELESCOPES AND IMTs
 The question has arisen as to why external telescopes used to screen study subjects did not provide the magnification predicted by their theoretical levels, why the IMTs did not provide the magnification predicted by their theoretical levels, and why the IMTs performed better than the external telescopes.

Theoretical improvement in lines of visual acuity for a telescope (external or internal) is calculated as 10 times the log (to the base 10) of the power of the telescope. Thus, for the 2.2X and 3.0X external telescopes used to screen study subjects, theoretical visual acuity gains are 3.4 lines and 4.8 lines, respectively. For the 2.2X and 3.0X (2.7X nominal) IMTs, theoretical visual acuity gains are 3.4 and 4.3 lines, respectively. As shown in Figures 8 and 9, the actual gains for these telescopes are less than the theoretical gains. The differences between theoretical and actual gains are relatively small, particularly for the IMTs. The smaller difference between actual and theoretical gain for the IMT compared to the external telescope is likely best accounted for by the difficulty of acquiring and maintaining a stable image with the external telescope compared to the IMT.

FIGURE 8
THEORETICAL GAIN COMPARED TO
ACTUAL GAIN (MEAN, CI) FROM EXTERNAL TELESCOPES (2.2X AND 3.0X) USED FOR
SUBJECT SCREENING
IMT-002
 A013, VOL 1, PAGE 27, FIGURE 7

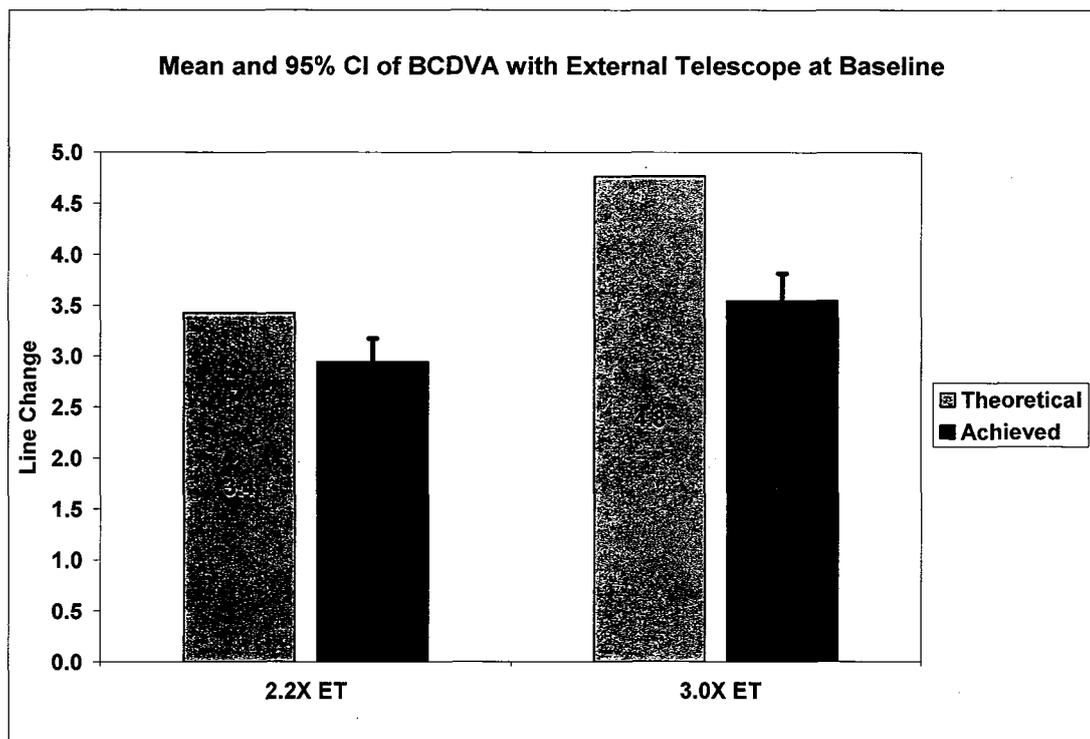
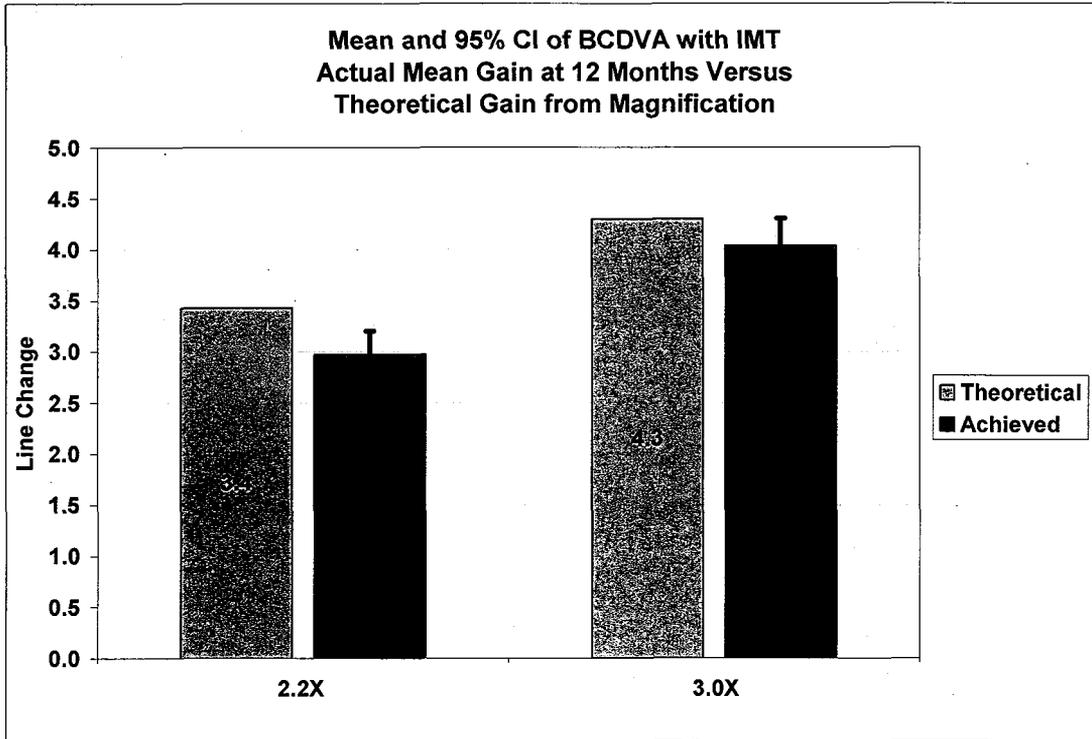


FIGURE 9
THEORETICAL GAIN COMPARED TO
ACTUAL GAIN (MEAN, CI) FROM IMT AT 12 MONTHS
IMT MODELS WA 2.2X AND WA 3.0X

IMT-002

A013, VOL 1, PAGE 28, FIGURE 8



5.2 QUALITY OF LIFE

Quality of life, as assessed by the National Eye Institute's Visual Function Questionnaire-25 (VFQ-25) and the Activities of Daily Living questionnaire (ADL), was a secondary outcome measure. The VFQ-25 and the ADL were administered at baseline, 3, 6, 9 and 12 months. As discussed in this section, implantation with the IMT improved quality of life in subjects with end-stage AMD and significant bilateral vision impairment.

The VFQ-25 is a 25-item version of the National Eye Institute's Vision Function Questionnaire (VFQ) (Mangione et al, 2001). It measures vision-targeted health status for persons with chronic eye diseases including macular degeneration (Clemons et al, 2003). The VFQ-25 consists of a base set of 25 vision-targeted questions ("items") representing 11 vision-related constructs ("subscales"). The composite VFQ-25 score is an unweighted average of the 11 subscales. The VFQ-25 also has an additional single-item general health rating question that is not part of the subscales or composite score. A minimum of a five (5) point difference in a subscale or composite score is clinically significant (Globe et al, 2004; SST 19, 2007).

The Activities of Daily Living questionnaire is a modified version of the Activities of Daily Vision Scale (ADVS) (Mangione et al, 1992), a questionnaire used to assess the effects of visual impairment due to cataract and related vision disorders. The ADL modifications made by advisors to VisionCare to the ADVS consisted of adjusting questions to address the challenges facing individuals with end-stage macular degeneration.

The VFQ-25 and ADL use scoring systems where 100 represents a perfect score and 0 the lowest possible score for subscale and composite analyses.

Copies of the VFQ-25 and the ADL questionnaires and scoring instructions may be found in Protocol IMT-002, provided in Appendix 7 of this amendment.

VFQ-25 RESULTS

Outcomes for all subscales of the VFQ-25 and the composite score are summarized in Table 14.

TABLE 14
MEAN SCORE CHANGE AT 12 MONTHS
NEI 25-ITEM VISUAL FUNCTION QUESTIONNAIRE (VFQ-25)
IMT-002
A013, VOL 1, PAGE 29, TABLE 13.1

VFQ-25 Subscale	Preop Mean Score (95%CI) N = 206	12 Months Mean Score (95%CI) N = 193	Change from Preop Mean Score (95%CI) N = 193	P-value¹
General Vision	35.3 (33.2, 37.4)	50.3 (47.5, 53.1)	14.1 (11.0, 17.2)	<.0001
Near Activities	25.5 (23.6, 27.5)	37.3 (34.6, 40.0)	11.2 (8.4, 13.9)	<.0001
Distance Activities	34.3 (31.7, 36.8)	42.4 (39.1, 45.7)	7.9 (4.4, 11.4)	<.0001
Color Vision	63.9 (60.1, 67.8)	67.7 (63.9, 71.5)	3.4 (-0.2, 6.9)	NS
Social Functioning	49.3 (46.0, 52.7)	58.3 (55.1, 61.4)	8.6 (4.8, 12.4)	<.0001
Mental Health	39.8 (36.5, 43.1)	49.3 (45.5, 53.0)	9.3 (6.1, 12.5)	<.0001
Role Difficulties	37.4 (34.2, 40.7)	44.8 (41.0, 48.5)	7.3 (3.5, 11.0)	0.0002
Dependency	37.7 (34.0, 41.4)	48.3 (44.4, 52.2)	10.0 (6.1, 13.9)	<.0001
Ocular Pain	88.2 (86.0, 90.4)	88.5 (86.1, 90.9)	0.6 (-2.1, 3.3)	NS
Driving	2.3 (1.0, 3.6)	1.9 (0.6, 3.2)	-0.5 (-1.6, 0.5)	NS
Peripheral Vision	67.6 (63.9, 71.3)	62.9 (59.7, 66.1)	-5.9 (-10.4, -1.5)	0.0091
Overall Composite ²	44.0 (42.1, 45.8)	50.3 (48.2, 52.4)	6.0 (4.0, 8.1)	<.0001
General Health	64.0 (60.8, 67.1)	59.7 (56.4, 63.0)	-5.1 (-8.1, -2.0)	0.0015

VFQ-25 scores on a scale of 0 (low) to 100 (maximum).

95%CI = 95% Confidence Interval.

1 P-value for testing that mean VFQ change = 0.

2 General Health not included in Overall Composite per NEI VFQ-25 scoring guidelines.

VISION SPECIFIC AND PSYCHOSOCIAL SUBSCALES

The VFQ-25 subscales of general vision, near activities, and distance activities are particularly important in assessing the ability of affected patients to perform daily activities, especially those dependent on central vision (Cahill et al, 2005). As shown in Table 14, at 12 months post-IMT implant, subscale scores for general vision, near activities, and distance activities improved by 14, 11, and 8 points, respectively. These clinically significant improvements were accompanied by clinically significant improvements in vision-specific subscales of dependency (+10 points), social functioning (+9 points), mental health (+9 points), and role difficulties (+7 points).

OTHER SUBSCALES

As expected, subscale scores for ocular pain and driving were generally unchanged. Color vision scores improved somewhat over the 12 month assessment period but not to a clinically significant degree. As also expected with an IMT implanted in one eye, peripheral vision subscale scores declined by a clinically significant 6 points at 12 months.

At 12 months, the mean score of the general health subscale declined by 5 points, likely reflecting the impact of other health-related events on the general health of the elderly study population (Martin et al, 2004).

COMPOSITE SCORE

The mean overall VFQ-25 composite score increased by a clinically significant amount from 44 at baseline to 50, an increase of 6 points at 12 months.

As a means of evaluating the extent of improvement in the study population the proportion of study subjects with changes of 5 points, either increases or decreases, is also shown in Table 15. Twice as many subjects experienced an increase of 5 or more points as subjects whose score decreased by at least 5 points, i.e., 52% vs 22%, respectively.

TABLE 15
VFQ-25 SCORE PERCENT OF SUBJECTS ACHIEVING
A CLINICALLY MEANINGFUL 5 POINT CHANGE IN COMPOSITE SCORE
IMT-IMPLANTED EYES
IMT-002
A013, VOL 1, PAGE 30, TABLE 13.2

Change in VFQ-25 Composite Score	12 Months (N = 193)	
	%	n/N
Subjects with increase \geq 5 points	51.8%	100/193
Subjects with decrease \geq 5 points	22.3%	43/193

OTHER ANALYSES OF VFQ-25 COMPOSITE SCORE

Change in VFQ-25 composite score was stratified by patient's age at implant, gender, IMT model, preoperative BCDVA and 12-month visual acuity improvement to determine whether any of these factors had an effect on this quality of life measurement. None had an effect other than gender. These analyses are provided in Appendix 2.

ACTIVITIES OF DAILY LIVING (ADL) RESULTS

The Activities of Daily Living (ADL) questionnaire consists of 36 questions and three constructs, i.e., mobility, distance activities, and near activities.

The total ADL score, as well as the three constructs of mobility, distance activities and near activities, improved substantially from baseline, with the largest improvement reported for near activities (Table 16).

TABLE 16
CHANGE FROM PREOPERATIVE IN ADL SCORES
IMT-IMPLANTED EYES
IMT-002
A013, VOL 1, PAGE 31, TABLE 14

ADL Subscale	Preop Mean Score (95%CI) N = 206	12 Months Mean Score (95%CI) N = 193	Change from Preop Mean Score (95%CI) N = 193	P-value¹
Mobility	53.8 (51.1, 56.4)	66.0 (63.1, 68.9)	12.0 (8.7, 15.2)	<.0001
Distance Activities	43.7 (41.6, 45.8)	57.3 (54.4, 60.2)	13.4 (10.4, 16.3)	<.0001
Near Activities	30.9 (28.3, 33.5)	48.5 (45.3, 51.7)	17.0 (13.8, 20.2)	<.0001
Total	41.4 (39.2, 43.5)	55.9 (53.1, 58.6)	14.2 (11.4, 16.9)	<.0001

95%CI = 95% Confidence Interval.

¹ P-value for testing that mean ADL change = 0.

SUMMARY OF QUALITY OF LIFE OUTCOMES

The IMT improved quality of life as measured by both the VFQ-25 and the ADL.

6.0 SAFETY

Data on safety are available from Protocol IMT-002 and Protocol IMT-002-LTM. The IMT-002 protocol identifies three safety outcomes: 1) preservation of visual acuity, 2) corneal endothelial cell density loss at 12 months, and 3) complications and adverse events, including corneal edema, corneal decompensation and IMT explantation. These safety outcomes, as well as several other safety considerations (anterior chamber depth and clearance from the IMT, intraocular pressure, posterior capsular opacification, and retinal findings) are discussed in this section.

The safety endpoint for preservation of visual acuity was met as discussed in Section 6.1, on the following pages. The safety endpoint for corneal endothelial cell loss, addressed in Section 6.2, was not met. ECD loss was 25% at 12 months; the goal was 17%. Use of an ECD grid identifying minimum ECD required for IMT implantation, based on patient age and life expectancy, is described in Section 6.3.

Complications and adverse events are discussed in Section 6.4. Detailed information on eyes with corneal edema and/or corneal decompensation, and IMT explantation are found following the summary tables on incidence densities of complications and adverse events. Information on anterior chamber depth, intraocular pressure, posterior capsule opacification, and choroidal neovascularization is provided in Section 6.5 to 6.8.

The loss of ECD greater than had been anticipated should not preclude approval for two reasons. First, the improvement in efficacy was considerably greater than had been anticipated. Because both the benefits and the risks (as to ECD loss) of the IMT were greater than had been anticipated in the protocol, the benefit-risk calculus remains at least as good as expected, and the balance is favorable. In addition and as discussed herein, VisionCare has identified and will implement several strategies to reduce the risk of ECD loss, which will further improve the balance of benefit to risk.

6.1 PRESERVATION OF VISUAL ACUITY

Protocol IMT-002 specified that preservation of visual acuity was to be assessed in terms of whether more than 10% of IMT-implanted eyes lost >2 lines of either BCDVA or BCNVA without a corresponding improvement in the other. This endpoint was met. At 12 months, 5% of eyes incurred such losses, and at 24 months, 6% of eyes incurred such losses (Table 17).

TABLE 17
PRESERVATION OF BCVA
OPERATED EYES (N = 217)
IMT-002
A013, VOL 1, PAGE 33, TABLE 15

	1 Month	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	% CI	% CI	% CI	% CI	% CI	% CI	% CI
N=	211	206	204	195	194	181	175
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	17 (8.1%) 5.2%, 11.8%	6 (2.9%) 1.3%, 5.7%	10 (4.9%) 2.7%, 8.2%	9 (4.6%) 2.4%, 7.9%	10 (5.2%) 2.8%, 8.6%	9 (5.0%) 2.6%, 8.5%	11 (6.3%) 3.6%, 10.2%
Binomial exact p-value for Ha: safety rate < 10%	0.2071	<.0001	0.0064	0.0048	0.0114	0.0111	0.0587

Loss of more than 2 lines of BCDVA was higher in fellow eyes than in IMT-implanted eyes at all visits in the IMT-002 study, Tables 18 and 19. Three IMT-implanted eyes (2%) lost more than 2 lines of BCDVA at 24 months versus 16 (9%) of fellow eyes.

In the IMT-002-LTM study, as shown in Tables 20 and 21, 4 IMT-implanted eyes (4%) lost more than 2 lines of BCDVA at 48 months as compared to 11 (11%) fellow eyes.

TABLE 18
LOSS OF BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)
IMT-IMPLANTED EYES
IMT-002
A013, VOL 1, PAGE 34, TABLE 16.1

BCDVA	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Loss > 2 lines	3	1.5%	6	3.1%	4	2.1%	4	2.2%	3	1.7%
One-sided upper 95% CL¹	3.8%		6.0%		4.7%		5.0%		4.4%	
N²	201		195		193		179		173	

1 CL = exact confidence limit calculated based on Clopper Pearson method.

2 N = number of eyes with available data.

TABLE 19
LOSS OF BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)
FELLOW EYES OF IMT-IMPLANTED EYES
IMT-002

A013, VOL 1, PAGE 34, TABLE 16.2

BCDVA	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Loss > 2 lines	14	7.0%	14	7.2%	15	7.8%	18	10.0%	16	9.2%
One-sided upper 95% CL ¹	10.7%		11.0%		11.7%		14.5%		13.6%	
N ²	200		195		193		180		174	

- 1 CL = exact confidence limit calculated based on Clopper Pearson method.
2 N = number of eyes with available data.

TABLE 20
LOSS OF BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)
IMT-IMPLANTED EYES
IMT-002-LTM

A013, VOL 1, PAGE 34, TABLE 17.1

BCDVA	36 Months		42 Months		48 Months		54 Months		60 Months	
	n	%	n	%	n	%	n	%	n	%
Loss > 2 lines	2	2.7%	9	8.7%	4	4.2%	2	5.9%	0	0.0%
One-sided upper 95% CL ¹	8.3%		14.6%		9.3%		17.4%		39.3%	
N ²	74		104		96		34		6	

- 1 CL = exact confidence limit calculated based on Clopper Pearson method.
2 N = number of eyes with available data.

TABLE 21
LOSS OF BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)
FELLOW EYES OF IMT-IMPLANTED EYES
IMT-002-LTM

A013, VOL 1, PAGE 35, TABLE 17.2

BCDVA	36 Months		42 Months		48 Months		54 Months		60 Months	
	n	%	n	%	n	%	n	%	n	%
Loss > 2 lines	10	13.5%	14	13.6%	11	11.5%	5	14.7%	1	16.7%
One-sided upper 95% CL ¹	21.8%		20.4%		18.3%		28.5%		58.2%	
N ²	74		103		96		34		6	

- 1 CL = exact confidence limit calculated based on Clopper Pearson method.
2 N = number of eyes with available data.

6.2 ENDOTHELIAL CELL DENSITY

Data on endothelial cell density (ECD) loss from implantation of the IMT are available from Protocols IMT-002 and IMT-002-LTM. ECD was assessed by specular microscopy preoperatively and at 3, 6, 9, 12, 24, 36, 42, and 48 months. The specular images were read by the central reading center at Emory University (H. Edelhauser, PhD and B. McCarey, PhD).

The endpoint for endothelial cell loss for the IMT-002 study specified ECD loss was not to exceed 17% one year after IMT implantation. The endpoint was not met; ECD loss at 12 months was 25%.

The mean ECD and percent change in ECD for available data as of the date of lock of the database are provided in Figures 10 and 11; these figures include 54 and 60 month data for the small number of subjects with data available at the time of data lock. The 54 and 60 month data are provided at the request of FDA. ECD data and analyses other than those presented in Figures 10 to 13 are provided through the 48 month visit. As can be seen in Figures 10 and 11, ECD loss for the cohorts of Operated Eyes and IMT-Implanted Eye are virtually identical. Further ECD analyses and discussion will therefore focus on IMT-implanted eyes.

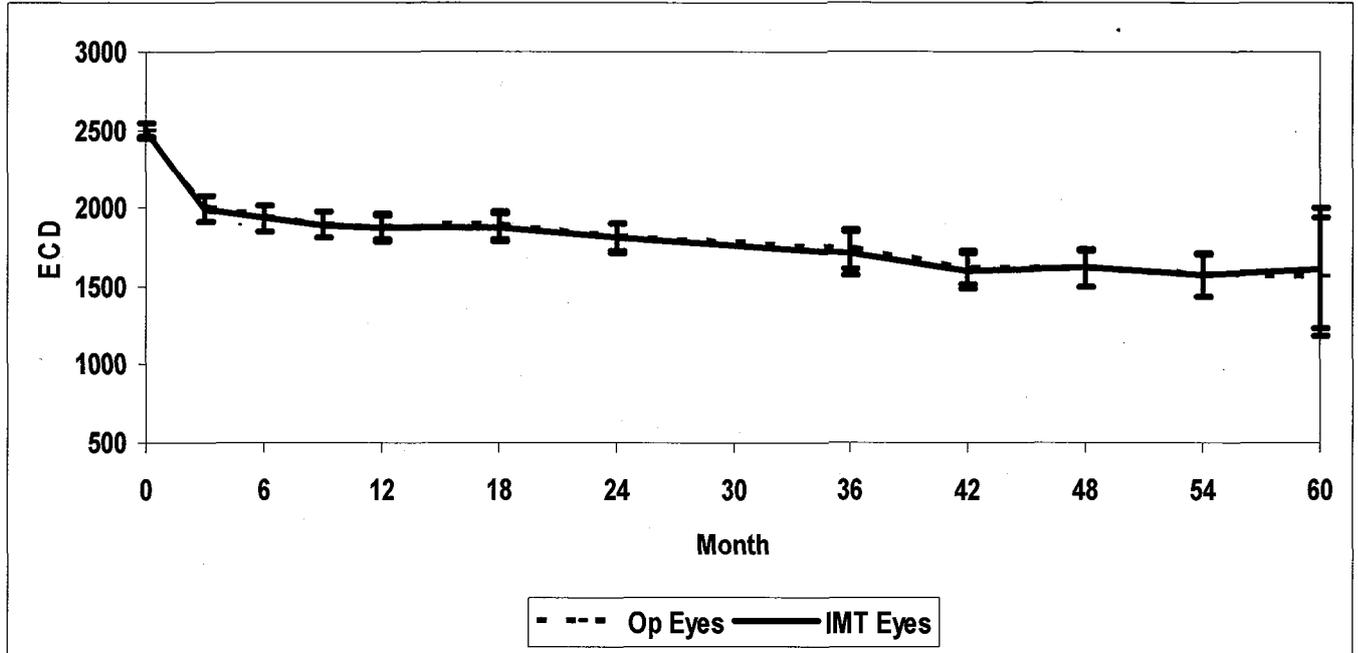
In this population of subjects with end-stage AMD and an average age of 76 at time of enrollment into the IMT-002 study, mean ECD at baseline was 2496 cells/mm². At 3 and 6 months after implantation, ECD was 1995 cells/mm² and 1937 cells/mm² respectively (Figure 10). ECD percent loss from baseline reported at 3 and 6 months post IMT implantation was 20% and 22%, respectively (Figure 11).

Mean ECD at 12 months after IMT-implantation was 1871 cells/mm², a 25% loss from baseline (Figures 10 and 11). Mean ECD at 24, 36 and 48 months was 1808, 1713, and 1620, respectively, with associated percent losses of 28%, 31%, and 35%, respectively. For the small number of subjects for whom data are available at 54 and 60 months, mean ECD was 1572 and 1616 cells/mm², respectively, a decline from baseline ECD of 37% at 54 months and 38% at 60 months.

The most significant loss of corneal endothelial cells occurred from baseline to 3 months and from baseline to 6 months. This acute ECD loss results primarily from the 11-12 mm surgical incision required for insertion of the IMT, as well as the manipulation of the IMT during implantation.

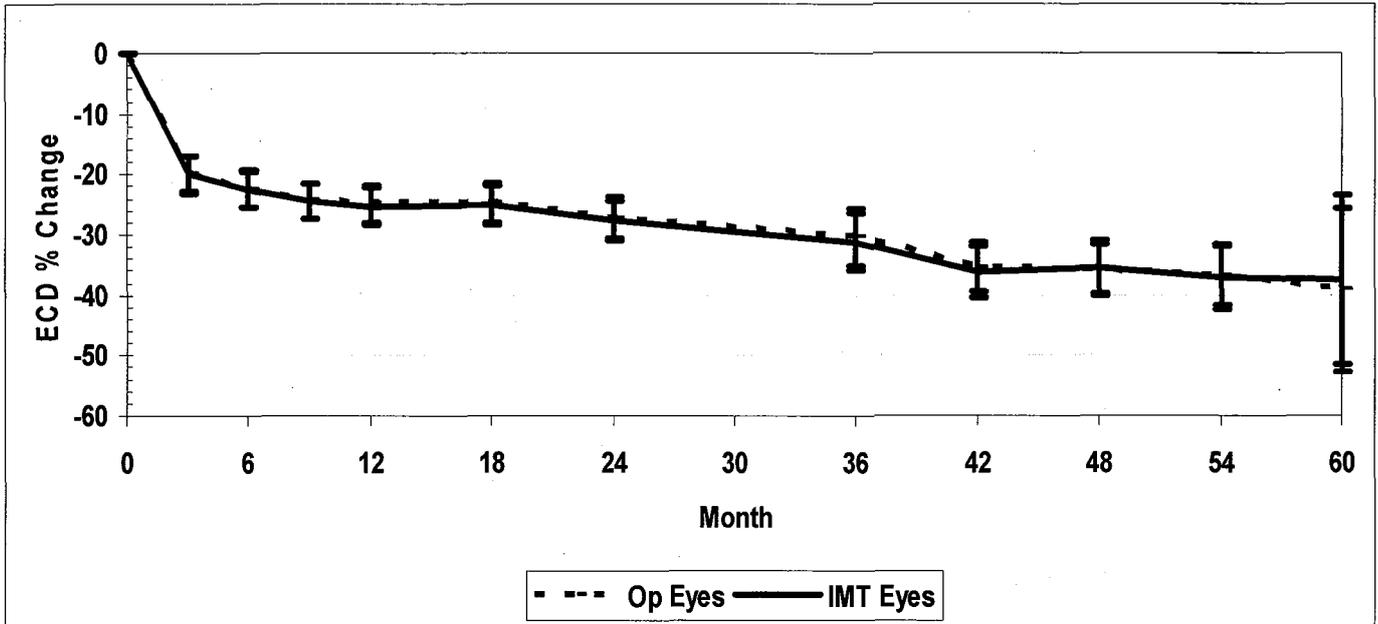
From 6 months and 12 months through 48 months, the rate of endothelial cell loss is relatively stable.

FIGURE 10
ECD (MEAN, CI)
OPERATED EYES AND IMT-IMPLANTED EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 37, FIGURE 9.1



		0	6	12	18	24	30	36	42	48	54	60	
Op Eyes	Mean	2498	2001	1936	1891	1881	1887	1813	1736	1612	1611	1572	1563
	95%CI	2451, 2546	1919, 2082	1855, 2016	1809, 1973	1795, 1967	1796, 1978	1723, 1903	1610, 1863	1505, 1720	1495, 1727	1439, 1706	1181, 1945
	N	216	198	200	190	190	182	173	79	110	94	65	18
	ECD<750	0 (0%)	6 (3%)	8 (4%)	9 (5%)	9 (5%)	13 (7%)	12 (7%)	3 (4%)	9 (8%)	7 (7%)	5 (8%)	3 (17%)
IMT Eyes	Mean	2496	1995	1937	1891	1871	1878	1808	1713	1595	1620	1572	1616
	95%CI	2447, 2545	1912, 2078	1856, 2018	1809, 1973	1786, 1957	1787, 1969	1718, 1898	1576, 1850	1481, 1709	1499, 1741	1431, 1713	1227, 2005
	N	206	193	198	190	186	180	171	70	101	88	60	17
	ECD<750	0 (0%)	6 (3%)	8 (4%)	9 (5%)	9 (5%)	13 (7%)	12 (7%)	3 (4%)	9 (9%)	7 (8%)	5 (8%)	2 (12%)

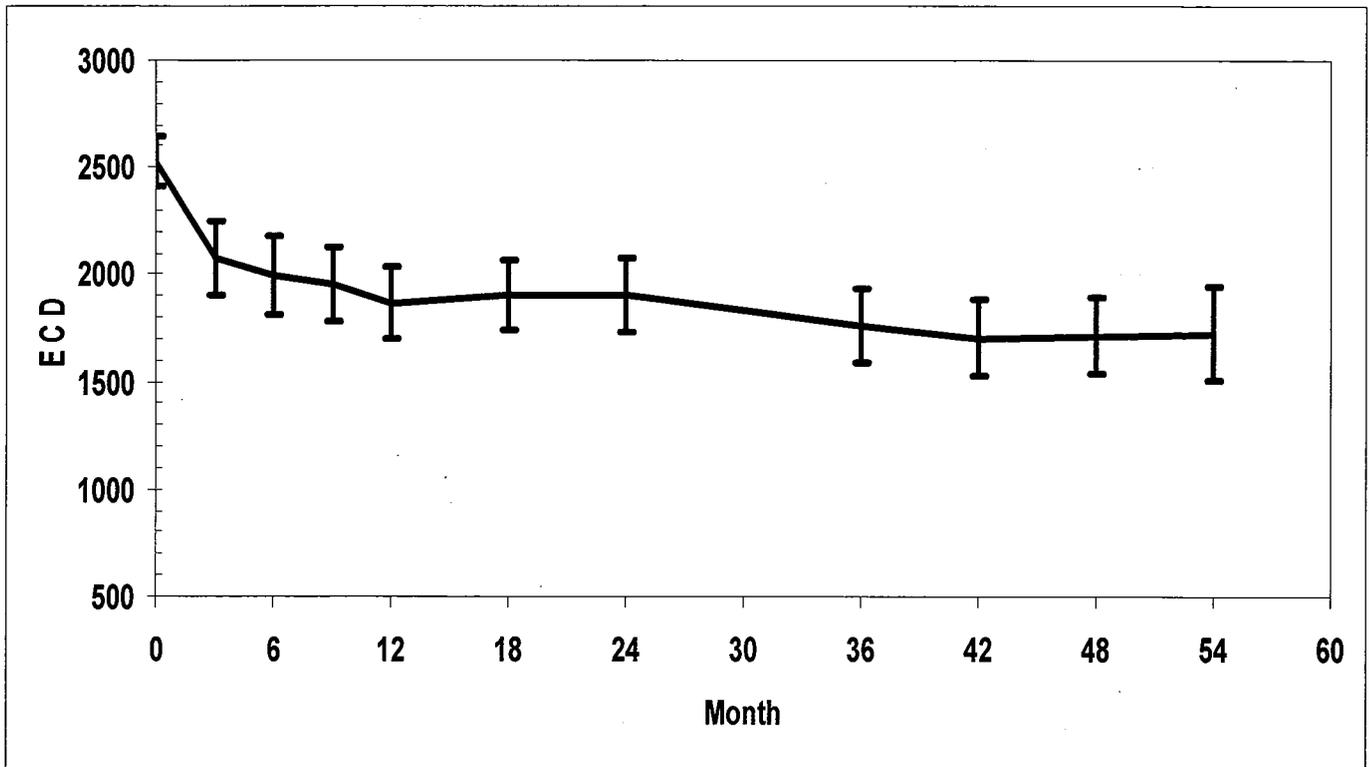
FIGURE 11
ECD % CHANGE (MEAN, CI) FROM BASELINE
OPERATED EYES AND IMT-IMPLANTED EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 38, FIGURE 9.2



		Preop	3 months	6 months	9 months	12 months	18 months	24 months	36 months	42 months	48 months	54 months	60 months
Op Eyes	Mean	0%	-20%	-22%	-24%	-25%	-25%	-27%	-30%	-35%	-36%	-37%	-39%
	95%CI		-23%, -17%	-25%, -20%	-27%, -21%	-28%, -22%	-28%, -21%	-31%, -24%	-35%, -26%	-40%, -31%	-40%, -32%	-42%, -32%	-53%, -26%
	N	216	198	200	190	190	182	173	79	110	94	65	18
IMT Eyes	Mean	0%	-20%	-22%	-24%	-25%	-25%	-28%	-31%	-36%	-35%	-37%	-38%
	95%CI		-23%, -17%	-25%, -19%	-27%, -21%	-28%, -22%	-28%, -22%	-31%, -24%	-36%, -26%	-40%, -32%	-40%, -31%	-43%, -32%	-51%, -24%
	N	206	193	198	190	186	180	171	70	101	88	60	17

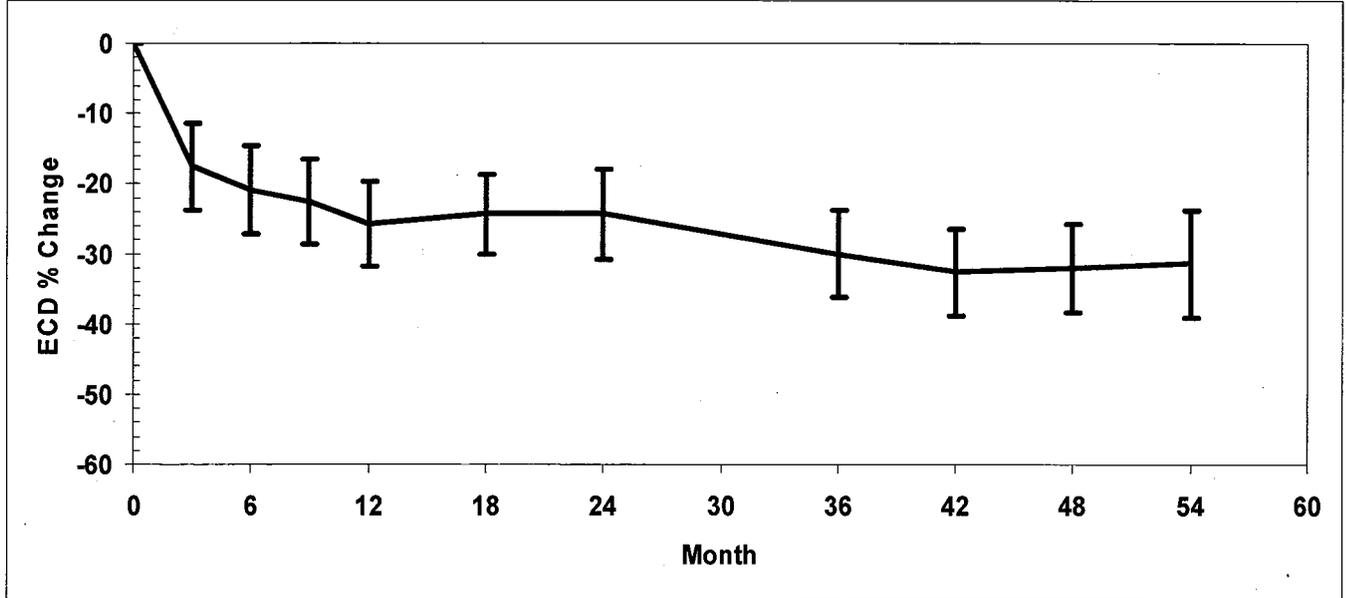
As can be seen from Figures 10 and 11, and for the 48-month consistent cohort shown in Figures 12 and 13 on the following pages, ECD loss is greatest in the first 3 to 6 months following implantation; the rate of loss then abates substantially. The effect of the 3 to 6 month loss carries over into the first year loss, which is 25%. In contrast, the annualized percent change in ECD loss was 3.4% for the period 6 to 48 months (see Table 25). The annual rate of loss from year 1 to year 2 was 2.2%, from year 2 to year 4 was 2.8%, and from year 3 to year 4 was 2.8% (Table 26). Mean ECD at 48 months post IMT implantation in these subjects with an average age of 80 was 1620 cells/mm² (Figure 10).

FIGURE 12
ECD (MEAN, CI)
48-MONTH CONSISTENT COHORT OF IMT-IMPLANTED EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 39, FIGURE 9.3



		Baseline	6 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months	54 Months	54 Months	
IMT	Mean	2525	2073	1993	1952	1866	1906	1900	1758	1702	1710	1723
Implanted	95%CI	2407, 2644	1900, 2246	1811, 2175	1777, 2127	1698, 2035	1743, 2069	1730, 2070	1584, 1933	1526, 1879	1532, 1887	1508, 1938
Eyes	N	43	43	43	43	43	43	43	43	43	43	27

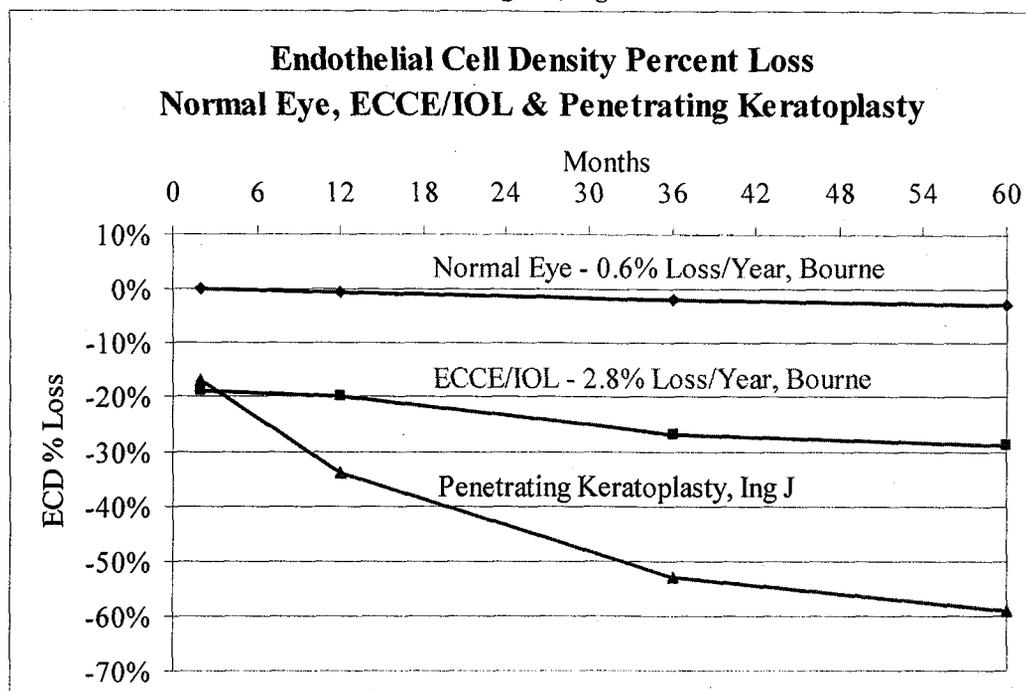
FIGURE 13
ECD % CHANGE (MEAN, CI) FROM BASELINE
48-MONTH CONSISTENT COHORT OF IMT-IMPLANTED EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 40, FIGURE 9.4



		Baseline	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months	54 Months
IMT Implanted Eyes	Mean	0%	-18%	-21%	-23%	-26%	-24%	-24%	-30%	-33%	-32%	-31%
	95% CI		-24% -11%	-27% -15%	-29% -17%	-32% -20%	-30% -19%	-31% -18%	-36% -24%	-39% -26%	-39% -26%	-39% -24%
	N	43	43	43	43	43	43	43	43	43	43	27

To provide additional context to ECD loss rates, adults have ECD levels of approximately 2500 cells/mm² at age 75. ECD loss over time in a normal adult eye is estimated at 0.6% per year (Bourne et al, 1997). Annual ECD loss in eyes undergoing extracapsular cataract extraction (ECCE) and IOL implant experienced a mean annual ECD loss of 2.8% per year (Bourne et al.,1994). The rate of annual ECD loss in penetrating keratoplasty cases is even higher (Ing et al. 1998). These data are displayed in Figure 14.

FIGURE 14
A013, Vol 1, Page 42, Figure 10



When ECD levels fall too low, the cornea may become edematous, will thicken and lose transparency, and corneal transplantation will be needed. The endothelial cell density needed to maintain corneal transparency is uncertain. One report states it is lower than 1,000 cells/mm² (Sugar et al, 1989), some report that several hundred, or 250-500 or 400-500 is high enough (Krachmer, Mannis, and Holland (editors), Cornea, second edition, Mosby; Armitage, 2003; Sobottka Ventura et al, 2001), and an informal survey of IMT-002 investigators yielded a consensus of 550-660 cells/mm.²

Loss of endothelial cells is an inevitable consequence of surgery to the cornea (Bourne et al, 2004; Bourne et al 1981), and surgery to implant an IMT is no exception. The acute ECD loss associated with any surgery is generally proportional to the size of the incision and associated surgical trauma. Patients undergoing extracapsular cataract extraction, for example, with incisions of approximately 8 to 12 mm, lost 13% (Diaz et al, 1998, 8 to 9 mm incisions) to 19% (Bourne et al, 1994, 12 mm incisions) of their endothelial cell density in the first 2 to 3 months post-surgery. Small-incision cataract surgery with phacoemulsification is associated with lower rates of ECD loss, on the order of 6 to 14%.

In eyes that underwent cataract removal and IOL implantation in fellow eyes of IMT-implanted eyes during the IMT-002 and IMT-002-LTM studies (N=21), mean ECD decreased by 14% from baseline to the first visit after surgery, and by 20% from baseline at the last available visit.

ECD loss from a surgical procedure, whether or not there is an implant, continues at a much slower rate after the sharp loss resulting from surgical trauma has abated (Bourne et al, 1994; Armitage et al, 2003). Thus, cataract surgery and other procedures such as penetrating keratoplasty incur an initial period of "fast loss" and thereafter an on-going period of "slow loss." The rate of slow loss is higher than the rate of loss associated with aging but much less rapid than the rapid component surgical loss. Armitage et al. (2003) and Bourne et al. (1994) investigated the loss from cataract extraction with and without implantation of an IOL, and found the median ECD loss was about 2.5% per year. They reported the annual ECD loss was not significantly different whether an IOL was implanted or the eye was aphakic.

ECD loss due to the surgical insult associated with IMT implantation followed the same pattern as reported for large incision cataract surgery and penetrating keratoplasty, specifically 22% at 6 months, and an average annual loss of approximately 3% thereafter. The 3% annualized rate of mean ECD loss in IMT-implanted eyes is generally consistent with the 2.8% long-term annual mean ECD loss reported by Bourne for eyes undergoing extracapsular cataract surgery and IOL implant (Bourne et al, 1994).

Because ECD was also measured in fellow eyes at each visit, it is also possible, as FDA suggested, to compare ECD loss in IMT-implanted eyes to ECD loss in the fellow eyes. The pattern of ECD loss in fellow eyes is similar to that in IMT-implanted eyes, but the rate of loss is somewhat lower. Paired analyses were performed for three cohorts: 1) fellow eyes of IMT-implanted eyes, 2) phakic fellow eyes of IMT-implanted eyes, and 3) pseudophakic fellow eyes of IMT-implanted eyes. The results of these analyses are presented in Tables 22 through 24.

In a paired analyses for the period 12 months post IMT implantation to the 48 month visit, ECD percentage change was -3% in fellow eyes and -6% in IMT-implanted eyes, a 3 percentage point difference over the three year period, Table 22.

ECD percentage change over the 36 months between 12 months and 48 months for phakic fellow eyes was -1% compared to a percentage change of -6% in the matched IMT-implanted eyes, a 5% difference (Table 23). Utilizing the annual rates of mean ECD loss reported by Bourne et al. (1997) for normal eyes, -0.6% annually, and eyes undergoing ECCE and IOL implant, -2.8% annually (Bourne et al., 1994), the estimated difference over 3 years in ECD percent change between normal eyes and eyes that have undergone ECCE and IOL implant is 6.6%, which is generally consistent with the 5% ECD percentage change difference between paired phakic fellow eyes and IMT-implanted eyes.

There was no difference in ECD percentage change between 12 months and 48 months for the cohort of matched pseudophakic fellow eyes compared to matched IMT-implanted eyes (Table 24).

TABLE 22
PAIRED ANALYSIS BETWEEN 12 TO 48 MONTHS FOR THE
DIFFERENCE IN ECD AND % CHANGE IN ECD BETWEEN
IMT-IMPLANTED EYES AND FELLOW EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 44, TABLE 19.1

	IMT-IMPLANTED EYES	FELLOW EYES	DIFFERENCE BETWEEN IMT-IMPLANTED AND FELLOW EYES
ECD Change from 12 to 48 Months			
N	87	87	87
Mean	-158	-58	99
95% CI	-233, -82	-121, 5	4, 195
Percent Change in ECD from 12 to 48 Months			
Mean	-6%	-3%	3%
95% CI	-11%, -1%	-6%, 0%	-2%, 9%

Difference = Fellow Eye - IMT-implanted Eye.

Subjects without ECD at 12 months or 48 Months were excluded.

TABLE 23
PAIRED ANALYSIS BETWEEN 12 TO 48 MONTHS FOR THE
DIFFERENCE IN ECD AND % CHANGE IN ECD BETWEEN
IMT-IMPLANTED EYES AND PHAKIC FELLOW EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 44, TABLE 19.2

	IMT-IMPLANTED EYES	PHAKIC FELLOW EYES	DIFFERENCE BETWEEN IMT-IMPLANTED AND FELLOW EYES
ECD Change from 12 to 48 Months			
N	56	56	56
Mean	-171	-9	162
95% CI	-259, -82	-58, 41	58, 265
Percent Change in ECD from 12 to 48 Months			
Mean	-6%	-1%	5%
95% CI	-13%, 0%	-3%, 2%	-2%, 12%

Difference = Fellow Eye - IMT-implanted Eye.

Subjects without ECD at 12 months or 48 Months were excluded.

Phakic Fellow Eyes = Fellow eyes without IOL implants at the beginning of study or during the study.

TABLE 24
PAIRED ANALYSIS BETWEEN 12 TO 48 MONTHS FOR THE
DIFFERENCE IN ECD AND % CHANGE IN ECD BETWEEN
IMT-IMPLANTED EYES AND PSEUDOPHAKIC FELLOW EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 45, TABLE 19.3

	IMT-IMPLANTED EYES	PSEUDOPHAKIC FELLOW EYES	DIFFERENCE BETWEEN IMT-IMPLANTED AND FELLOW EYES
ECD Change from 12 to 48 Months			
N	31	31	31
Mean	-134	-148	-14
95% CI	-281, 13	-302, 5	-208, 181
Percent Change in ECD from 12 to 48 Months			
Mean	-7%	-7%	0%
95% CI	-15%, 1%	-14%, 1%	-9%, 10%

Difference = Fellow Eye - IMT-implanted Eye.

Subjects without ECD at 12 months or 48 Months were excluded.

Pseudophakic Fellow Eyes = Fellow eyes with IOL implants at the beginning of study or during the study.

Because the principal cause of ECD loss in IMT-implanted eyes was the surgical insult, as evidenced by ECD loss of 20% and 22% at 3 and 6 months postoperatively, the risk factors potentially related to the acute loss of corneal endothelial cells were reviewed to assess the possibility of mitigating ECD loss and thereby improve the benefit to risk ratio. This review is discussed in the next section.

IDENTIFICATION OF RISK FACTORS FOR ENDOTHELIAL CELL LOSS

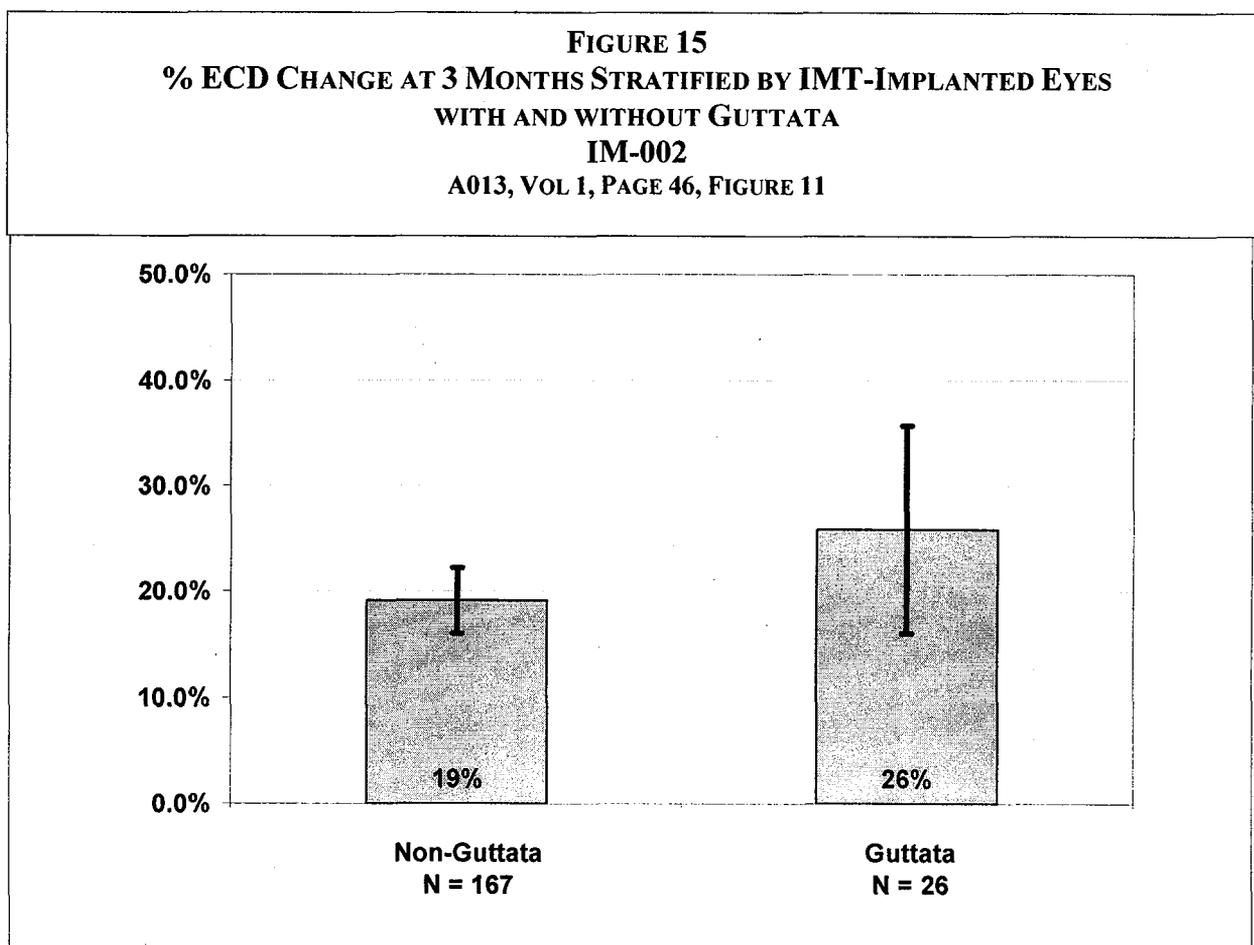
VisionCare evaluated a series of factors known to affect endothelial cell density for their contribution to the loss in ECD observed in the IMT implanted eyes. These factors included contact lens wear, history of diabetes, history of glaucoma and presence of chronic intraocular inflammatory reaction. These analyses were provided in Amendment 7, P050034. Patient medical histories and baseline information revealed there was no recent history of contact lens wear, i.e., within the 5-10 years prior to enrollment in the IMT clinical study. The small number of subjects with diabetic retinopathy at baseline or at any follow-up visit and the small number of eyes with glaucoma, defined as any report of IOP increase beyond 7 days postoperatively and requiring treatment, precluded any definitive conclusions from being drawn regarding the effect of these factors on ECD loss.

No statistically or clinically significant differences in ECD loss was observed for eyes with or without chronic inflammation, defined as inflammatory deposits on the IMT; iritis greater than 30 days in duration; pigment deposits and/or keratic precipitates on the IMT; synechiae; anterior chamber cells (>20 cells) and marked or severe flare on slit lamp examination for greater than 30 days.

Other risk factors potentially associated with ECD loss – presence of guttata in the eye, surgical specialty, learning curve, and anterior chamber depth – were also evaluated and are discussed below. These risk factors were previously discussed in Amendment 10, P050034.

GUTTATA

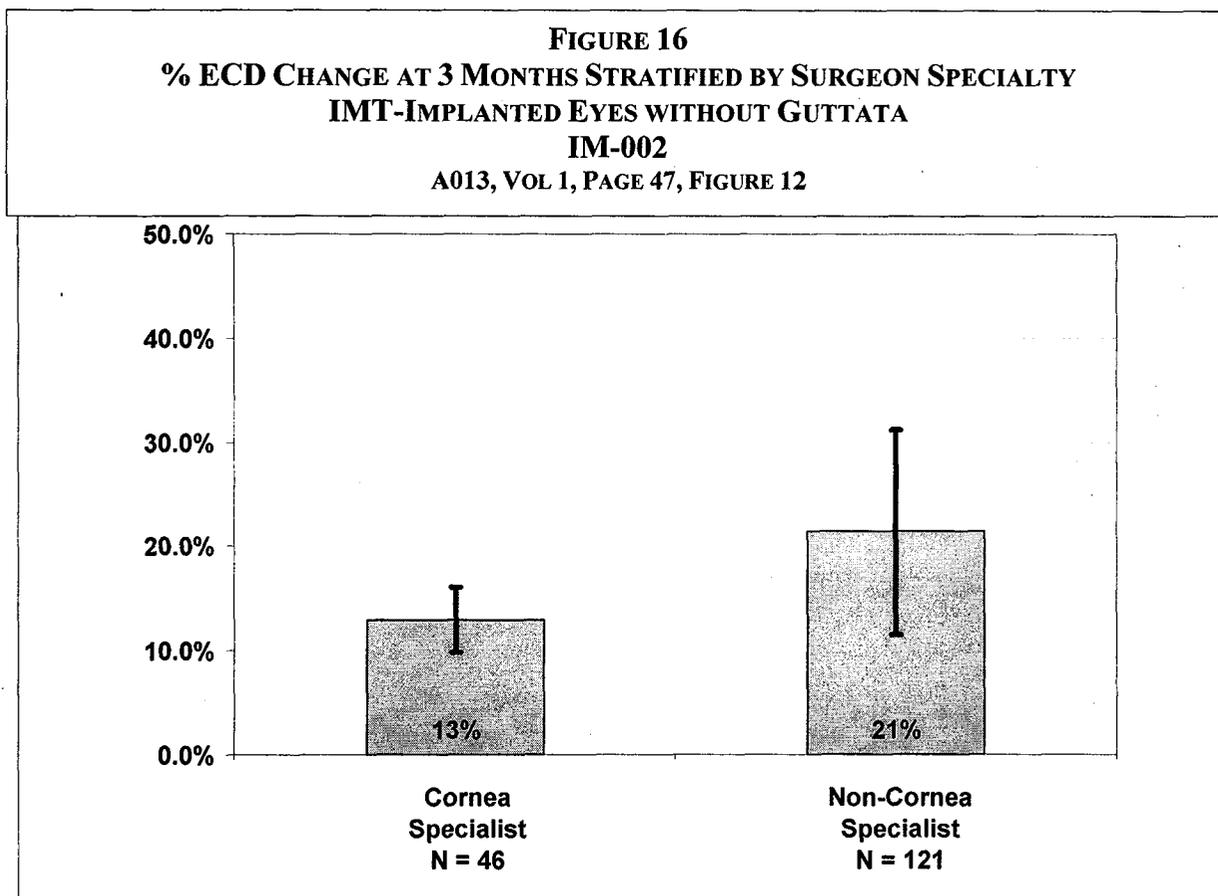
Corneal guttata has been shown to be a risk factor for endothelial cell loss following cataract surgery (Bourne et al, 1994). The same effect is seen in IMT surgery. As shown in Figure 15, the percent ECD loss at 3 months postoperatively was lower in non-guttata eyes, 19%, than in eyes with guttata, 26%.



Accordingly, VisionCare proposes to make the presence of guttata a contraindication to the use of the IMT. This and other contraindications, precautions, and warning issues are discussed below in the Labeling section, Section 7.

SURGEON SPECIALTY

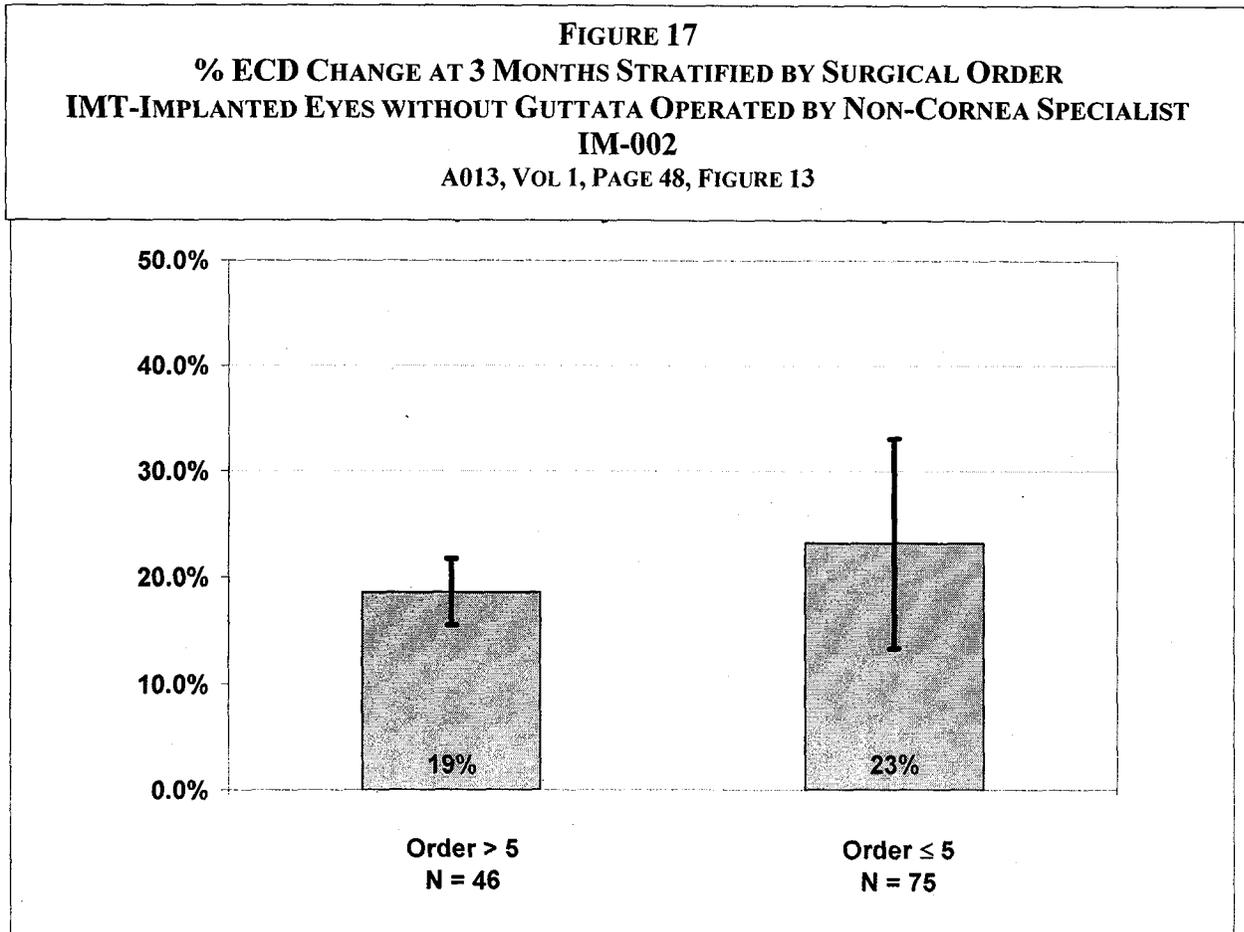
As shown in Figure 16, ECD loss was lower for eyes operated by cornea specialists than by non-cornea specialists. ("Cornea specialist" is defined as ophthalmologists who had fellowship or other specialty training in diseases and surgery of the cornea and who were at the time of the study regularly performing corneal surgical procedures such as penetrating keratoplasty.) At 3 months post-surgery, ECD loss for eyes operated by cornea specialist was 13%, while eyes operated by non-cornea specialists had mean ECD loss of 21%.



Although the number of subjects implanted by cornea specialist is modest, the lower ECD loss in these subjects compared to the loss in those implanted by non-cornea specialists suggests the desirability of labeling that limits implantation of the IMT to physicians who are experienced in the medical management and surgical treatment of the cornea. The discussion of labeling proposes such limitations.

LEARNING CURVE

A similar but less pronounced difference in ECD loss was observed for the learning curve, i.e., the first 5 eyes operated by non-cornea specialists (Figure 17). For these surgeons, lower ECD loss (19%) was observed in eyes operated after the learning curve of 5 eyes, compared to 23% ECD loss for eyes operated during the surgeon's first five cases.



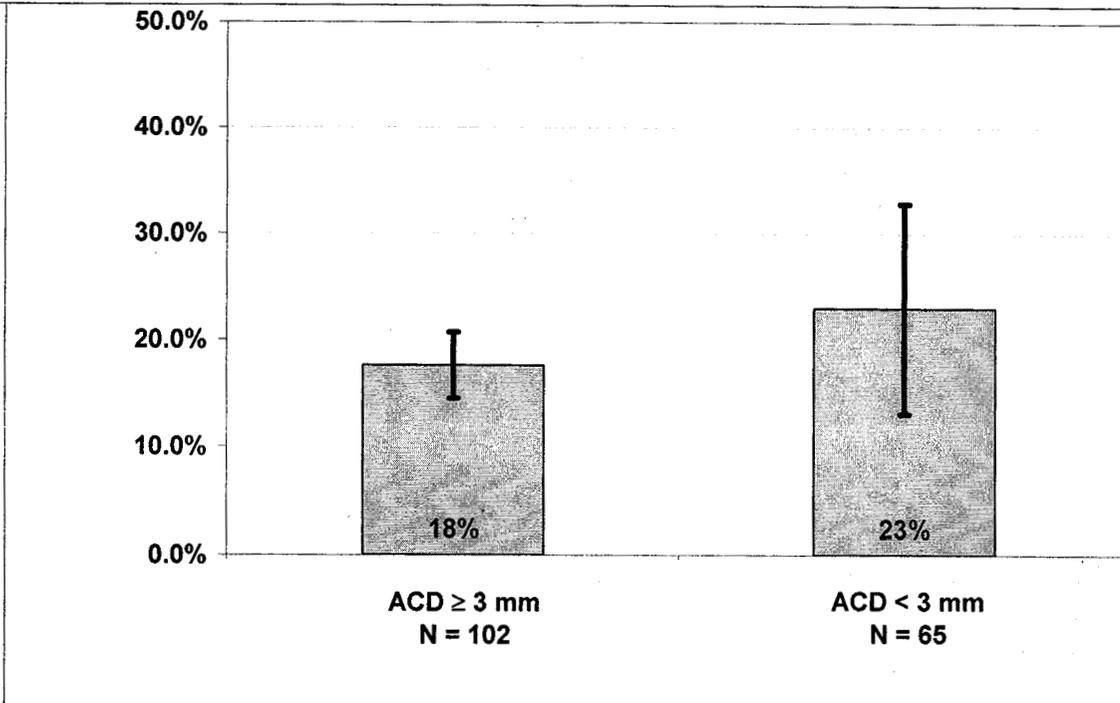
Surgical order had no effect on ECD loss when the surgery was performed by a cornea specialist. Although the learning curve effect for non-cornea specialists is modest, as part of its risk mitigation strategies, VisionCare will restrict use of the IMT to surgeons who have participated in training to be offered by the company.

ANTERIOR CHAMBER DEPTH (ACD)

ACD \geq 3.0 mm was associated with lower endothelial cell loss at 3 months post-implant. ECD percent change at 3 months post IMT implantation was 18% in subjects with an ACD \geq 3.0 mm as compared to 23% for subjects with an ACD $<$ 3.0 mm (Figure 18).

FIGURE 18
% ECD CHANGE AT 3 MONTHS STRATIFIED BY ACD
IMT-IMPLANTED EYES WITHOUT GUTTATA
IM-002

A013, VOL 1, PAGE 49, FIGURE 14



The finding of greater ECD loss in shallow anterior chambers (<3.0 mm) at 3 months is likely the result of less working space in the anterior chamber and more surgical trauma to the corneal endothelial monolayer. On this basis, the proposed labeling identifies a minimum ACD of 3.0 mm.

RELATIONSHIP AMONG AND BETWEEN COMBINED RISK FACTORS

As shown in the previous analyses, risk of endothelial cell loss can be substantially reduced by excluding eyes with guttata and eyes with shallow anterior chambers, by increasing surgeon experience and by limiting IMT implantation to cornea specialists.

An examination of the mean ECD and percent loss in ECD at 6 months further aids in establishing that the most substantive endothelial cell loss is a result of surgery, and that the risk factors identified can be used to mitigate cell loss. Mean ECD and percent loss in ECD at 6 months are presented in Table 25 for the following cohorts of eyes:

- IMT-implanted eyes;
- Non-guttata IMT-implanted eyes;
- Non-guttata IMT-implanted eyes with $ACD \geq 3.0$ mm; and
- IMT-implanted subjects age ≥ 65 , with no guttata eyes, with $ACD \geq 3.0$ mm, with surgery performed by a cornea specialist (fully risk-reduced cohort).

Information on the eyes that are excluded from each of these cohorts is also presented in Table 25. As shown, the percent loss in ECD at 6 months postoperatively is considerably lower in each of the risk-reduced cohorts (non-guttata eyes; non guttata eyes with $ACD \geq 3.0$ mm; and age ≥ 65 with no guttata, $ACD \geq 3.0$ mm with surgery performed by a cornea specialist) as compared to subjects that are excluded from the risk-reduced cohorts.

TABLE 25
MEAN ECD (MEAN, CI) AT BASELINE AND 6 MONTHS AND ECD % CHANGE (MEAN, CI) FROM BASELINE TO 6 MONTHS
POSTOPERATIVE VISIT
NON-RISK REDUCED COHORTS AND RISK REDUCED COHORTS
IMT-002 STUDY
(A019, PAGE 34, TABLE 4)

ECD	IMT-IMPLANTED EYES		IMT-IMPLANTED EYES NON-GUTTATA		IMT-IMPLANTED EYES NON-GUTTATA ACD ≥ 3.0 MM		IMT-IMPLANTED EYES RISK REDUCED COHORT ≥ 65 YEARS NON-GUTTATA ACD ≥ 3.0 MM IMPLANTED BY CORNEA SPECIALIST	
	BASELINE	6 MONTHS	BASELINE	6 MONTHS	BASELINE	6 MONTHS	BASELINE	6 MONTHS
N	206	198	180	172	112	107	33	33
ECD (MEAN)	2496	1937	2507	1970	2534	2046	2472	2063
95%CI	(2447, 2545)	(1856, 2018)	(2457, 2557)	(1884, 2056)	(2473, 2596)	(1945, 2146)	(2370, 2574)	(1887, 2239)
ECD % LOSS (MEAN)		22.4%		21.4%		19.0%		16.2%
95%CI		(19.4%, 25.3%)		(18.3%, 24.5%)		(15.3%, 22.7%)		(9.7%, 22.6%)
			IMT-IMPLANTED EYES EXCLUDED FROM COHORT ABOVE		IMT-IMPLANTED EYES EXCLUDED FROM COHORT ABOVE		IMT-IMPLANTED EYES NON-RISK REDUCED COHORT (EYES EXCLUDED FROM RISK REDUCED COHORT)	
N			26	26	94	91	173	165
ECD (MEAN)			2419	1719	2451	1809	2501	1912
95%CI			(2242, 2596)	(1476, 1963)	(2373, 2528)	(1680, 1937)	(2446, 2556)	(1820, 2003)
ECD % LOSS (MEAN)				28.8%		26.4%		23.6%
95%CI				(19.8%, 37.7%)		(21.8%, 30.9%)		(20.3%, 26.9%)

The effect of risk reduction for the periods 6 to 24 months, 12 to 24 months, 6 to 48 months, 24 to 48 months and 36 to 48 months is shown in Table 26, which presents mean ECD, mean percent ECD loss and annual percent ECD loss for the four cohorts:

- IMT-implanted eyes;
- Non-guttata IMT-implanted eyes;
- Non-guttata IMT-implanted eyes with $ACD \geq 3.0$ mm; and
- IMT-implanted subjects age ≥ 65 , with no guttata eyes, with $ACD \geq 3.0$ mm, with surgery performed by a cornea specialist (fully risk reduced cohort).

Eyes excluded from each of these cohorts are shown as well.

The annual percent loss in ECD for the period 6 to 48 months was approximately 3.4% for all cohorts except for the fully risk reduced cohort, which had an annual loss of 2.7%. A similar annual percent loss in ECD for the period from 24 to 48 months of approximately 3% was observed for all cohorts except for the fully risk reduced cohort, which had a lower annual loss per year.

These data establish that the annual rate of ECD loss did not increase over time for any of the cohorts, and the annual rate of ECD loss for each of the cohorts of eyes was generally stable and consistent with the long-term annual rate of ECD loss of 2.8% reported by Bourne and colleagues (1994) for extracapsular cataract extraction and IOL implantation.

TABLE 26
MEAN ECD, ECD % CHANGE FROM BASELINE, ANNUAL ECD % LOSS (MEAN, CI)
NON-RISK REDUCED COHORTS AND RISK REDUCED COHORTS
IMT-002 AND IMT-002-LTM STUDIES
(A019, PAGE 36, TABLE 5)

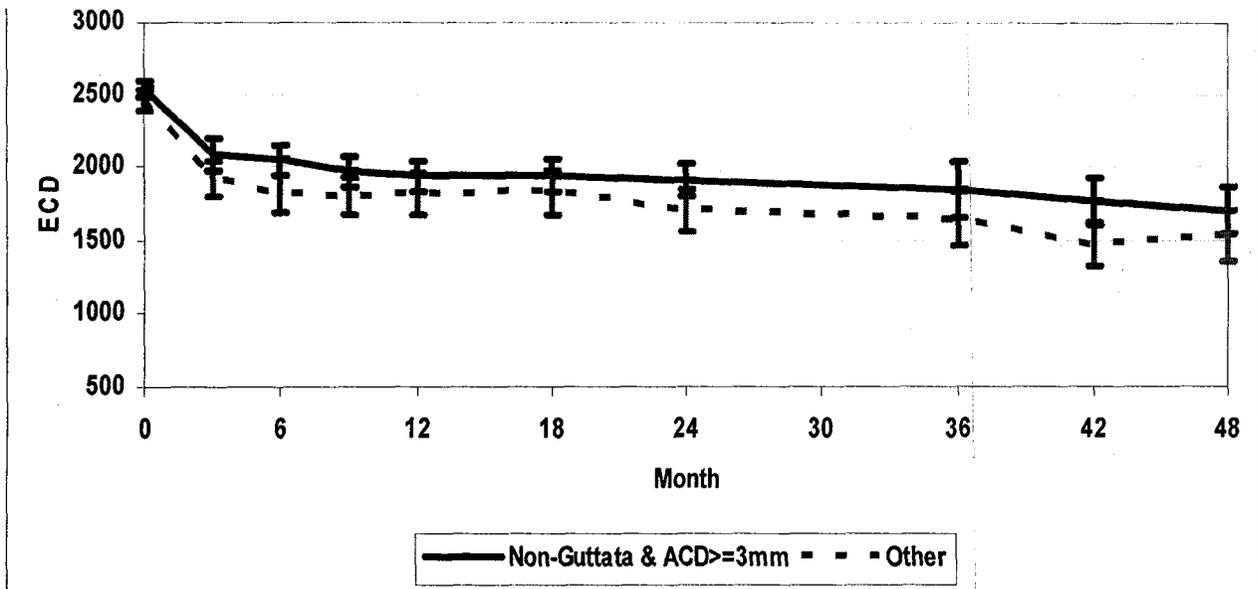
ECD	IMT-IMPLANTED EYES		NON-GUTTATA IMT-IMPLANTED EYES		NON-GUTTATA ACD ≥ 3.0 MM IMT-IMPLANTED EYES		≥ 65 YEARS NON-GUTTATA ACD ≥ 3.0 MM IMT-IMPLANTED EYES IMPLANTED BY CORNEA SPECIALISTS	
	6 MONTHS	24 MONTHS	6 MONTHS	24 MONTHS	6 MONTHS	24 MONTHS	6 MONTHS	24 MONTHS
	N	198	171	172	150	107	95	33
ECD (MEAN)	1937	1808	1970	1848	2046	1907	2063	1992
95%CI	(1856, 2018)	(1718, 1898)	(1884, 2056)	(1753, 1942)	(1945, 2146)	(1795, 2019)	(1887, 2239)	(1797, 2187)
ECD % LOSS (MEAN)	22.4%	27.7%	21.4%	26.5%	19.0%	25.0%	16.2%	19.4%
95%CI	(19.4%, 25.3%)	(24.4%, 31.0%)	(18.3%, 24.5%)	(23.0%, 29.9%)	(15.3%, 22.7%)	(21.0%, 29.1%)	(9.7%, 22.6%)	(12.0%, 26.7%)
ANNUAL % ECD LOSS 6 TO 24 MONTHS,								
N		168		147		94		27
MEAN		5.4%		5.3%		5.1%		3.1%
95%CI		(3.2%, 7.6%)		(3.0%, 7.7%)		(2.4%, 7.8%)		(-2.0%, 8.2%)
N	186	171	162	150	103	95	30	27
ECD (MEAN)	1871	1808	1904	1848	1935	1907	2018	1992
95%CI	(1786, 1957)	(1718, 1898)	(1815, 1993)	(1753, 1942)	(1831, 2039)	(1795, 2019)	(1834, 2202)	(1797, 2187)
ECD % LOSS (MEAN)	25.3%	27.7%	24.3%	26.5%	23.6%	25.0%	18.5%	19.4%
95%CI	(22.2%, 28.4%)	(24.4%, 31.0%)	(21.1%, 27.5%)	(23.0%, 29.9%)	(19.7%, 27.5%)	(21.0%, 29.1%)	(11.4%, 25.7%)	(12.0%, 26.7%)
ANNUAL % ECD LOSS 12 TO 24 MONTHS,								
N		169		148		94		26
MEAN		2.2%		2.3%		1.5%		3.6%
95%CI		(-1.0%, 5.5%)		(-1.3%, 5.9%)		(-3.0%, 6.0%)		(-4.3%, 11.5%)

TABLE 26 (CONTINUED)
MEAN ECD, ECD % CHANGE FROM BASELINE, ANNUAL ECD % LOSS (MEAN, CI)
NON-RISK REDUCED COHORTS AND RISK REDUCED COHORTS AND
IMT-002 AND IMT-002-LTM STUDIES
(A019, PAGE 36, TABLE 5)

ECD	IMT-IMPLANTED EYES		NON-GUTTATA IMT-IMPLANTED EYES		NON-GUTTATA IMT-IMPLANTED EYES		NON-GUTTATA ACD ≥ 3.0 MM IMT-IMPLANTED EYES		≥ 65 YEARS, NON-GUTTATA ACD ≥ 3.0 MM IMT-IMPLANTED EYES IMPLANTED BY CORENA SPECIALISTS	
	6 MONTHS	48 MONTHS	6 MONTHS	48 MONTHS	6 MONTHS	48 MONTHS	6 MONTHS	48 MONTHS	6 MONTHS	48 MONTHS
N	198	88	172	76	107	45	33	12		
ECD (MEAN)	1937 (1856, 2018)	1620 (1499, 1741)	1970 (1884, 2056)	1670 (1542, 1798)	2046 (1945, 2146)	1704 (1544, 1864)	2063 (1887, 2239)	1817 (1507, 2126)		
95%CI										
ECD % LOSS (MEAN)	22.4% (19.4%, 25.3%)	35.4% (31.0%, 39.8%)	21.4% (18.3%, 24.5%)	34.1% (29.4%, 38.8%)	19.0% (15.3%, 22.7%)	33.3% (27.2%, 39.4%)	16.2% (9.7%, 22.6%)	25.6% (13.1%, 38.1%)		
95%CI										
ANNUAL % ECD LOSS 6 TO 48 MONTHS (N)										
MEAN		3.4%		3.3%		3.6%		2.7%		
95%CI		(2.1%, 4.7%)		(1.9%, 4.7%)		(1.9%, 5.2%)		(-1.2%, 6.5%)		
N	171	88	150	76	95	45	24 MONTHS	48 MONTHS	24 MONTHS	48 MONTHS
ECD (MEAN)	1808 (1718, 1898)	1620 (1499, 1741)	1848 (1753, 1942)	1670 (1542, 1798)	1907 (1795, 2019)	1704 (1544, 1864)	1992 (1797, 2187)	1817 (1507, 2126)		
95%CI										
ECD % LOSS (MEAN)	27.7% (24.4%, 31.0%)	35.4% (31.0%, 39.8%)	26.5% (23.0%, 29.9%)	34.1% (29.4%, 38.8%)	25.0% (21.0%, 29.1%)	33.3% (27.2%, 39.4%)	19.4% (12.0%, 26.7%)	25.6% (13.1%, 38.1%)		
95%CI										
ANNUAL % ECD LOSS 24 TO 48 MONTHS (N)										
MEAN		2.8%		2.6%		3.5%		0.8%		
95%CI		(1.0%, 4.6%)		(0.6%, 4.6%)		(1.1%, 5.9%)		(-5.8%, 7.3%)		
N	70	88	63	76	36	45	9	12		
ECD (MEAN)	1713 (1576, 1850)	1620 (1499, 1741)	1728 (1580, 1875)	1670 (1542, 1798)	1843 (1659, 2027)	1704 (1544, 1864)	1871 (1553, 2189)	1817 (1507, 2126)		
95%CI										
ECD % LOSS (MEAN)	31.2% (26.3%, 36.0%)	35.4% (31.0%, 39.8%)	30.9% (25.6%, 36.1%)	34.1% (29.4%, 38.8%)	28.4% (21.7%, 35.0%)	33.3% (27.2%, 39.4%)	21.9% (10.7%, 33.2%)	25.6% (13.1%, 38.1%)		
95%CI										
ANNUAL % ECD LOSS 36 TO 48 MONTHS (N)										
MEAN		2.8%		2.5%		3.2%		-2.6%		
95%CI		(-1.4%, 7.0%)		(-2.0%, 6.9%)		(-2.9%, 9.2%)		(-7.6%, 2.5%)		

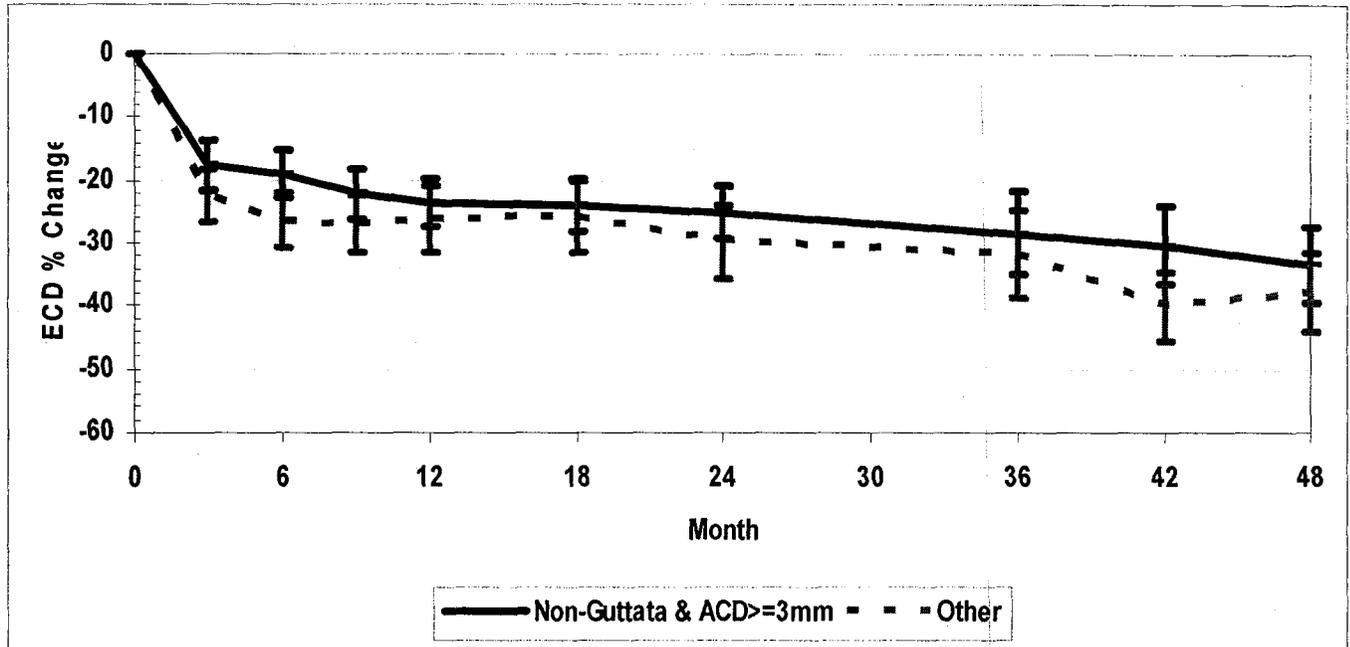
The effects of combining these risk reduction factors are illustrated in Figures 19 and 20. For subjects with no guttata and ACD ≥ 3.0 mm, mean ECD loss and percent ECD loss were lower than for subjects with guttata and ACD < 3.0 mm at 3 months (-454 cells/mm² versus -543 cells/mm², and -19% versus -22%) and at 6 months (-480 cells/mm² versus -651 cells/mm² and -19% versus -26%) after IMT implantation. As described earlier in this executive summary, this reduced acute surgical risk at 3 and 6 months was maintained at later study visits, i.e., through 48 months.

FIGURE 19
ECD (MEAN, CI) IN IMT-IMPLANTED EYES WITHOUT GUTTATA AND WITH ACD ≥ 3.0 MM
VS OTHER EYES
IM-002 AND IMT-002-LTM
A013, VOL 1, PAGE 50, FIGURE 15



		Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months
Non-Guttata & ACD ≥ 3 mm	Mean	2534	2080	2046	1968	1935	1935	1907	1843	1769	1704
	95%CI	2473, 2596	1970, 2189	1945, 2146	1864, 2072	1831, 2039	1823, 2048	1795, 2019	1659, 2027	1614, 1925	1544, 1864
	N	112	102	107	103	103	100	95	36	50	45
	ECD < 750	0 (0%)	2 (2%)	2 (2%)	4 (4%)	4 (4%)	5 (5%)	3 (3%)	1 (3%)	3 (6%)	4 (9%)
Other	Mean	2460	1917	1809	1799	1817	1823	1701	1647	1469	1528
	95%CI	2387, 2532	1795, 2039	1683, 1934	1670, 1928	1674, 1961	1672, 1975	1554, 1847	1463, 1830	1322, 1617	1356, 1700
	N	104	96	93	87	87	81	77	41	58	48
	ECD < 750	0 (0%)	4 (4%)	6 (6%)	5 (6%)	5 (6%)	8 (10%)	9 (12%)	2 (5%)	6 (10%)	3 (6%)

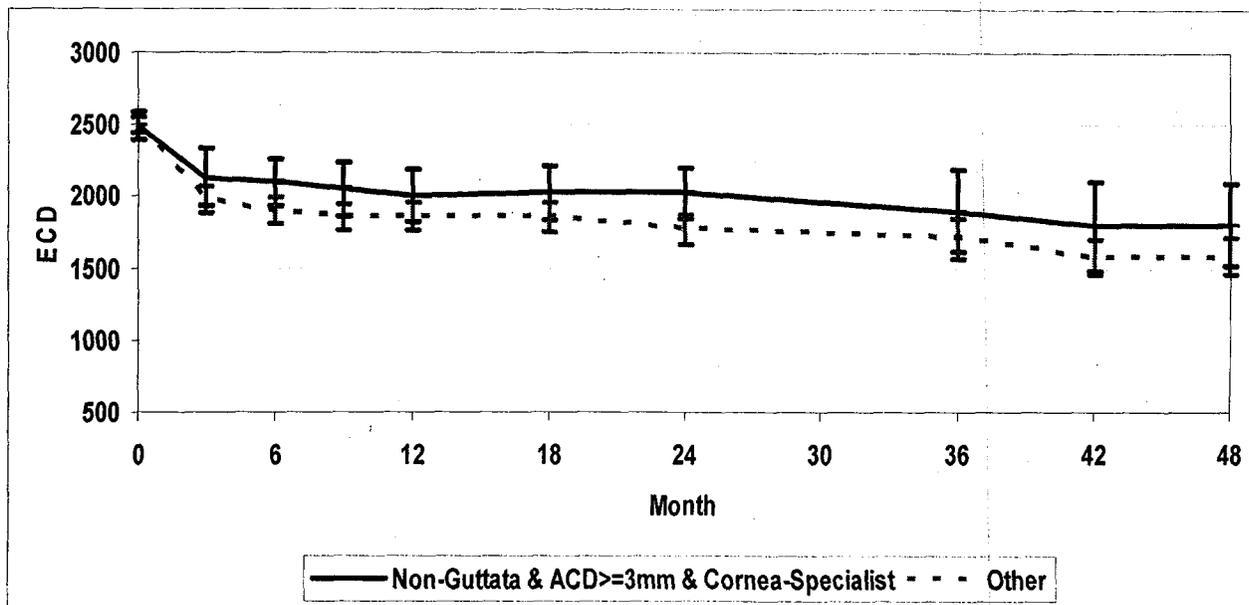
FIGURE 20
ECD % CHANGE (MEAN, CI) FROM BASELINE IN IMT-IMPLANTED EYES
WITHOUT GUTTATA AND WITH ACD ≥ 3.0 MM VS OTHER EYES
IM-002 AND IMT-002-LTM
A013, VOL 1, PAGE 51, FIGURE 16



		Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months
Non-Guttata & ACD ≥ 3mm	Mean	0%	-18%	-19%	-22%	-24%	-24%	-25%	-28%	-30%	-33%
	95%CI		-22%, -14%	-23%, -15%	-26%, -18%	-28%, -20%	-28%, -20%	-29%, -21%	-35%, -22%	-36%, -24%	-39%, -27%
	N	112	102	107	103	103	100	95	36	50	45
Other	Mean	0%	-22%	-26%	-27%	-26%	-26%	-30%	-32%	-40%	-38%
	95%CI		-27%, -18%	-31%, -22%	-31%, -23%	-32%, -21%	-31%, -20%	-36%, -24%	-39%, -25%	-46%, -34%	-44%, -32%
	N	104	96	93	87	87	81	77	41	58	48

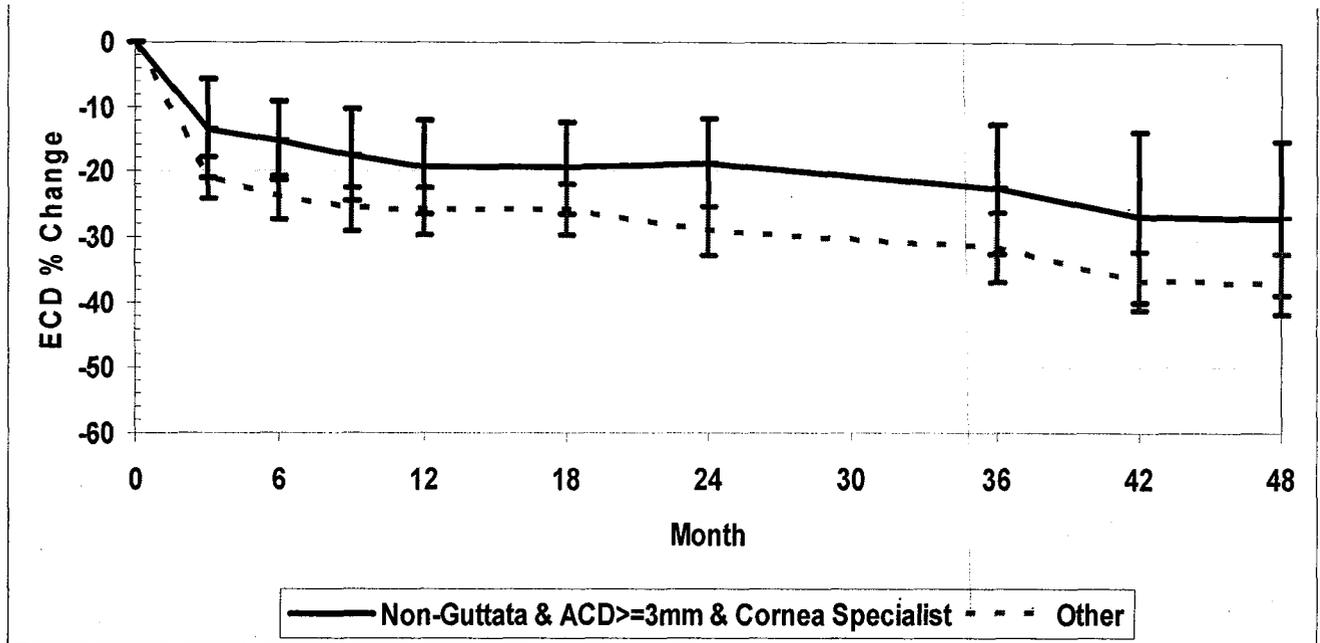
Acute ECD loss can be further reduced by limiting implantation of the IMT to cornea specialists. The effects of this limitation in non-guttata eyes with ACD ≥ 3.0 mm are illustrated in Figures 21 and 22. The reduction in mean ECD at 3 and 6 months resulting from surgical risk was maintained at later visits.

FIGURE 21
ECD (MEAN, CI) IN IMT-IMPLANTED EYES WITHOUT GUTTATA AND WITH ACD ≥ 3.0 MM
IMPLANTED BY CORNEA SPECIALIST VS OTHER EYES
IM-002 AND IMT-002-LTM
 A013, VOL 1, PAGE 52, FIGURE 17



		Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months
Non-Guttata	Mean	2488	2128	2099	2047	2007	2024	2024	1897	1793	1803
	95%CI	2391, 2586	1926, 2330	1932, 2265	1862, 2233	1826, 2189	1834, 2214	1843, 2204	1612, 2182	1489, 2096	1520, 2086
Cornea-Specialist	N	36	31	36	32	33	31	30	10	13	13
	ECD<750	0 (0%)	1 (3%)	1 (3%)	1 (3%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)
Other	Mean	2500	1977	1900	1859	1855	1859	1768	1710	1581	1580
	95%CI	2447, 2554	1887, 2067	1809, 1991	1768, 1950	1758, 1952	1756, 1961	1667, 1870	1568, 1852	1464, 1698	1453, 1708
	N	180	167	164	158	157	151	143	68	96	81
	ECD<750	0 (0%)	5 (3%)	7 (4%)	8 (5%)	8 (5%)	12 (8%)	12 (8%)	3 (4%)	8 (8%)	6 (7%)

FIGURE 22
ECD % CHANGE (MEAN, CI) FROM BASELINE IN IMT-IMPLANTED EYES WITHOUT GUTTATA
AND WITH ACD \geq 3.0 MM
IMPLANTED BY CORNEA SPECIALIST VS OTHER EYES
IM-002 AND IMT-002-LTM
A013, VOL 1, PAGE 53, FIGURE 18



		Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months
Non-Guttata ACD \geq 3mm Cornea- trained	Mean	0%	-14%	-15%	-17%	-19%	-19%	-19%	-23%	-27%	-27%
	95%CI		-21%, -6%	-21%, -9%	-25%, -10%	-26%, -12%	-26%, -12%	-26%, -12%	-33%, -13%	-40%, -14%	-39%, -15%
	N	36	31	36	32	33	31	30	10	13	13
Other	Mean	0%	-21%	-24%	-26%	-26%	-26%	-29%	-32%	-37%	-37%
	95%CI		-24%, -18%	-27%, -21%	-29%, -23%	-30%, -22%	-30%, -22%	-33%, -25%	-37%, -26%	-41%, -32%	-42%, -33%
	N	180	167	164	158	157	151	143	68	96	81

INCIDENCE OF KEY RISK FACTORS FOR ECD LOSS IN EYES WITH ECD <1,000 CELLS/MM² AND WITH ECD <750 CELLS/MM²

As a means of further examining and defining contributors to endothelial cell loss, IMT-implanted eyes in Protocols IMT-002 and IMT-002-LTM who presented with within-eye mean ECD <1,000 cells/mm² during the course of the studies were assessed for the presence of guttata, surgical order/learning curve (one of first 5 eyes operated by any study surgeon), baseline ACD <3.0 mm, and surgeon specialty, i.e., cornea trained or non-cornea trained. (Within-eye mean ECD is the average of the ECD at each visit for an individual study eye.)

The incidence of these risk factors in the subset of 22 eyes is presented in Table 27. As shown, the majority of these eyes (86%) were operated by non-cornea trained surgeons, 73% were in the learning curve for these surgeons, and 59% had anterior chamber depth of <3.00 mm at baseline. To further evaluate the impact of these risk factors on endothelial cell loss, the 22 eyes with ECD <1000 cells/mm² were categorized into cumulative risk levels (Table 28). All of the eyes in this group had at least one risk factor (Table 28), and the large majority (90%) presented more than one risk factor associated with greater endothelial cell loss. The most common risk factor was represented by IMT placement performed by a non-cornea specialist, followed by surgical order, and shallow anterior chamber (<3.0 mm). All three of these risk factors were present in 27% of the 22 eyes, and 2 of the 3 risks are found in combination in 50% of the 22 eyes in this cohort.

TABLE 27
INCIDENCE OF RISK FACTORS IN EYES WITH MEAN ECD <1000 CELLS/MM²
IMT-IMPLANTED EYES (WITHIN-EYE MEAN FROM 6 TO 48 MONTHS)
IMT-002 AND IMT-002-LTM
A010, VOL 1, PAGE 27, TABLE 18

Presence of Guttata	4/22 (18.2%)
Learning Curve (First 5 Eyes of Any Surgeon)	16/22 (72.7%)
ACD <3.0 mm	13/22 (59.1%)
Surgeon Specialty (Non-cornea Specialist)	19/22 (86.4%)

TABLE 28
COMBINATION OF RISK FACTORS IN EYES WITH MEAN ECD <1000 CELLS/MM²
IMT-IMPLANTED EYES (WITHIN-EYE MEAN FROM 6 TO 48 MONTHS)
IMT-002 AND IMT-002-LTM
A010, VOL 1, PAGE 28, TABLE 19

ONE RISK FACTOR	2/22 (9.1%)
TWO RISK FACTORS	11/22 (50.0%)
THREE RISK FACTORS	6/22 (27.3%)
FOUR RISK FACTORS	2/22 (9.1%)

The contribution of the identified risk factors was also evaluated by considering IMT-implanted eyes with post-surgical ECD <750 cells/mm². As shown in Tables 29 and 30, the most common risk factor in this cohort of eyes was surgery by a non-cornea specialist. In the majority of these subjects (8 of 10), IMT implantation was performed by non-cornea specialists, and 7 of the 10 eyes were in the learning curve for these surgeons. Six of the 10 eyes in this cohort also had anterior chamber depth of <3.00 mm at baseline.

TABLE 29
INCIDENCE OF RISK FACTORS IN EYES WITH MEAN ECD < 750 CELLS/MM²
IMT-IMPLANTED EYES (WITHIN-EYE MEAN FROM 6 TO 48 MONTHS)
IMT-002 AND IMT-002 LTM
A013, VOL 1, PAGE 54, TABLE 20.1

PRESENCE OF GUTTATA	1/10 (10.0%)
LEARNING CURVE (FIRST 5 EYES OF ANY SURGEON)	7/10 (70.0%)
ACD < 3.0 MM	6/10 (60.0%)
SURGEON SPECIALTY (NON-CORNEA SPECIALIST)	8/10 (80.0%)

Nine of ten subjects with ECD <750 cells/mm² presented with two or more risk factors, as shown in Table 30.

TABLE 30
COMBINATION OF RISK FACTORS IN EYES WITH MEAN ECD < 750 CELLS/MM²
IMT-IMPLANTED EYES (WITHIN-EYE MEAN FROM 6 TO 48 MONTHS)
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 54, TABLE 20.2

NO RISK FACTORS	1/10 (10.0%)
ONE RISK FACTOR	0/10 (0.0%)
TWO RISK FACTORS	6/10 (60.0%)
THREE RISK FACTORS	2/10 (20.0%)
FOUR RISK FACTORS	1/10 (10.0%)

These findings confirm that ECD <1000 cells/mm² and ECD <750 cells/mm² are associated with well-defined risk factors for endothelial cell loss identified in the current proposed labeling for the IMT. The identification of these risk factors is important in the development of labeling intended to significantly mitigate the risk of mean ECD <1000 cells/mm² and <750 cells/mm².

The utility of labeling that identifies the key risk factors for endothelial cell loss is further supported by the analyses presented in Tables 31 and 32, which display the within-eye change in mean ECD between 6 and 48 months. Within-eye mean ECD from 6 to 48 months is higher, and the number and proportion of eyes with ECD < 1000 and < 750 cells/mm² is substantially decreased for eyes without guttata, for eyes with ACD of at least 3 mm, and for eyes in which the IMT is implanted by a cornea-trained specialist. IMT implantation performed after the surgeon had previously performed 5 cases was also associated with higher within-eye mean ECD and lower numbers of eyes with ECD < 1000 and < 750 cells/mm².

Thus, the most substantial risk mitigation for ECD loss is represented by the risk-reduced cohort, i.e., non-guttata eyes with ACD ≥ 3.0 mm, with IMT placement performed by a cornea trained surgeon. This combination of factors decreased the incidence of ECD < 1000 cells/mm² from 10.9% for all IMT-implanted eyes to 2.8% for the risk-reduced cohort. A similar decrease is observed for the incidence of ECD < 750 cells/mm².

While the confidence intervals for this analysis are relatively large, the consistency of this finding across the descriptive analyses of ECD loss and the clear clinical relevance of these factors in decreasing risk of ECD loss supports the utility of applying these findings to labeling for the IMT.

Importantly, the three factors with the most significant contribution to mitigation of risk for ECD loss are also factors that can be readily implemented in labeling and employed prospectively in screening patients for IMT implantation and ensuring that physicians are adequately warned of the need for training in surgery of the cornea. Finally, the finding of less endothelial cell loss with surgeon experience in performing IMT implantation further underscores the need for surgeon training in the procedure for IMT placement. A requirement that all prospective IMT surgeons complete a formal training course has been proposed by VisionCare in P050034. (Information on physician training is provided in Appendix 15.)

TABLE 31
WITHIN-EYE MEAN ECD FOR 6 TO 48 MONTHS
PREDICTED PROBABILITY OF ECD < 1000 CELLS/MM²
IMT-IMPLANTED EYES
IMT-002 AND IMT-002-LTM
(A013, VOL 1, PAGE 174, TABLE 20.4)

SUBSET	TOTAL NUMBER OF EYES	MEAN (SD) OF WITHIN-EYE MEAN ECD CELLS/MM ²	NUMBER OF EYES WITH WITHIN-EYE MEAN ECD < 1000 CELLS/MM ²	% OF EYES WITH WITHIN-EYE MEAN ECD < 1000 CELLS/MM ²	95% CI ¹ FOR % OF EYES WITH WITHIN-EYE MEAN ECD < 1000 CELLS/MM ²
IMT EYES	201	1830.6 (571.7)	22	10.9%	(7.0%, 16.1%)
NON-GUTTATA EYES	175	1861.9 (562.3)	18	10.3%	(6.2%, 15.8%)
NON-GUTTATA EYES WITH SURGICAL ORDER >5	72	1902.1 (545.1)	5	6.9%	(2.3%, 15.5%)
NON-GUTTATA EYES WITH ACD ≥3	108	1924.9 (513.3)	7	6.5%	(2.6%, 12.9%)
NON-GUTTATA EYES IMPLANTED BY CORNEA SPECIALISTS	53	1963.4 (524.8)	3	5.7%	(1.2%, 15.7%)
RISK-REDUCED COHORT					
≥ 65 YEARS NON-GUTTATA EYES ACD ≥ 3.0 MM IMPLANTED BY CORNEA SPECIALISTS	33	1985.9 (496.0)	1	3.0%	(0.1%, 15.8%)
NON-RISK REDUCED COHORT					
EYES EXCLUDED FROM THE RISK REDUCED COHORT	168	1800.1 (581.9)	21	12.5%	(7.9%, 18.5%)

¹Exact confidence interval per Clopper-Pearson method.

TABLE 32
WITHIN-EYE MEAN ECD FOR 6 TO 48 MONTHS
PREDICTED PROBABILITY OF ECD < 750 CELLS/MM²
IMT-IMPLANTED EYES
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 55, TABLE 20.3

SUBSET	TOTAL NUMBER OF EYES	MEAN (SD) OF WITHIN-EYE MEAN ECD CELLS/MM ²	NUMBER OF EYES WITH WITHIN-EYE MEAN ECD < 1000 CELLS/MM ²	% OF EYES WITH WITHIN-EYE MEAN ECD < 1000 CELLS/MM ²	95% CI ¹ FOR % OF EYES WITH WITHIN-EYE MEAN ECD < 1000 CELLS/MM ²
IMT EYES	201	1830.6 (571.7)	10	5.0%	(2.4%, 9.0%)
NON-GUTTATA EYES	175	1861.9 (562.3)	9	5.1%	(2.4%, 9.5%)
NON-GUTTATA EYES WITH SURGICAL ORDER >5	72	1902.1 (545.1)	3	4.2%	(0.9%, 11.7%)
NON-GUTTATA EYES WITH ACD ≥3	108	1924.9 (513.3)	4	3.7%	(1.0%, 9.2%)
NON-GUTTATA EYES IMPLANTED BY CORNEA SPECIALISTS	53	1963.4 (524.8)	2	3.8%	(0.5%, 13.0%)
RISK-REDUCED COHORT					
≥ 65 YEARS NON-GUTTATA EYES ACD ≥ 3.0 MM IMPLANTED BY CORNEA SPECIALISTS	33	1985.9 (496.0)	1	3.0%	(0.1%, 15.8%)
NON-RISK REDUCED COHORT					
EYES EXCLUDED FROM THE RISK REDUCED COHORT	168	1800.1 (581.9)	9	5.4%	(2.5%, 9.9%)

¹Exact confidence interval per Clopper-Pearson method.

BCVA FOR THE RISK REDUCED COHORT

While it would not be anticipated that the BCVA outcomes might be different for the risk reduced and non-risk reduced cohorts of eyes since ECD loss and the factors contributing to this loss are unrelated to visual outcomes, at FDA's suggestion, BCVA was assessed for these cohorts.

Table 33 presents the primary effectiveness endpoint, i.e., ≥ 2 lines gain of BCDVA or BCNVA achieved by $\geq 50\%$ of the study population at 12 months, the proportion of eyes with gains ≥ 2 lines of BCDVA and BCNVA, with gains ≥ 2 lines of BCDVA and gains of ≥ 3 lines of BCDVA at 12 and 24 months for the following cohorts:

- Operated eyes
- IMT-implanted eyes
- Risk reduced cohort (eyes of subjects age ≥ 65 , with no guttata, with ACD ≥ 3.0 mm, and implanted by cornea specialist)
- IMT-implanted eyes excluded from the risk reduced cohort, i.e., the non-risk reduced cohort.

The visual acuity endpoint was achieved for all cohorts, and the percent of subjects with 2 and 3 lines of improvement in BCDVA was consistent across the cohorts at both 12 and 24 months.

TABLE 33
PRIMARY EFFECTIVENESS ENDPOINTS
PRIMARY ENDPOINT AND PROPORTION OF EYES WITH GAIN OF ≥ 2 OR ≥ 3 LINES BCDVA
IMT-002 STUDY
A019, PAGE 32, TABLE 3

VISUAL ACUITY	12 MONTHS				24 MONTHS			
	OPERATED EYES	IMT-IMPLANTED EYES	RISK REDUCED COHORT IMT-IMPLANTED EYES ≥ 65 YEARS NON-GUTTATA WITH ACD ≥ 3.0 MM AND BY CORNEA SPECIALIST	NON-RISK REDUCED COHORT IMT-IMPLANTED EYES EXCLUDED FROM THE RISK REDUCED COHORT	OPERATED EYES	IMT-IMPLANTED EYES	RISK REDUCED COHORT IMT-IMPLANTED EYES ≥ 65 YEARS NON-GUTTATA WITH ACD ≥ 3.0 MM AND BY CORNEA SPECIALIST	NON-RISK REDUCED COHORT IMT-IMPLANTED EYES EXCLUDED FROM THE RISK REDUCED COHORT
EFFECTIVENESS, N=	194	192	31	161	175	173	27	146
PRIMARY EFFECTIVENESS ENDPOINT: ≥ 2 LINES GAIN OF BCDVA OR BCNVA N (%), 95% CI	171 (88.1%) 83.6%, 91.8%	173 (90.1%) 85.8%, 93.4%	29 (93.5%) 81.1%, 98.8%	144 (89.4%) 84.6%, 93.2%	150 (85.7%) 80.6%, 89.9%	149 (86.1%) 81.0%, 90.2%	25 (92.6%) 78.5%, 98.7%	124 (84.9%) 79.2%, 89.6%
≥ 2 LINES GAIN OF BCDVA AND BCNVA N (%), 95% CI	141 (72.7%) 66.9%, 77.9%	141 (73.4%) 67.7%, 78.6%	24 (77.4%) 61.7%, 88.9%	117 (72.7%) 66.3%, 78.4%	115 (65.7%) 59.4%, 71.7%	114 (65.9%) 59.5%, 71.9%	19 (70.4%) 52.9%, 84.3%	95 (65.1%) 58.0%, 71.6%
BCDVA, N=	194	193	31	162	175	173	27	146
BCDVA INCREASED ≥ 2 LINES N (%), 95% CI	154 (79.4%) 74.0%, 84.1%	155 (80.3%) 75.0%, 84.9%	27 (87.1%) 72.9%, 95.5%	128 (79.0%) 73.1%, 84.2%	130 (74.3%) 68.3%, 79.7%	129 (74.6%) 68.5%, 80.0%	20 (74.1%) 56.8%, 87.1%	109 (74.7%) 68.0%, 80.5%
BCDVA INCREASED ≥ 3 LINES N (%), 95% CI	128 (66.0%) 60.0%, 71.6%	128 (66.3%) 60.3%, 72.0%	21 (67.7%) 51.5%, 81.3%	107 (66.0%) 59.4%, 72.2%	103 (58.9%) 52.4%, 65.1%	103 (59.5%) 53.0%, 65.8%	16 (59.3%) 41.7%, 75.2%	87 (59.6%) 52.5%, 66.4%

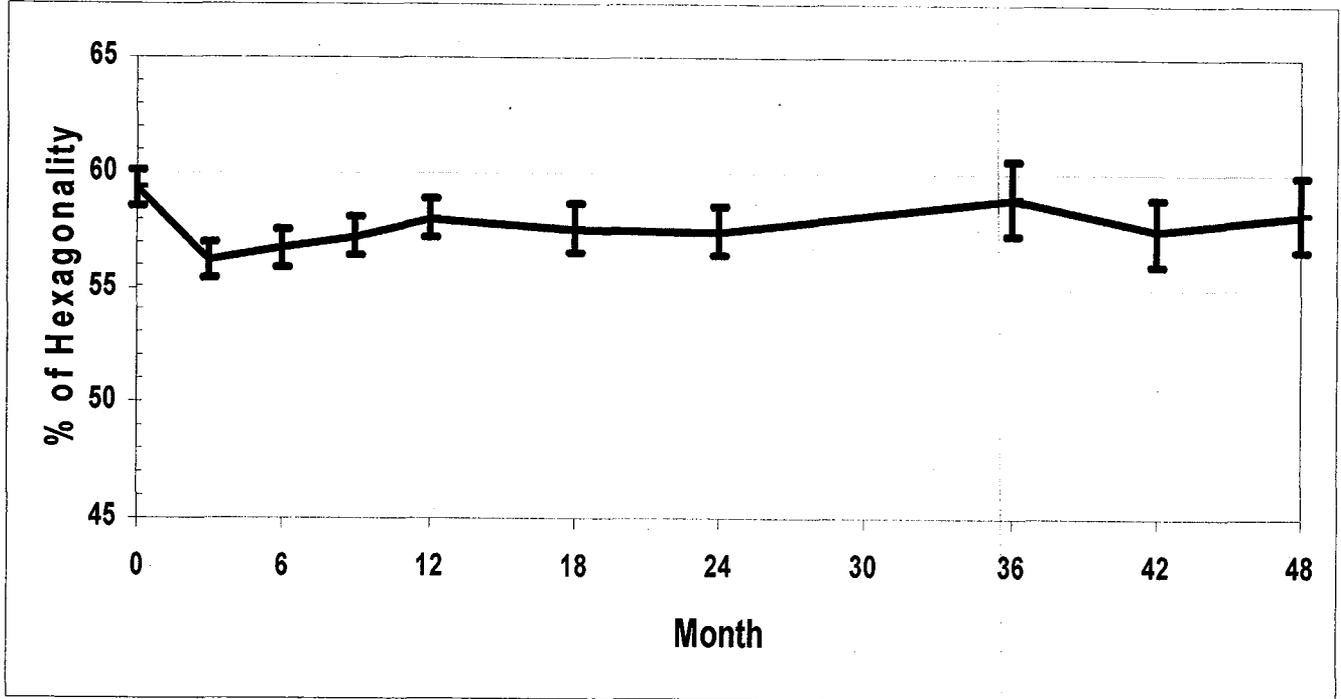
ENDOTHELIAL MORPHOLOGY (%HEXAGONALITY) AND MORPHOMETRY (COEFFICIENT OF VARIATION)

Analyses of corneal endothelial shape and variation in size (pleomorphism and polymegathism) are reported to be sensitive indicators of endothelial function and endothelial cell damage and recovery (Glasser et al, 1985). Reduction in pleomorphism (% hexagonality or % Hex) and increase in polymegathism (coefficient of variation or CV) serve as indicators of low functional reserve of the cellular monolayer and as markers for continuing rapid cell loss (Rao et al, 1984; Schultz et al, 1984; MacRae et al, 1994; and Matsuda et al, 1988). Increase in % Hex to normal levels and decrease in CV reflect increasing stability of the corneal endothelial cells over time (Edelhauser, 2004). Absence of continuing change in % Hex and CV suggests the corneal endothelium is not stressed.

Corneal endothelial cells are hexagonally shaped and are, under normal conditions, close in size one to another. (If they were not close to the same size, the hexagons would not fit together.) As described in Adler's Physiology of the Eye (Kaufman and Alm, editors, 10th edition, Mosby), "after surgery, when the cells at the site of the incision are destroyed or damaged, cells migrate to the wound, elongating toward the center of the wound, and finally spreading as the wound closes. This is followed by remodeling into a more normal hexagonal shape and consistent cell size."

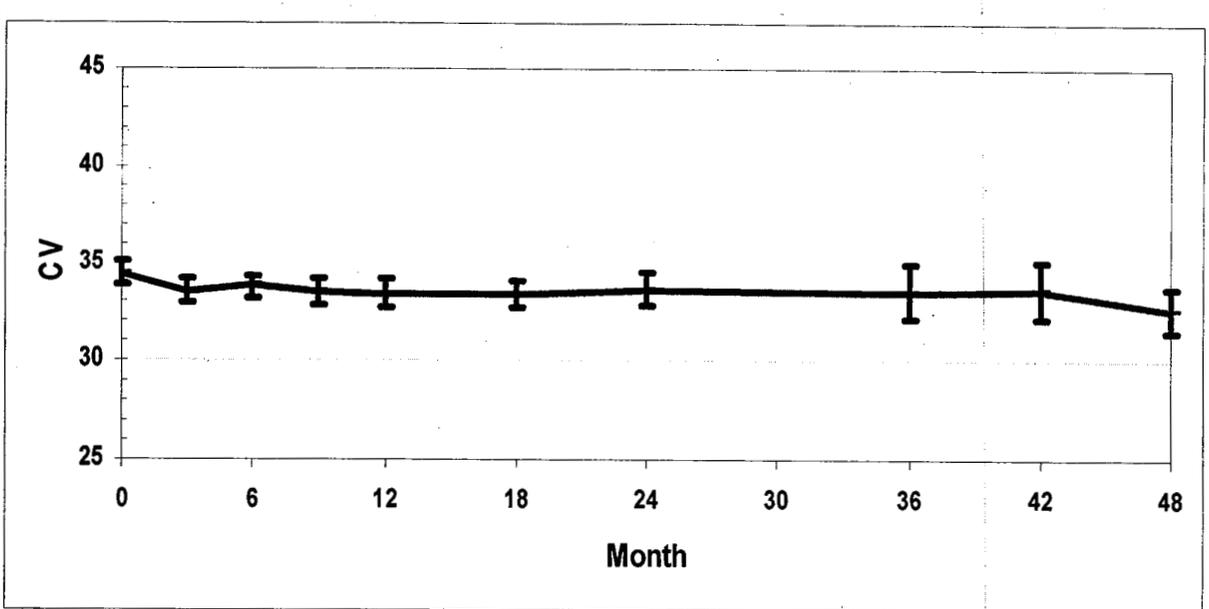
A decrease in % Hex and stable CV at 3 months were observed in the IMT-implanted eyes. This decrease in % Hex, indicative of the stress induced by surgical trauma, began to reverse itself shortly after 3 months, returning to near baseline levels (Figure 23). Changes in CV (Figure 24) were small throughout the 24 month IMT-002 study and for the 36 and 48 month visits under the IMT-002-LTM study. These findings suggest the corneal endothelial cell monolayer returned to normal % Hex and CV values after surgery and remained stable at 48 months.

FIGURE 23
% HEXAGONALITY (MEAN, CI)
IMT-IMPLANTED EYES
IM-002 AND IMT-002-LTM
A013, VOL 1, PAGE 56, FIGURE 19



	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months
Mean	59	56	57	57	58	58	57	59	57	58
95%CI	58, 60	55, 57	56, 57	56, 58	57, 59	57, 59	56, 58	57, 60	56, 59	57, 60
N	206	193	198	190	186	180	171	69	101	88

FIGURE 24
COEFFICIENT OF VARIATION (MEAN, CI)
IMT-IMPLANTED EYES
IM-002 AND IMT-002-LTM
A013, VOL 1, PAGE 57, FIGURE 20



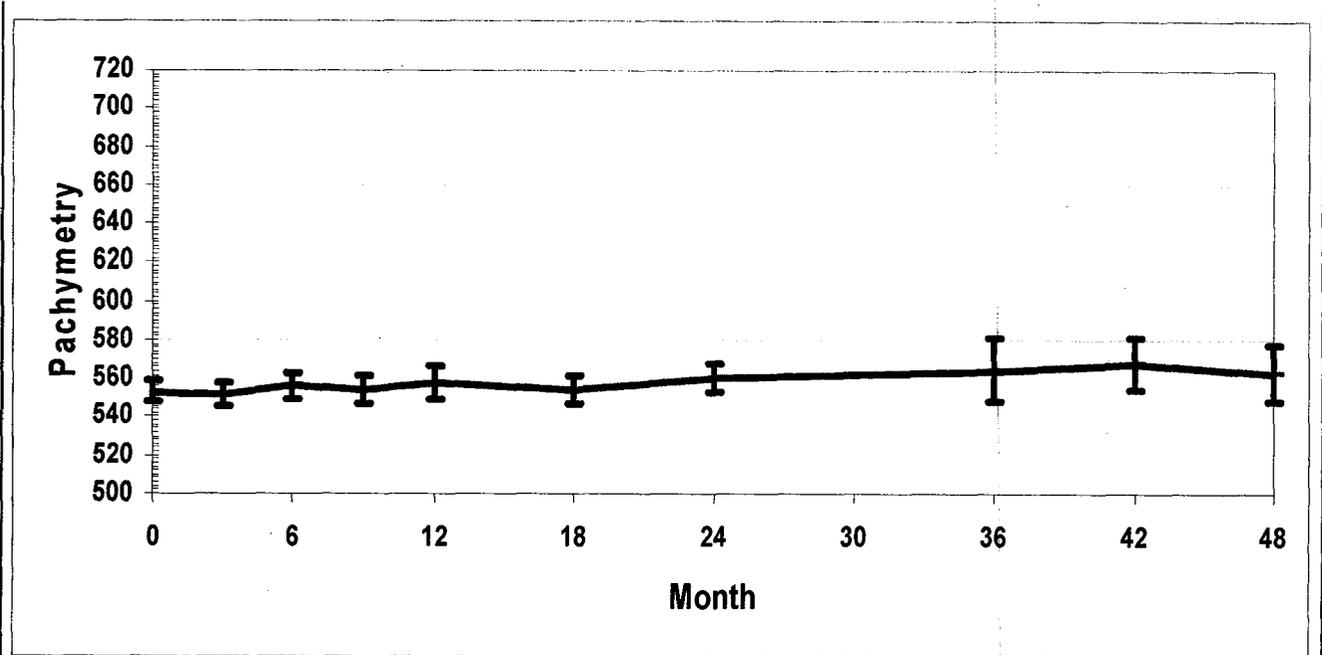
	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months
Mean	34	34	34	33	33	33	34	34	34	33
95%CI	34, 35	33, 34	33, 34	33, 34	33, 34	33, 34	33, 34	32, 35	32, 35	32, 34
N	205	193	198	190	186	180	171	70	101	88

The availability of 36 and 48 month morphology and morphometry data confirm previous observations that CV and % Hex remain at normal levels, suggesting a stable corneal endothelial monolayer.

CORNEAL PACHYMETRY

Because an increase in corneal thickness may indicate corneal edema and inadequate functionality, central corneal thickness was assessed by ultrasonic pachymetry in IMT-002 and IMT-002-LTM studies. As shown in Figure 25, central corneal thickness did increase by 5 to 10 microns after IMT implantation, and the thickness was generally within normal limits of 550-570 microns.

FIGURE 25
CENTRAL CORNEAL THICKNESS (MEAN, CI)
IMT-IMPLANTED EYES
IM-002 AND IMT-002-LTM
A013, VOL 1, PAGE 58, FIGURE 21



	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months	36 Months	42 Months	48 Months
Mean	553	552	556	554	558	554	561	565	568	562
95% CI	548, 559	546, 558	550, 563	547, 561	549, 567	547, 562	553, 568	548, 581	554, 582	548, 577
N	206	198	200	191	192	177	172	43	82	84

6.3 USE OF A GRID TO ALLOW PHYSICIANS AND PATIENTS TO ASSESS LIKELIHOOD THAT PATIENTS WILL RETAIN SUFFICIENT ENDOTHELIAL CELL DENSITY OVER THE PATIENT'S LIFE SPAN

A further risk mitigation strategy would allow physicians and patients to calculate the minimum ECD needed before IMT implantation such that the patient would be able to obtain the benefits of improved visual acuity from implantation of an IMT without an undue risk of loss of ECD to a level potentially leading to corneal decompensation and requiring corneal transplant. CDRH has previously used this risk mitigation strategy in the labeling for commercially available phakic refractive intraocular lenses. The phakic IOL labeling utilizes a grid (copy provided in Appendix 5) based on pre-operative ECD, chronic ECD loss, and a "target" ECD at age 75 on which physicians and patients can base their decisions.

VisionCare has constructed a grid similar to the phakic IOL grid for IMT implantation. Its elements are as follows:

1. The grid uses an ECD of 750 cells/mm² as a reasonable target ECD.

The phakic IOL grid uses 1000 cells/mm² as the "target" for age 75. That target was adopted in recognition that patients undergoing phakic IOL implantation at a relatively early age might later require cataract surgery affecting the cornea and therefore needed some reserve ECD, which will result in a post-cataract surgery ECD of approximately 750 cells/mm² at the end of an average life span. Because cataract surgery will have been performed in conjunction with implantation of the IMT, the cataract reserve is not needed in the IMT grid. Therefore, VisionCare has set the target ECD in this grid at 750 cells/mm².

2. Actuarial data on life expectancy data are taken from National Vital Statistics Reports, Vol. 53, No. 6, November 10, 2004.
3. A biexponential model utilizing IMT-002 and IMT-002-LTM ECD data provides predicted annual ECD percent loss.
 - a. ECD data utilized in the biexponential model is consistent with the proposed labeling, excluding subjects with guttata and anterior chamber depths < 3.0 mm.
 - b. Although labeling will warn that cornea specialists should perform IMT implantation, the model utilizes a conservative approach of using ECD data from both cornea specialists and non-cornea specialists.

VisionCare has previously presented a piecewise regression model with breakpoints at 3 and 9 months to predict long-term ECD loss. This model was discussed at the July 2006 Ophthalmic Devices Panel meeting. On the basis of questions raised by the Panel and then CDRH regarding this model, VisionCare sought a more appropriate model and identified a biexponential model described by Armitage, Dick and Bourne (Armitage et al, 2003) and by Patel, Hodge and Bourne (Patel et al, 2004). This model was presented by VisionCare in Amendment 7 submitted January 31, 2007 to P050034 and further elaborated on in

subsequent amendments.

The biexponential model is defined by the equation

$$\text{ECD}_{\text{month}} = p \times e^{-a \times \text{month}} + q \times e^{-b \times \text{month}} + \varepsilon.$$

The model was used to fit the ECD pattern from baseline to 48 months after IMT implantation. For each eye at each visit, the average of all available ECD readings was used as the ECD measurement for the eye at that visit. ECD readings made after IMT explantation were not used since these readings were confounded by the removal of the IMT and implantation of a conventional IOL, however all available ECD readings made prior to IMT explantation were included in the model. To simplify the non-linear model fitting, each ECD measurement was treated as independent. These methods were discussed with W. Bourne, M.D., Professor of Ophthalmology, Mayo Clinic, who was retained as a consultant to VisionCare on methods for analysis of endothelial cell loss. Dr. Bourne confirmed that the methods, as presented in this document, employed by VisionCare are appropriate.

The first term, $p \times e^{-a \times \text{month}}$, of the bi-exponential model represents the “rapid” rate of loss rate associated with the surgical trauma while the second term, $q \times e^{-b \times \text{month}}$ represents the “slow” rate of loss that occurs after stabilization. The quantity ε is an error term.

Having fit the model, the annual loss after stabilization is estimated as $(1 - e^{-b \times 12}) \times 100\%$. The predicted mean ECD at 3, 12, 24, 36, and 48 months and the corresponding 95% confidence intervals were calculated from the fitted model.

Applying the biexponential model to the data available from IMT-002 and IMT-002-LTM through 48 months, for eyes without corneal guttata and with anterior chamber depth ≥ 3.0 mm, the mean ECD at 12 months (to incorporate the full effect of surgical loss) was 1954 cells/mm², and the mean annual loss thereafter was 3.8% (Tables 34 and 35). To make the grid more conservative (i.e., to increase the likelihood that patients will have sufficient ECD to preserve corneal transparency through their life spans), the lower 90% confidence interval for the 1 year mean ECD and the upper 90% confidence interval for annual ECD percent loss are utilized in constructing the grid.

Summarizing, the following assumptions were used to develop the grid of baseline ECD:

- ECD data from the IMT-002 and IMT-002-LTM studies through 48 months, for eyes without corneal guttata and with anterior chamber depth ≥ 3.0 mm
- 12-month ECD loss of 24.6%, the lower 90% confidence interval for 12-month ECD, 1911 cells/mm², estimated by the biexponential model, and
- Annual ECD loss of 5.5%, the upper 90% confidence interval for annual loss estimated by the biexponential model, utilizing 48 month data.

The resulting grid, shown in Figure 26, sets minimum endothelial cell density criteria as a function of age that should result in at least 750 cells/mm² at the end of the average life span. Detailed results of the biexponential model are shown in Tables 34 through 36.

FIGURE 26
PROPOSED GRID OF PREOPERATIVE ECD REQUIRED FOR IMT IMPLANTATION
BASED ON IMT-IMPLANTED EYES WITHOUT GUTTATA AND WITH ACD ≥ 3.0 MM
A013, VOL 1, PAGE 61, FIGURE 22

Age Range		65-69		70-74		75-79		80-84		85-89		90 or Greater	
Gender		Male	Female	Male	Female								
Avg. Life Span		16.6	19.5	13.2	15.8	10.3	12.4	7.8	9.4	5.7	6.9	4.2	5.0
Minimum Cell Density		2460	2755	2000	2325	2000	2000	2000	2000	1800	1800	1800	1800
EDC at year	1	1855	2077	1508	1753	1508	1508	1508	1508	1357	1357	1357	1357
	2	1753	1963	1425	1657	1425	1425	1425	1425	1283	1283	1283	1283
	3	1657	1855	1347	1566	1347	1347	1347	1347	1212	1212	1212	1212
	4	1565	1753	1273	1480	1273	1273	1273	1273	1145	1145	1145	1145
	5	1479	1657	1203	1398	1203	1203	1203	1203	1082	1082	1082	1082
	6	1398	1566	1137	1321	1137	1137	1137	1137	1023	1023	1023	1023
	7	1321	1480	1074	1249	1074	1074	1074	1074	967	967	967	967
	8	1248	1398	1015	1180	1015	1015	1015	1015	913	913	913	913
	9	1180	1321	959	1115	959	959	959	959	863	863	863	863
	10	1115	1249	906	1054	906	906	906	906	816	816	816	816
	11	1054	1180	857	996	857	857	857	857	771	771	771	771
	12	996	1115	809	941	809	809	809	809	728	728	728	728
	13	941	1054	765	889	765	765	765	765	688	688	688	688
	14	889	996	723	840	723	723	723	723	651	651	651	651
	15	840	941	683	794	683	683	683	683	615	615	615	615
	16	794	889	646	750	646	646	646	646	581	581	581	581
	17	750	840	610	709	610	610	610	610	549	549	549	549
	18	709	794	576	670	576	576	576	576	519	519	519	519
	19	670	750	545	633	545	545	545	545				
	20	633	709	515	598	515	515	515	515				
	21	598	670		566								
	22	565	633		534								
	23	534	598		505								
	24	505	566										
	25		534										
	26		505										

Life expectancy -- National Vital Statistics Reports, Vol. 53, No. 6, November 10, 2004

Cell density at end of life

Years post implant when cell density reaches 500 cell per mm²

TABLE 34

BI-EXPONENTIAL MODEL FOR ECD

$$ECD_{\text{month}} = p \times e^{-a \times \text{month}} + q \times e^{-b \times \text{month}} + \epsilon$$

NON-GUTTATA IMT-IMPLANTED EYES WITH ACD ≥ 3 MM

BASED ON DATA FROM BASELINE TO 48 MONTHS

IMT-002 AND IMT-002-LTM

A013, VOL 1, PAGE 62, TABLE 21.1

Parameter	Estimate	Approx Std Error	95% Lower	95% Upper	t-value	Approx Pr > t
p	506.7	65.5	378.1	635.3	7.7	<.001
a	0.5	0.2	0.1	1.0	2.5	0.012
q	2029.7	45.0	1941.4	2118.0	45.1	<.001
b	0.003	0.001	0.001	0.005	3.5	<.001

Annual ECD % Loss (90% CI) based on the slow exponential rate: 3.8% (2.0%, 5.5%).

TABLE 35

PREDICTED MEAN ECD BASED ON BI-EXPONENTIAL MODEL FOR

NON-GUTTATA IMT-IMPLANTED EYES WITH ACD ≥ 3 MM

BASED ON DATA FROM BASELINE TO 48 MONTHS

IMT-002 AND IMT-002-LTM

A013, VOL 1, PAGE 62, TABLE 21.2

Time	Mean ECD	90% Confidence Intervals
3 Months	2109.2	2029.4, 2189.0
12 Months	1954.0	1911.0, 1997.1
24 Months	1879.7	1842.2, 1917.3
36 Months	1808.9	1753.7, 1864.1
48 Months	1740.8	1660.4, 1821.2
60 Months	1675.2	1569.3, 1781.1

TABLE 36

PREDICTED PROBABILITY OF ECD LESS THAN THRESHOLD BASED ON

BI-EXPONENTIAL MODEL FOR

NON-GUTTATA IMT-IMPLANTED EYES WITH ACD ≥ 3 MM

BASED ON DATA FROM BASELINE TO 48 MONTHS

IMT-002 AND IMT-002-LTM (EXCLUDING PREOP RESIDUALS)

A013, VOL 1, PAGE 62, TABLE 21.3

Probability of ECD			
Time	< 1000 cell/mm ²	< 750 cell/mm ²	< 500 cell/mm ²
3 Months	5.0	1.6	0.1
12 Months	7.1	3.2	0.9
24 Months	8.5	4.3	1.3
36 Months	8.9	6.1	1.9
48 Months	9.8	6.9	2.6
60 Months	10.5	7.7	3.5

The empirical frequency of residuals was used to estimate these probabilities.

BIEXPONENTIAL MODEL AND ECD GRID FOR ALL IMT-IMPLANTED EYES

VisionCare has also generated an ECD grid using endothelial cell counts for all IMT-implanted eyes, including eyes with guttata, ACD <3.00 mm, and operated by cornea specialists and non-cornea specialists. Applying the biexponential model to these data, the 12 month ECD at the lower 90% confidence interval is 1839 cells/mm², 26.3% loss at 12 months, and the annual rate thereafter (at the upper 90% confidence interval) is 6.20% (Table 37). Additional results of the biexponential model are displayed in Tables 38 and 39.

As shown in the resulting ECD grid displayed in Figure 27, the difference between this grid and the ECD grid generated for the population of eyes without guttata and with ACD of at least 3.0 mm is that this grid is more restrictive and is generally limited to higher baseline ECD required for patients under age 75.

FIGURE 27
GRID OF PREOPERATIVE ECD REQUIRED FOR IMT IMPLANTATION BASED ON
ALL IMT-IMPLANTED EYES
A013, VOL 1, PAGE 64, FIGURE 23

Age Range		65-69		70-74		75-79		80-84		85-89		90-	
Gender		Male	Female	Male	Female								
Avg. Life Span		16.6	19.5	13.2	15.8	10.3	12.4	7.8	9.4	5.7	6.9	4.2	5.0
Minimum Cell Density		2834	3223	2195	2659	2000	2058	2000	2000	1800	1800	1800	1800
ECD at year	1	2088	2374	1617	1959	1473	1516	1473	1473	1326	1326	1326	1326
	2	1958	2227	1517	1837	1382	1422	1382	1382	1244	1244	1244	1244
	3	1837	2089	1423	1723	1296	1334	1296	1296	1167	1167	1167	1167
	4	1723	1959	1334	1617	1216	1251	1216	1216	1094	1094	1094	1094
	5	1616	1838	1252	1516	1141	1174	1141	1141	1026	1026	1026	1026
	6	1516	1724	1174	1422	1070	1101	1070	1070	963	963	963	963
	7	1422	1617	1101	1334	1004	1033	1004	1004	903	903	903	903
	8	1334	1517	1033	1251	941	969	941	941	847	847	847	847
	9	1251	1423	969	1174	883	909	883	883	795	795	795	795
	10	1174	1335	909	1101	828	852	828	828	745	745	745	745
	11	1101	1252	853	1033	777	799	777	777	699	699	699	699
	12	1033	1174	800	969	729	750	729	729	656	656	656	656
	13	969	1101	750	909	683	703	683	683	615	615	615	615
	14	908	1033	704	852	641	660	641	641	577	577	577	577
	15	852	969	660	800	601	619	601	601	541	541	541	541
	16	799	909	619	750	564	580	564	564	508	508	508	508
	17	750	853	581	703	529	544	529	529				
	18	703	800	545	660		511						
	19	660	750	511	619								
	20	619	704		581								
	21	580	660		545								
	22	544	619		511								
	23	511	581										
	24		545										
	25		511										

Life expectancy -- National Vital Statistics Reports, Vol. 53, No. 6, November 10, 2004
 Cell density at end of life using average life span
 Years post implant when cell density reaches 500 cell per mm²

TABLE 37
BI-EXPONENTIAL MODEL FOR ECD

$$ECD_{\text{month}} = p \times e^{-a \times \text{month}} + q \times e^{-b \times \text{month}} + \epsilon$$
ALL IMT-IMPLANTED EYES
BASED ON DATA FROM BASELINE TO 48 MONTHS
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 63, TABLE 22.1

Parameter	Estimate	Approx Std Error	95% Lower	95% Upper	t-value	Approx Pr > t
p	530.0	51.4	429.1	630.9	10.3	<.001
a	0.6	0.2	0.2	1.1	3.0	0.003
q	1967.1	34.2	1900.0	2034.3	57.5	<.001
b	0.004	0.001	0.003	0.006	5.6	<.001

Annual ECD % Loss (90% CI) based on the slow exponential rate: 4.8% (3.4%, 6.2%).

TABLE 38
PREDICTED MEAN ECD BASED ON BI-EXPONENTIAL MODEL FOR
ALL IMT-IMPLANTED EYES
BASED ON DATA FROM BASELINE TO 48 MONTHS
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 63, TABLE 22.2

Time	Mean ECD	90% Confidence Intervals
3 Months	2019.7	1955.5, 2083.9
12 Months	1872.2	1838.8, 1905.6
24 Months	1781.4	1752.0, 1810.9
36 Months	1695.3	1652.1, 1738.4
48 Months	1613.3	1551.8, 1674.8
60 Months	1535.3	1455.7, 1614.9

TABLE 39
PREDICTED PROBABILITY OF ECD LESS THAN THRESHOLD
BASED ON BI-EXPONENTIAL MODEL FOR ALL IMT-IMPLANTED EYES
BASED ON DATA FROM BASELINE TO 48 MONTHS
IMT-002 AND IMT-002-LTM (EXCLUDING PREOP RESIDUALS)
A013, VOL 1, PAGE 64, TABLE 22.3

Time	Probability of ECD		
	< 1000	< 750	< 500
3 Months	7.2	2.8	0.3
12 Months	9.4	5.0	1.4
24 Months	11.4	6.7	2.6
36 Months	13.1	8.2	3.9
48 Months	15.4	9.6	5.1
60 Months	17.4	11.4	6.7

The empirical frequency of residuals was used to estimate these probabilities.

BIEXPONENTIAL MODEL FOR RISK REDUCED COHORT

Predicted ECD annual percent loss and related information is presented in Tables 40 through 41 based on a biexponential model utilizing data from baseline to 48 months for the risk reduced cohort consisting of subjects age ≥ 65 , with no guttata, ACD ≥ 3.0 mm, and implanted by a cornea specialist.

The predicted annual ECD loss for this cohort is 3.4% with a 95% confidence level of 0.3%, 6.4%.

TABLE 40

BI-EXPONENTIAL MODEL FOR ECD

$$ECD_{\text{month}} = p \times e^{-a \times \text{month}} + q \times e^{-b \times \text{month}} + \epsilon$$

**IMT-IMPLANTED EYES OF SUBJECTS ≥ 65 YEARS WITH NO GUTTATA, ACD ≥ 3.0 MM AND OPERATED BY CORNEA SPECIALISTS
BASED ON DATA FROM BASELINE TO 48 MONTHS
A019, PAGE 25, TABLE 2.D.1**

PARAMETER	ESTIMATE	APPROX STD ERROR	95% LOWER	95% UPPER	T-VALUE	APPROX PR > T
p	399.9	111.5	180.3	619.5	3.6	<.001
a	0.6	0.5	-0.5	1.6	1.1	0.270
q	2074.2	76.1	1924.3	2224.1	27.3	<.001
b	0.003	0.002	-0.000	0.006	1.8	0.069

Annual ECD % Loss (90% CI) based on the slow exponential rate: 3.4% (0.3%, 6.4%).

TABLE 41

PREDICTED MEAN ECD BASED ON BI-EXPONENTIAL MODEL FOR

**IMT-IMPLANTED EYES OF SUBJECTS ≥ 65 YEARS WITH NO GUTTATA, ACD ≥ 3.0 MM AND BY OPERATED BY CORNEA SPECIALISTS
BASED ON DATA FROM BASELINE TO 48 MONTHS
A019, PAGE 25, TABLE 2.D.2**

TIME	MEAN ECD	90% CONFIDENCE INTERVALS
3 Months	2125.4	1987.8, 2263.0
12 Months	2004.0	1930.3, 2077.8
24 Months	1935.5	1868.8, 2002.2
36 Months	1869.7	1769.4, 1970.0
48 Months	1806.1	1660.4, 1951.9
54 Months	1775.2	1606.2, 1944.1
60 Months	1744.7	1552.9, 1936.6

TABLE 42
PREDICTED PROBABILITY OF ECD LESS THAN THRESHOLD BASED ON
BI-EXPONENTIAL MODEL FOR
IMT-IMPLANTED EYES OF SUBJECTS ≥ 65 YEARS WITH NO GUTTATA, $ACD \geq 3.0$ MM AND
OPERATED BY CORNEA SPECIALISTS
BASED ON DATA FROM BASELINE TO 48 MONTHS
(EXCLUDING PREOP RESIDUALS)
A019, VOL 1, PAGE 26, TABLE 2.D.3

TIME	PROBABILITY OF ECD						
	< 1000	< 750	< 700	< 650	< 600	< 550	< 500
3 MONTHS	3.8	2.4	2.4	2.4	2.4	2.4	1.9
12 MONTHS	4.3	2.9	2.9	2.4	2.4	2.4	2.4
24 MONTHS	4.8	2.9	2.9	2.9	2.9	2.4	2.4
36 MONTHS	5.3	3.8	3.3	2.9	2.9	2.9	2.4
48 MONTHS	5.7	3.8	3.8	3.3	2.9	2.9	2.9
54 MONTHS	5.7	4.3	3.8	3.8	3.3	2.9	2.9
60 MONTHS	5.7	4.3	4.3	3.8	3.8	2.9	2.9

The empirical frequency of residuals was used to estimate these probabilities.

RELIABILITY OF BIEXPONENTIAL MODEL

The mean ECD predicted by the biexponential models using ECD from baseline to 24 months, baseline to 36 months and baseline to 48 months as well as actual mean ECD observed in the study population, and percentage of eyes with ECD < 1000 and < 750 cells/mm² for IMT-implanted eyes are presented in Table 43. The reliability of the biexponential model can be examined by comparing the predicted values with the actual mean ECD reported for the study population, and the proportion of eyes presenting with ECD < 1000 cells/mm² and < 750 cells/mm². While small differences were found between the predicted and actual values, in general, the values predicted by the biexponential model were very close to the actual outcomes at 36 and 48 months.

TABLE 43
PREDICTED AND ACTUAL MEAN ECD AND
PERCENTAGE OF EYES WITH ECD < 1000 AND < 750 CELLS/MM²
IMT-IMPLANTED EYES
A019, Page 16, Table 2.A.2

	BIEXPONENTIAL MODEL PREDICTION		ACTUAL VALUES 6 TO 48 MONTHS
	BASED ON ACTUAL ECD VALUES	BASED ON ACTUAL ECD VALUES	
	BASELINE TO 24M	BASELINE TO 36M	
Annual % ECD Loss	3.6%	3.9%	3.4%*
Mean (90% CI)	(-0.7%, 7.8%)	(1.3%, 6.5%)	(2.1%, 4.7%)
Mean ECD (cells/mm²)			
36 Months	1740 (NA)	1728 (NA)	1713 (70)
48 Months	1678 (NA)	1660 (NA)	1620 (88)
% of Eyes with <1000 cells/mm²			
36 Months	12%	12%	11% (8/70)
48 Months	14%	14%	17% (15/88)
% of Eyes with <750 cells/mm²			
36 Months	8%	8%	4% (3/70)
48 Months	9%	9%	8% (7/88)

*Observed annual mean ECD loss based on observed values 6 to 48 months postoperatively

6.4 COMPLICATIONS AND ADVERSE EVENTS

Tables displaying incidence densities for ocular complications and ocular adverse events are included in the following sections of this document.

OCULAR COMPLICATIONS AND DEVICE MALFUNCTIONS

Ocular complications were defined as events directly related to the surgical procedure for implantation of the IMT, whether successful or not, occurring in the operative and immediate postoperative period. Events occurring after the immediate postoperative period were classified not as ocular complications but as adverse events.

Incidence densities are shown in Table 44 for ocular complications reported during the IMT-002 study for all operated eyes, and in Table 45 for operated eyes of subjects enrolled in the IMT-002-LTM study. Ocular complications were included whether they were noted at a regularly scheduled visit, an unscheduled visit, or following IMT removal.

As shown in Tables 44 and 45, the most common ocular complication was increased IOP requiring treatment ≤ 7 days. (Increased IOP reported beyond 7 days and requiring treatment was classified as an adverse event, not as an ocular complication). Increased IOP classified as an ocular complication was likely associated with the liberal use of high molecular weight viscoelastic material (Healon V) in the eye.

Other commonly reported ocular complications ($\geq 3\%$) included corneal edema, iris prolapse, corneal abrasions, posterior capsule rupture and posterior capsule opacification. Fourteen (14) cases of corneal edema occurred within 30 days of surgery; all 14 cases were first reported on postoperative Day 1 and three of these cases of corneal edema were still noted at the 1 month visit.

Iris prolapse was observed in 12 eyes and 11 eyes had corneal abrasions. In general, the ocular complications were transient.

DEVICE FAILURES

There were four device failures have been reported in IMT-implanted study subjects. Two of the device failures occurred during surgery and involved a broken haptic; one occurred before implantation and the device was not used, and one occurred during implantation, necessitating intraoperative replacement. Two involved condensation in the telescope portion of the IMT occurring one month postoperatively, resulting in IMT removal. These two devices exhibited small cracks in the telescope tube; the cracks may have been caused by improper handling during surgery or during the manufacturing process. Corrective actions were taken in the form of surgeon training on the proper handling of the device and a review of manufacturing processes.

TABLE 44
OCULAR COMPLICATIONS DENSITY
OPERATED EYES (N=217)
IMT-002

Page 1 of 2

A013, VOL 1, PAGE 209, TABLE 25

COMPLICATIONS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON-YEAR ¹	RATE PER 100 PERSON-YEAR (DENSITY) ²
Aborted surgery	5	337.1	1.48
Anterior chamber hemorrhage	1	338.2	0.30
Anterior segment neovascularization	1	339.6	0.29
Anterior synechiae	3	337.3	0.89
Bleb	1	339.5	0.29
Blepharitis	7	335.6	2.09
Blurred vision	1	340.0	0.29
Chalazion	2	339.2	0.59
Choroidal detachment	2	338.8	0.59
Choroidal hemorrhage	1	339.4	0.29
Conjunctival injection	4	336.1	1.19
Corneal abrasion	11	323.1	3.40
Corneal edema ≤ 30 days	14	315.9	4.43
Corneal endothelial touch	3	335.0	0.90
Cortical remnants	2	338.0	0.59
Cyclitic membrane ≤ 7 days	1	338.3	0.30
Cyclodialysis cleft	1	338.3	0.30
Descemet's membrane separation	3	336.3	0.89
Ectropion	2	338.7	0.59
Endothelial folds	2	338.9	0.59
Flat anterior chamber ≤ 21 days	2	336.7	0.59
Folds in corneal graft	1	339.3	0.29
Glaucoma	1	339.3	0.29
Haze	2	336.5	0.59
Hyphema	10	324.2	3.08
Hypotony	2	337.6	0.59
IMT dislocation (intraoperative)	1	339.9	0.29
IMT removal (intraoperative)	6	339.0	1.77
IMT replacement (interoperative)	1	338.1	0.30

TABLE 44 (CONTINUED)
OCULAR COMPLICATIONS DENSITY
OPERATED EYES (N=217)
IMT-002

Page 2 of 2

A013, VOL 1, PAGE 209, TABLE 25

COMPLICATIONS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON-YEAR ¹	RATE PER 100 PERSON-YEAR (DENSITY) ²
Increased IOP requiring treatment ≤ 7 days	59	248.7	23.72
Increased IOP ≤ 15 days	3	337.3	0.89
Iridotomy ≤ 7 days	3	334.6	0.90
Iris atrophy ≤ 7 days	4	333.7	1.20
Iris damage	8	328.7	2.43
Iris incarceration	3	336.7	0.89
Iris prolapse	12	321.0	3.74
Iris transillumination defects ≤ 21 days	8	329.1	2.43
Iritis ≤ 30 days	2	338.6	0.59
Ophthalmic migraine	1	339.1	0.29
Peribulbar hemorrhage	1	339.5	0.29
Peripapillary hemorrhage	1	338.2	0.30
Phthisis	1	339.6	0.29
Posterior capsular rupture	10	334.0	2.99
Posterior capsule opacification	8	333.4	2.40
Significant anterior chamber bleeding	3	335.0	0.90
Strabismus surgery	1	339.5	0.29
Surgical mydriasis	1	339.0	0.29
Suture rupture	4	336.3	1.19
Uveitis	1	339.3	0.29
Vitreous bulge	1	339.4	0.29
Vitreous hemorrhage ≤ 7 days	1	339.4	0.29
Vitreous in anterior chamber ≤ 7 days	3	335.0	0.90
Vitreous loss	3	337.8	0.89
Vitreous loss - vitrectomy required	7	336.5	2.08
Watery eyes	3	338.6	0.89
Worsening of subretinal scarring	1	339.6	0.29
Wound leak	3	337.6	0.89
Zonular dehiscence ≤ 7 days	1	339.8	0.29

¹ Total Person-Year = Sum of follow-up days for subjects without the corresponding event and the follow-up days up to the date of the reported event for the subjects reported with the corresponding event, divided by 365.25. The follow-up day for each subject = last available visit date (or event reported date) - surgical date + 1. The "+ 1" was to consider the event reported at the surgical day.

² Density = Total Number of Eyes with Reports ÷ Total Person-Year × 100.

TABLE 45
OCULAR COMPLICATIONS DENSITY
OPERATED EYES FOLLOWED IN IMT-002-LTM
(N = 129)

Page 1 of 2

A013, VOL 1, PAGE 211, TABLE 26

COMPLICATIONS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON-YEAR ¹	RATE PER 100 PERSON-YEAR (DENSITY) ²
Aborted surgery	3	380.3	0.79
Afferent pupil defect	1	386.1	0.26
Alternating exotropia	1	385.7	0.26
Anterior synechiae	3	380.1	0.79
Asthenopia	1	384.0	0.26
Blepharitis	6	374.5	1.60
Chalazion	1	384.3	0.26
Choroidal detachment	1	384.5	0.26
Choroidal hemorrhage	1	384.7	0.26
Conjunctival injection	2	380.0	0.53
Corneal abrasion	10	357.8	2.79
Corneal edema ≤ 30 days	10	355.0	2.82
Corneal endothelial touch	2	380.7	0.53
Corneal neovascularization	1	385.5	0.26
Descemet's membrane separation	1	383.2	0.26
Ecchymoses on eyelid	1	386.6	0.26
Ectropion	1	386.6	0.26
Endothelial folds	2	382.9	0.52
Epithelial basement membrane dystrophy	1	386.6	0.26
Esotropia	1	387.1	0.26
Flashes	1	383.7	0.26
Flat anterior chamber ≤ 21 days	1	383.7	0.26
Folds in corneal graft	1	384.6	0.26
Glare	1	385.6	0.26
Glaucoma	1	384.5	0.26
Haze	2	382.3	0.52
Hyphema	3	376.4	0.80
IMT dislocation (intraoperative)	1	385.0	0.26
IMT posteriorly positioned	1	386.6	0.26

TABLE 45 (CONTINUED)
OCULAR COMPLICATIONS DENSITY
OPERATED EYES FOLLOWED IN IMT-002-LTM
(N = 129)

Page 2 of 2

A013, VOL 1, PAGE 211, TABLE 26

COMPLICATIONS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON-YEAR ¹	RATE PER 100 PERSON-YEAR (DENSITY) ²
IMT removal (intraoperative)	3	381.6	0.79
Increased IOP requiring treatment ≤ 7 days	31	294.0	10.54
Increased IOP ≤ 15 days	1	384.1	0.26
Iris atrophy ≤ 7 days	2	381.8	0.52
Iris damage	6	372.0	1.61
Iris incarceration	2	380.8	0.53
Iris prolapse	5	372.7	1.34
Iris transillumination defects ≤ 21 days	2	381.8	0.52
Meibomian gland dysfunction	1	386.6	0.26
Ophthalmic migraine	1	384.1	0.26
Peripapillary hemorrhage	1	384.6	0.26
Posterior capsular rupture	5	376.8	1.33
Posterior capsule opacification	11	366.7	3.00
Significant anterior chamber bleeding	2	381.1	0.52
Strabismus	1	386.6	0.26
Strabismus surgery	1	385.0	0.26
Superficial punctate keratitis	1	385.8	0.26
Surgical mydriasis	1	384.3	0.26
Suture rupture	1	384.6	0.26
Treatment of PCO	1	385.6	0.26
Uveitis	1	384.5	0.26
Uveitis/vitritis	1	386.6	0.26
Vitreous hemorrhage ≤ 7 days	1	384.7	0.26
Vitreous in anterior chamber ≤ 7 days	3	378.4	0.79
Vitreous loss	1	383.8	0.26
Vitreous loss - vitrectomy required	3	380.3	0.79
Watery eyes	2	382.6	0.52
Wound leak	1	385.1	0.26
Zonular dehiscence ≤ 7 days	1	385.1	0.26

¹ Total Person-Year = Sum of follow-up days for subjects without the corresponding event and the follow-up days up to the date of the reported event for the subjects reported with the corresponding event, divided by 365.25. The follow-up day for each subject = last available visit date (or event reported date) - surgical date + 1. The "+ 1" was to consider the event reported at the surgical day.

² Density = Total Number of Eyes with Reports ÷ Total Person-Year × 100.

OCULAR ADVERSE EVENTS

As mentioned in the previous section, ocular complications were defined as events occurring during the operative and immediate post-operative periods. Ocular complications occurring thereafter were classified as ocular adverse events, and non-ocular adverse events occurred at any time during the IMT-002 and IMT-002-LTM studies.

Incidence density for ocular adverse events observed in operated eyes in the IMT-002 study, (operative visit to 24-month visit), and in operated eyes enrolled in the IMT-002-LTM study, (operative visit to 60-month visit) are summarized in Tables 46 and 47, respectively. These tables display adverse events for regularly scheduled visits, unscheduled interim visits, and all available visits following postoperative IMT removal.

Adverse events with an incidence density of 3% or greater in the IMT-002 study were inflammatory deposits and pigment deposits on the iris, guttae, posterior synechiae, iritis, and iris transillumination defects.

In the IMT-002 study, inflammatory deposits on the IMT were observed in 51 eyes (18%). Pigment deposits on the IMT were reported in 23 eyes (7%). In the majority of eyes, deposits resolved over the course of patient follow-up; neither the inflammatory deposits nor the pigment deposits on the IMT affected visual acuity. Pigmentary and inflammatory deposits were managed medically with a standardized course of anti-inflammatory agents, starting with a sub-Tenon's injection of betamethasone depot administered at the end of surgery followed by topical administration of prednisolone acetate 1% or equivalent tapering over 2-3 months.

Guttata was reported in 16 eyes (4.9%), posterior synechiae were reported for 15 eyes (4.6%), and iritis at 30 days or later was reported for 12 eyes (3.6%). Iris transillumination defects were also observed in 12 eyes (3.6%).

All remaining adverse events in study IMT-002 were reported at a frequency of less than 3.0%.

In the IMT-002-LTM study, the only ocular adverse events reported at an incidence of 3.0% or more were precipitates or deposits on the IMT (18%), guttae (4.5%), posterior synechiae (4%) and corneal edema occurring later than 30 days, in 13 eyes (3.5%).

There were no cases of endophthalmitis, retinal detachment, or retinal tear. Significant adverse events included corneal edema, choroidal neovascularization (CNV), IMT removal during the course of the study and corneal decompensation leading to penetrating keratoplasty. These events are discussed in subsequent sections of this document, following Tables 46 and 47.

TABLE 46
OCULAR ADVERSE EVENTS DENSITY
OPERATED EYES (N=217)
IMT-002

Page 1 of 2

A013, VOL 1, PAGE 221, TABLE 30

ADVERSE EVENTS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON- YEAR ¹	RATE PER 100 PERSON- YEAR (DENSITY) ²
Anterior chamber inflammation > 30 days	6	333.2	1.80
Anterior ischemic optic neuropathy	1	339.4	0.29
Choroidal neovascularization	1	339.8	0.29
Conjunctivitis	5	335.9	1.49
Corneal decompensation > 7 days	2	338.4	0.59
Corneal edema > 30 days	6	337.4	1.78
Cyclitic membrane > 7 days	1	338.3	0.30
Cystoid macular edema	1	338.5	0.30
Decrease in visual acuity	4	334.8	1.19
Device failure	2	339.1	0.59
Diplopia	3	335.6	0.89
Distorted pupil	9	330.1	2.73
Dry eye	10	331.5	3.02
Entropion	2	336.3	0.59
Exposed suture	3	336.2	0.89
Eye pain	3	337.1	0.89
Flat anterior chamber > 21 days	1	339.0	0.30
Floaters	3	337.2	0.89
Focal striae	1	338.4	0.30
Foreign body sensation	9	330.4	2.72
Guttae	16	326.0	4.91
IMT dislocation	2	337.0	0.59
IMT removal	8	336.0	2.38
Increased IOP requiring treatment > 7 days	7	333.8	2.10
Inflammatory deposits on IMT	51	283.0	18.02
Inflammatory membrane	1	338.6	0.30
Iridotomy > 7 days	3	336.6	0.89

¹ Total Person-Year = Sum of follow-up days for subjects without the corresponding event and the follow-up days up to the date of the reported event for the subjects reported with the corresponding event, divided by 365.25. The follow-up day for each subject = last available visit date (or event reported date) - surgical date + 1. The "+ 1" was to consider the event reported at the surgical day.

² Density = Total Number of Eyes with Reports ÷ Total Person-Year × 100.

TABLE 46 (CONTINUED)
OCULAR ADVERSE EVENTS DENSITY
OPERATED EYES (N=217)
IMT-002

Page 2 of 2

A013, VOL 1, PAGE 222, TABLE 30

ADVERSE EVENTS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON- YEAR ¹	RATE PER 100 PERSON- YEAR (DENSITY) ²
Iris atrophy > 7 days	8	331.9	2.41
Iris transillumination defects > 21 days	12	326.8	3.67
Iritis > 30 days	12	329.5	3.64
Keratic precipitates on IMT > 30 days	3	338.1	0.89
Obstructed iridectomy	1	338.7	0.30
Ocular allergy	1	338.2	0.30
Pigment deposits on IMT	23	320.0	7.19
Pigment epithelium around the peripheral iridectomy > 30 days	1	339.1	0.29
Posterior synechiae	15	323.2	4.64
Ptosis	4	336.3	1.19
Secondary glaucoma	2	336.8	0.59
Subconjunctival hemorrhage	9	329.5	2.73
Subretinal hemorrhage	3	338.8	0.89
Synechiae	1	338.8	0.30
Tearing	1	338.4	0.30
Visual disturbance	1	338.1	0.30
Vitreous flare	1	338.3	0.30
Vitreous hemorrhage > 7 days	3	337.1	0.89
Vitreous in anterior chamber > 7 days	4	334.4	1.20
Zonular dehiscence > 7 days	1	340.0	0.29

¹ Total Person-Year = Sum of follow-up days for subjects without the corresponding event and the follow-up days up to the date of the reported event for the subjects reported with the corresponding event, divided by 365.25. The follow-up day for each subject = last available visit date (or event reported date) - surgical date + 1. The "+ 1" was to consider the event reported at the surgical day.

² Density = Total Number of Eyes with Reports ÷ Total Person-Year × 100.

TABLE 47
OCULAR ADVERSE EVENTS DENSITY
OPERATED EYES FOLLOWED IN IMT-002-LTM
(N = 129)

Page 1 of 2

A013, VOL 1, PAGE 223, TABLE 31

ADVERSE EVENTS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON- YEAR ¹	RATE PER 100 PERSON- YEAR (DENSITY) ²
Anterior chamber inflammation > 30 days	4	376.7	1.06
Choroidal neovascularization	3	385.2	0.78
Conjunctivitis	5	378.0	1.32
Corneal decompensation > 7 days	4	381.8	1.05
Corneal edema > 30 days	13	371.4	3.50
Corneal transplant	2	385.4	0.52
Decrease in visual acuity	1	384.0	0.26
Diplopia	3	380.3	0.79
Distorted pupil	6	373.3	1.61
Dry eye	6	373.3	1.61
Entropion	1	382.9	0.26
Exposed suture	2	380.7	0.53
Eye pain	2	380.9	0.53
Flat anterior chamber > 21 days	1	384.5	0.26
Floaters	2	380.6	0.53
Focal striae	2	383.4	0.52
Foreign body sensation	5	373.0	1.34
Guttae	16	356.5	4.49
IMT dislocation	4	378.8	1.06
IMT removal	7	375.8	1.86
Increased IOP requiring treatment > 7 days	4	378.0	1.06
Iridotomy > 7 days	2	381.4	0.52
Iris atrophy > 7 days	6	376.1	1.60
Iris transillumination defects > 21 days	5	376.1	1.33
Iritis > 30 days	9	366.3	2.46
Ocular allergy	1	384.2	0.26
Posterior synechiae	15	358.3	4.19
Precipitates or deposits on IMT	49	267.4	18.32
Ptosis	2	385.7	0.52
Secondary glaucoma	1	383.4	0.26

¹ Total Person-Year = Sum of follow-up days for subjects without the corresponding event and the follow-up days up to the date of the reported event for the subjects reported with the corresponding event, divided by 365.25. The follow-up day for each subject = last available visit date (or event reported date) - surgical date + 1. The "+ 1" was to consider the event reported at the surgical day.

² Density = Total Number of Eyes with Reports ÷ Total Person-Year × 100.

TABLE 47 (CONTINUED)
OCULAR ADVERSE EVENTS DENSITY
OPERATED EYES FOLLOWED IN IMT-002-LTM
(N = 129)

Page 2 of 2

A013, VOL 1, PAGE 224, TABLE 31

ADVERSE EVENTS	TOTAL NUMBER OF EYES WITH REPORTS	TOTAL PERSON- YEAR ¹	RATE PER 100 PERSON- YEAR (DENSITY) ²
Subconjunctival hemorrhage	8	364.4	2.20
Subretinal hemorrhage	3	383.5	0.78
Visual disturbance	1	383.0	0.26
Vitreous flare	1	383.1	0.26
Vitreous in anterior chamber > 7 days	4	378.6	1.06
Zonular dehiscence > 7 days	1	385.2	0.26

¹ Total Person-Year = Sum of follow-up days for subjects without the corresponding event and the follow-up days up to the date of the reported event for the subjects reported with the corresponding event, divided by 365.25. The follow-up day for each subject = last available visit date (or event reported date) - surgical date + 1. The "+ 1" was to consider the event reported at the surgical day.

² Density = Total Number of Eyes with Reports ÷ Total Person-Year × 100.

CHOROIDAL NEOVASCULARIZATION

CNV was identified in one (1) eye in the IMT-002 study for an incidence of 0.5%, a rate consistent with that reported by Sunness et al., 1999. An additional 3 cases of CNV were observed during the IMT-002-LTM study. These cases of CNV were successfully treated with thermal laser photocoagulation (Garfinkel et al., 2006), photodynamic therapy or intravitreal injection of anti-VEGF therapeutic agents.

CORNEAL EDEMA

The proportion of eyes with corneal edema at each study visit is shown in Table 48. The highest incidence of corneal edema was observed in the early postoperative period, i.e., Day 1 and Day 7, as a result of the incision size and manipulation required to insert the IMT.

TABLE 48
CORNEAL EDEMA
IMT-IMPLANTED EYES
A015, PAGE 17, TABLE 5

VISIT	NUMBER OF AVAILABLE EYES	NUMBER OF EYES WITH CORNEAL EDEMA	% OF EYES WITH CORNEAL EDEMA
Day 1	206	14	6.8%
Day 7	205	7	3.4%
1 Month	206	3	1.5%
3 Months	201	1	0.5%
6 Months	202	1	0.5%
9 Months	196	1	0.5%
12 Months	194	0	0.0%
18 Months	180	0	0.0%
24 Months	174	3	1.7%
30 Months	3	0	0.0%
36 Months	79	3	3.8%
42 Months	110	6	5.5%
48 Months	102	2	2.0%
54 Months	35	1	2.9%
60 Months	6	0	0.0%

The following 3 IMT-implanted eyes were reported with corneal edema at unscheduled visits without being reported at the scheduled visits: 011-203 at 211 days; 022-203 at 1445 days, 1470 days and 1563 days; 026-209 at 1662 days.

CORNEAL EDEMA OCCURRING > 3 MONTHS POSTOPERATIVE (LATE CORNEAL EDEMA)

Tables 49 and 50 present the occurrences of corneal edema observed more than 3 months postoperatively in eyes without ECD loss (N = 1), and with early ECD loss (N = 12), respectively. Late-occurring corneal edema, occurring > 3 months postoperatively, was observed in 13 eyes, with 6 cases reported during Protocol IMT-002 and 7 cases reported in Protocol IMT-002-LTM).

Corneal thickness was within the normal range for 8 of the 10 eyes with unresolved corneal edema; 2 eyes had corneal edema >700 micron at 24 months.

Additional detail on the 13 eyes with corneal edema occurring >3 months postoperatively is provided in Appendix 2.

TABLE 49
OCCURRENCES OF LATE CORNEAL EDEMA WITH (EARLY) ECD LOSS
(N = 12)

Page 1 of 3

A013, VOL 1, PAGE 69, TABLE 32.1

PATIENT ID	TIME OF LATE CORNEAL EDEMA ONSET	ECD (CELLS/MM ²)		CORNEAL THICKNESS (MICRONS)		COMPLICATION & RELEVANT PERIOPERATIVE FINDINGS
IMT-002-LTM	42 Months	Preop 6M 9M 12M 18M 24M 42M 48M 52M 60M	2642 2274 2326 1855 1929 1011 508 660 556 505	Preop 3M 6M 9M 12M 18M 24M 48M 52M	546 574 561 578 569 586 597 656 642	3+Edema at D1 1+Edema at 42M 1+Edema at 48M 1+Edema at 52M Increased IOP requiring treatment ≤ 7 days
IMT-002-LTM	36 Months	Preop 3M 6M 9M 12M 18M	2908 432 452 397 361 351	Preop 3M 6M 9M 12M 18M 24M 42M 48M	607 621 677 601 694 700 771 771 920	1+Edema at D7 1+Edema at 3M 1+Edema at 9M 1+Edema at 12M 1+Edema at 18M 2+Edema at 24M 4+Edema at 36M 3+Edema at 42M 4+Edema at 48M Increased IOP requiring treatment ≤ 7 days
IMT-002	24 Months	Preop 3M 6M 9M 12M 18M 24M	2763 1684 1380 1070 845 604 529	Preop 3M 6M 9M 12M 18M 24M 48M 52M 60M	516 528 508 516 499 569 580 550 558 602	2+Edema at D1 1+Edema at D7 2+Edema at 24M 3+Edema at 42M Iris damage
IMT-002-LTM	36 Months	Preop 6M Post IMT R Post IMT R Post IMT R Post IMT R	2457 1906 1354 1861 1106 1480	Preop 3M 6M	524 546 546	2+Edema at D1 1+Edema at 1M 1+Edema at 36M 1+Edema at 42M 1+Edema at 48M Choroidal hemorrhage, vitreous hemorrhage ≤ 7 days, intraoperative. IMT removal

TABLE 49 (CONTINUED)
OCCURRENCES OF LATE CORNEAL EDEMA WITH (EARLY) ECD LOSS
(N = 12)

Page 3 of 3

A013, VOL 1, PAGE 71, TABLE 32.1

PATIENT ID	TIME OF LATE CORNEAL EDEMA OBSERVATION	ECD (CELLS/MM ²)		CORNEAL THICKNESS (MICRONS)		COMPLICATION & RELEVANT PERIOPERATIVE FINDINGS
IMT-002	24 Months	Preop	2738	Preop	557	1+Edema at D1 1+Edema at D7 1+Edema at 24M 1+Edema at 42M
		3M	1315	3M	519	
		6M	846	6M	619	
		9M	656	9M	646	
		12M	446	12M	604	
		18M	628	24M	715	
		24M	676	48M	598	
		42M	983			
		48M	851			
IMT-002-LTM	55 Months	Preop	2463	Preop	599	1+Edema at D1 Increased IOP requiring treatment ≤ 7 days Vitreous in anterior chamber ≤ 7 days
		3M	1901	3M	536	
		6M	1554	6M	559	
		9M	1170	9M	658	
		12M	901	12M	588	
		18M	638	18M	534	
		24M	544	24M	640	
		36M	386	42M	553	
		42M	393	48M	612	
IMT-002-LTM	36 Months	Preop	1769	Preop	600	3+Edema at 36M 2+Edema at 42M
		3M	916	3M	576	
		6M	646	6M	705	
		9M	531	9M	433	
		12M	519	12M	570	
		18M	457	18M	589	
		24M	505	24M	631	
		36M	324	42M	712	
		42M	709			
IMT-002	3 Months	Preop	2118	Preop	607	3+Edema at D1 2+Edema at D7 1+Edema at 1M 1+Edema at 3M 1+Edema at 6M 3+Edema at 9M IMT dislocation, Increased IOP requiring treatment ≤ 7 days, iris atrophy ≤ 7 days
		6M	385	3M	706	
		Post CT	1857	6M	742	
				12M	955	
				36M	641	
				42M	622	
				48M	622	

TABLE 49 (CONTINUED)
OCCURRENCES OF LATE CORNEAL EDEMA WITH (EARLY) ECD LOSS
(N = 12)

Page 2 of 3

A013, VOL 1, PAGE 70, TABLE 32.1

PATIENT ID	TIME OF Late Corneal Edema Observation	ECD (CELLS/MM ²)		CORNEAL THICKNESS (MICRONS)		COMPLICATION & RELEVANT PERIOPERATIVE FINDINGS
IMT-002	24 Months	Preop	2455	Preop	546	1+Edema at D1 1+Edema at 24M 1+Edema at 42M Precipitates or Deposits on IMT
		3M	2211	3M	542	
		6M	1074	6M	559	
		9M	1048	9M	567	
		12M	955	12M	633	
		18M	553	18M	662	
		24M	519	24M	716	
		42M	618	36M	658	
		48M	719	42M	724	
		48M	719	48M	633	
IMT-002	9 Months	Preop	1909	Preop	553	2+Edema at D1 2+Edema at D7 2+Edema at 9M 2+Edema at 12M Anterior synechiae, flat anterior chamber
		3M	633	3M	565	
		6M	463	6M	635	
		Post PKP	3442	9M	730	
		Post PKP	3133	12M	155	
		Post PKP	2984	42M	533	
		Post PKP	3128	48M	532	
		Post PKP	2483			
		Post PKP	1987			
		Post PKP	1529			
		Post PKP	1264			
IMT-002-LTM	48 Months	Preop	2465	Preop	551	1+Edema at 48M
		3M	782	3M	590	
		6M	431	6M	626	
		9M	309	9M	708	
		12M	311	12M	736	
		18M	664	18M	641	
		24M	503	24M	611	
		36M	823	42M	706	
		42M	594	48M	741	
		48M	501			
IMT-002-LTM	36 Months	Preop	2774	Preop	565	3+Edema at 36M 3+Edema at 42M Increased IOP requiring treatment ≤ 7 days
		6M	2566	3M	585	
		9M	2814	6M	590	
		12M	2959	9M	596	
		18M	2748	12M	599	
		24M	2860	18M	605	
		36M	2444	24M	640	
		42M	841	36M	655	
		48M	2153	42M	770	
		52M	1405	48M	534	

TABLE 50
OCCURRENCES OF LATE CORNEAL EDEMA WITH NO ECD LOSS
FOLLOWING IMT IMPLANTATION
(N=1)

A013, VOL 1, PAGE 228, TABLE 32.2

PATIENT ID	TIME OF Late Corneal Edema Observation	ECD (CELLS/MM ²)		CORNEAL THICKNESS (MICRONS)		COMPLICATION & RELEVANT PERIOPERATIVE FINDINGS
		Preop	3M	Preop	3M	
IMT-002	7 Months	Preop	2860	Preop	610	Corneal edema (no grade) and iritis reported at 7 months. Corneal edema not observed at 12 and 36 months.
		3M	2694	3M	602	
		6M	2737	6M	607	
		9M	2816	9M	592	
		12M	2434	12M	595	
		36M	2336	36M	593	

An analysis of the incidence of late onset corneal edema and/or corneal decompensation is presented in Table 51. At 24 months in the IMT-002 study, none of the eyes in the risk reduced cohort (age 65 or older, with no guttata, ACD \geq 3.0 mm, implanted by cornea specialists) presented with late corneal edema or corneal decompensation. In the non-risk reduced cohort, the incidence of corneal edema was 3.3% and 1.1% of these eyes had corneal decompensation.

In the IMT-002-LTM study at 48 months there were 2 reports (11.8%) of late corneal edema and 1 report (5.9%) of corneal decompensation in the risk reduced cohort. In the non-risk reduced cohort of eyes, late corneal edema was reported in 11 eyes (9.8%), and 3 eyes (2.7%) presented with corneal decompensation.

TABLE 51
INCIDENCE OF LATE CORNEAL EDEMA AND/OR CORNEAL DECOMPENSATION
IMT-002 AND IMT-002-LTM STUDIES

A019, PAGE 23, TABLE 2.C

SUBSETS	LATE CORNEAL EDEMA (> 30 DAYS) (CUMULATIVE)	CORNEAL DECOMPENSATION (CUMULATIVE)
IMT-002 STUDY (24 MONTHS)		
ENROLLED (N)	217	217
REPORTED EVENTS (N) AND PERCENT (%) OF ENROLLED	6 (2.8%)	2 (0.9%)
RISK REDUCED COHORT		
IMT-IMPLANTED EYES OF SUBJECTS ≥ 65 YEARS WITHOUT GUTTATA, ACD ≥ 3.0 MM AND OPERATED BY CORNEA SPECIALIST (N)	33	33
REPORTED EVENTS (N) AND PERCENT (%) OF ENROLLED	0 (0.0%)	0 (0.0%)
NON-RISK REDUCED COHORT (N)	184	184
REPORTED EVENTS (N) AND PERCENT (%) OF ENROLLED	6 (3.3%)	2 (1.1%)
IMT-002-LTM STUDY (48 MONTHS)		
ENROLLED (N)	129	129
REPORTED EVENTS (N) AND PERCENT (%) OF ENROLLED	13 (10.1%)	4 (3.1%)
RISK REDUCED COHORT		
IMT-IMPLANTED EYES OF SUBJECTS ≥ 65 YEARS WITHOUT GUTTATA, ACD ≥ 3.0 MM AND OPERATED BY CORNEA SPECIALIST (N)	17	17
REPORTED EVENTS (N) AND PERCENT (%) OF ENROLLED	2 (11.8%)	1 (5.9%)
NON-RISK REDUCED COHORT (N)	112	112
REPORTED EVENTS (N) AND PERCENT (%) OF ENROLLED	11 (9.8%)	3 (2.7%)

POSTOPERATIVE IMT EXPLANTATION

Postoperatively, the IMT was removed from 8 eyes of subjects during the IMT-002 study and an additional 4 eyes were explanted during the IMT-002-LTM study, for a total of 12 postoperative IMT explants in the postoperative period. (Because 3 eyes explanted during the IMT-002 study were subsequently enrolled into the IMT-002-LTM study and 4 eyes were explanted during IMT-002-LTM study, IMT removal is shown for a total of 7 eyes in the IMT-002-LTM study.)

Eight subjects were dissatisfied with the IMT and requested removal, 4 during the IMT-002 study and 4 during the IMT-002-LTM study. In 4 of these 8 eyes, visual acuity was improved from baseline, and in 2 eyes, visual acuity decreased from baseline. In all cases, explantation was uneventful and resulted in resolution of the dissatisfaction.

The IMT was removed from two eyes in the IMT-002 study at 1 month after implant due to condensation of the telescope portion of the IMT. This was previously discussed in Amendment 7, P050034.

Removal of the IMT was performed in two eyes that underwent corneal transplantation as a result of corneal decompensation in the IMT-002 study. The two eyes with corneal decompensation requiring penetrating keratoplasty are further described in the following section of this document.

Preoperative and last available BCDVA for eyes that underwent IMT removal are shown in Table 52.

TABLE 52
PREOPERATIVE AND LAST AVAILABLE BCDVA
EYES THAT UNDERWENT POSTOPERATIVE IMT REMOVAL (N = 12)
A013, VOL 1, PAGE 229, TABLE 33

PATIENT ID	EXPLANT DATE (MONTHS FROM DATE OF IMPLANT)	PREOP BCDVA (LOGMAR)	LAST AVAILABLE BCDVA (LOGMAR) POST EXPLANT	ECD PRIOR TO EXPLANT CELLS/MM ²	ECD MOST RECENT VISIT POST EXPLANT CELLS/MM ²	COMMENTS
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SUBJECT DISSATISFACTION

	03/29/2006 (31 Months)	20/604 (1.48)	20/399 (1.30)	2544	1926	Patient was dissatisfied with IMT
	05/03/2006 (31 Months)	20/551 (1.44)	20/726 (1.56)	1675	1454	Patient was dissatisfied with IMT
	02/24/2005 (22 Months)	20/502 (1.40)	20/276 (1.14)	1772	666	Patient was dissatisfied with IMT
	04/19/2004 (10 Months)	20/317 (1.20)	20/289 (1.16)	1625	1100	Patient was dissatisfied with IMT
	06/30/2004 (12 Months)	20/219 (1.04)	20/240 (1.08)	2891	2199	Patient was dissatisfied with IMT
	08/16/2004 (12 Months)	20/381 (1.28)	NAV	1858	NAV	Patient was dissatisfied with IMT No BCDVA reported post IMT removal
	02/08/2005 (19 Months)	20/276 (1.14)	20/166 (0.92)	2408	1389	Patient was dissatisfied with IMT
	03/08/2007 (41 Months)	20/200 (1.00)	NAV	2258	NAV	Patient was dissatisfied with IMT No BCDVA reported post IMT removal

DEVICE FAILURE OR CORNEAL DECOMPENSATION

	03/24/2003 (1 Month)	20/348 (1.24)	NAV	2316	NAV	Postoperative IMT removal due to device failure (condensation) No BCDVA reported post IMT removal
	11/18/2003 (1 Month)	20/348 (1.24)	20/458 (1.36)	2529	1234	Postoperative IMT removal due to device failure (condensation)
	09/01/2004 (12 Months)	20/303 (1.18)	20/348 (1.24)	463	1264	Postoperative IMT removal due to corneal decompensation, PKP
	08/10/2004 (10 Months)	20/551 (1.44)	20/1002 (1.70)	385	1857	Postoperative IMT removal due to corneal decompensation, PKP Last available BCDVA was reported 8 days post IMT removal

NAV = not available.

*Prior to IMT implant

CORNEAL DECOMPENSATION AND TRANSPLANTATION

Four (4) study eyes (Subjects [REDACTED], [REDACTED], [REDACTED], [REDACTED]) have undergone corneal transplantation to date. In 2 of these cases (Subjects [REDACTED] and [REDACTED]), reported in the original PMA, the IMT was removed. The IMT was left in place in the other 2 cases (Subjects [REDACTED] and [REDACTED]), which were reported during follow-up under Protocol IMT-002-LTM. The 4 cases are described as follows:

In Subject [REDACTED], during implantation of the IMT, spontaneous prolapse of the superior iris occurred, preventing visualization of the capsular bag. The IMT was placed in the ciliary sulcus, and at the end of the procedure, the IMT was in place with moderate depth of the anterior chamber. A flat anterior chamber was reported as a surgical complication and 2+ edema was reported on postoperative Day 1. The superior iris was atrophic due to the prolapse and did not constrict with a miotic agent. ECD was 633 cells/mm² at 3 months, and decreased to 463 cells/mm² at 6 months; corneal decompensation was diagnosed. Corneal transplantation was performed, with removal of the IMT and placement of a conventional IOL. Surgery and postoperative recovery were uneventful, and at 6 months following transplantation, slit lamp examination revealed normal cornea, normal endothelium, and no cells and no flare in the anterior chamber.

In Subject [REDACTED], intraoperative positive vitreous pressure resulted in iris prolapse. On the first postoperative day, intraocular pressure was increased and the inferior aspect of the IMT was covered by the inferior iris. Over the course of follow-up, the IMT was observed to be decentered inferiorly, with one of the haptics in the sulcus rather than in the capsular bag. Over the next several months, the patient's visual acuity gradually deteriorated and corneal edema worsened. At 6 months, endothelial cell density had decreased to 385 cells/mm², the cornea was edematous, and a decision was made to perform corneal transplantation. Corneal transplantation was performed, the IMT was removed, and a conventional IOL was implanted. Postoperatively, no complications were reported and the eye was quiet, with normal IOP and appearance of the cornea during slit lamp examination.

In Subject [REDACTED], iris damage and corneal touch were reported intraoperatively. BCVA improved following surgery through 12 months, but decreased over time as a result of corneal edema. ECD had decreased to 529 cells/mm² at 24 months. At approximately 48 months postoperatively, penetrating keratoplasty was performed, and the IMT was left in place. Post-keratoplasty, recovery was uneventful and visual acuity improved from 20/800 to 20/160.

In Subject [REDACTED], the IMT was successfully implanted, however the device was tilted, such that the superior haptic pressed against the temporal iris. In this eye ECD was 2444 cells/mm² through 36 months of follow-up, when the patient presented with localized corneal edema in the inferotemporal cornea corresponding to intermittent touch of the IMT to the endothelium. The position of the IMT was initially managed with the use of 1% pilocarpine, however, since proper positioning of the IMT was achieved only intermittently, the study investigator attempted repositioning of the IMT during a vitrectomy, and caused further trauma to the endothelium with corneal touch. Following this attempt at repositioning the IMT, there was significant ECD loss and deterioration of the cornea, with corneal edema and loss of visual acuity. Corneal transplantation was performed

approximately 48 months following original placement of the IMT, and the device was left in place. Recovery was uneventful, with a clear graft and good visual rehabilitation.

The four eyes requiring corneal transplantation presented with risk factors for endothelial cell loss: ACD > 3 mm, surgery performed by non-cornea specialists, and within the learning curve (first 5 cases) for the surgeon.

In 3 of the 4 eyes, the intraoperative trauma observed during the initial surgery to place the IMT was reflected in very substantial ECD loss at 3 and 6 months. In the fourth case, endothelial cell loss was gradual; likely due to intermittent between the IMT and the endothelium. This unsuccessful attempt at repositioning of the IMT, associated with additional corneal touch and resulting trauma led to more significant ECD loss, followed by corneal edema and loss of BCVA, resulting in the need for penetrating keratoplasty.

It is noteworthy that in the 2 cases in which the IMT was left in place (Subjects [REDACTED] and [REDACTED]), the visual outcome following keratoplasty was excellent, with a return to the level of BCVA originally achieved with the IMT, prior to onset of corneal edema. This finding suggests that if the IMT is not tilted or malpositioned, it is possible to leave the device in place and preserve the visual benefit following replacement of an edematous cornea. Additional experience with this approach, and longer-term follow-up post-keratoplasty is needed to establish the utility and safety of this approach.

Additional detail on each of the 4 eyes that underwent corneal transplantation is provided in Table 53.

TABLE 53
CORNEAL TRANSPLANTATION IN IMT-IMPLANTED EYES (N = 4)

SUBJECT ID	INTRAOPERATIVE FINDINGS	POSTOPERATIVE FINDINGS		OUTCOME OF CORNEAL TRANSPLANTATION
		CLINICAL FINDINGS	ECD	
██████████	Iris damage Corneal touch		2763 cells/mm ² at baseline 529 cells/mm ² at 24 months	Corneal transplantation performed, IMT left in place Recovery uneventful and improvement in BCVA achieved with IMT retained
██████████	Iris prolapse prevented capsular bag visualization; IMT placed in sulcus	Anterior chamber flattening, 2+ corneal edema on postop Day 1.	1909 cells/mm ² at baseline 633 cells/mm ² at 3 months 463 cells/mm ² at 6 months	Corneal transplantation performed, standard IOL placed Graft clear and eye quiet
██████████	IMT tilted, superior haptic pressed against temporal iris	Localized corneal edema in inferotemporal cornea resulting from touch of IMT to endothelium Investigator attempted IMT repositioning against recommendation of sponsor and medical monitor, with further trauma to endothelium, corneal edema, decreased BCVA	2774 cells/mm ² at baseline Significant ECD loss after repositioning to 841 cells/mm ²	Corneal transplantation performed, IMT left in place Recovery uneventful and improvement in BCVA achieved with IMT retained
██████████	Positive vitreous pressure resulted in iris prolapse	IMT decentered inferiorly Haptic in sulcus Corneal edema	2118 cells/mm ² 385 cells/mm ² at 6 months	Corneal transplantation performed, standard IOL placed Graft clear and eye quiet

OTHER SECONDARY SURGICAL INTERVENTIONS

Seven secondary surgical interventions not involving IMT removal were performed during the 24-month IMT-002 study and none has been reported to date in the IMT-002-LTM. These procedures, summarized in Table 54, consisted of one YAG laser treatment of the anterior surface of the IMT telescope to eliminate pigment deposits; 4 YAG laser peripheral iridotomies; one surgical repair of a distorted pupil; and one removal of a cortical fragment resulting from inadequate cataract removal.

TABLE 54
SECONDARY SURGICAL INTERVENTIONS IN IMT-IMPLANTED EYES
A013, VOL 1, PAGE 231, TABLE 34

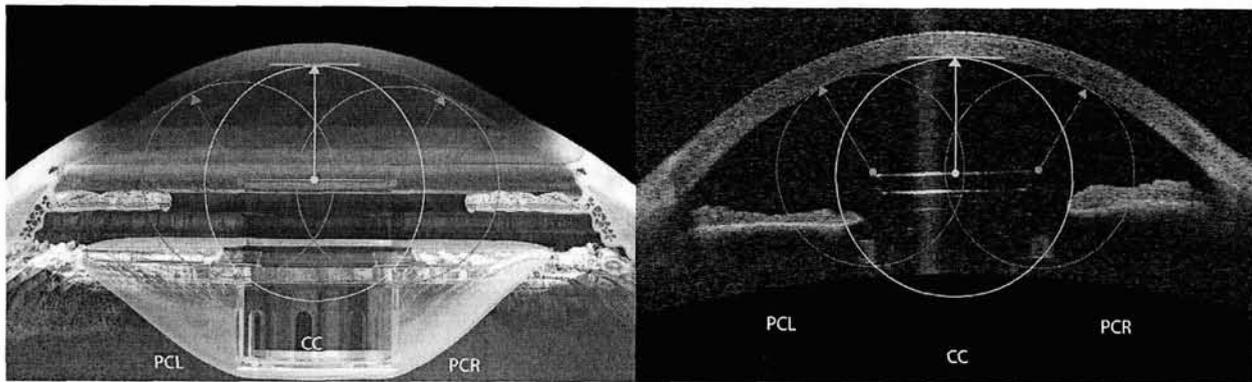
SUBJECT ID	ADVERSE EVENT	SEVERITY	INTERVENTION	OUTCOME
[REDACTED]	Pigment deposits on IMT	Moderate	YAG laser to anterior surface of IMT	Event resolved with no sequelae
[REDACTED]	Iridotomy > 7 days	Mild	Re-open PI with YAG laser	Event resolved with no sequelae
[REDACTED]	Iridotomy > 7 days	Mild	Re-open PI with YAG laser	Event resolved with no sequelae
[REDACTED]	Iritis > 30 days	Mild	Re-open PI with YAG laser	Event resolved with no sequelae
[REDACTED]	Pigment epithelium around the peripheral iridectomy > 30 days	Mild	Re-open PI with YAG laser	Event resolved with no sequelae
[REDACTED]	Decrease in visual acuity	Moderate	Cortical fragment removed	Event resolved with no sequelae, ie, visual acuity improved after cortical fragment removal
[REDACTED]	Distorted pupil	Moderate	Surgery to repair	Event resolved with no sequelae

6.5 ANTERIOR CHAMBER DEPTH (ACD) AND CLEARANCE

To address a question regarding clearance of the IMT from the corneal endothelium postoperatively, subjects who participated in Protocol IMT-002 were solicited to return for anterior segment imaging, to allow assessment of the clearance of the IMT from the corneal endothelial surface, centrally and peripherally. Ultrasound biomicroscopic (UBM) or anterior segment ocular coherence tomographic (AC OCT) images were obtained for 45 IMT-implanted eyes, and hard copies of each image of each image were printed.

A standard means of measuring left peripheral clearance, right peripheral clearance and cornea-to-iris distance was utilized as illustrated in Figure 28. These methods have been previously described in Amendment 7, Attachment 2.1.

FIGURE 28
CENTRAL CLEARANCE AND PERIPHERAL CLEARANCE MEASUREMENTS
 A013, VOL 1, PAGE 78, FIGURE 24



The 45 eyes imaged represent a distribution of ACD strata, as requested by FDA (Table 55). Baseline ACD was determined by A-scan. This distribution is reasonably consistent with that observed for the overall study population.

TABLE 55
DISTRIBUTION OF EYES IMAGED BY PREOPERATIVE ACD
 A013, VOL 1, PAGE 78, TABLE 37.1

PREOPERATIVE ACD CATEGORY	DISTRIBUTION OF ALL IMT-IMPLANTED EYES BY BASELINE ACD (N=206)	NUMBER OF EYES IMAGED (N=45)
<3.0 mm (Mean 2.8 mm)	80 (39%)	15 (33%)
3.0 mm to 3.5 mm (Mean 3.2 mm)	92 (45%)	24 (53%)
>3.5 mm (Mean 3.6mm)	34 (16%)	6 (13%)

Mean clearance for the total cohort of 45 eyes with UBM or AC OCT imaging was 2.51 mm (SD 0.33), with a median of 2.53 mm (Table 56). The difference between the three categories in mean distance from the IMT to the cornea was small. Mean clearance for the 15 eyes with ACD <3.0 mm was 2.48 mm, as compared to 2.53 mm for the eyes with ACD >3.0 mm to 3.5 mm, and ACD >3.5 mm. Thus, baseline differences in ACD did not appear to translate into similar differences in postoperative clearance from the anterior surface of the IMT to the endothelium.

TABLE 56
CENTRAL CLEARANCE FROM ANTERIOR SURFACE OF IMT
TO THE CORNEAL ENDOTHELIUM
ALL EYES WITH IMAGES VS EYES GROUPED BY BASELINE ACD
A013, VOL 1, PAGE 79, TABLE 37.2

	Distance from IMT to Cornea	Distance from IMT to Cornea	Distance from IMT to Cornea	Distance from IMT to Cornea
	All Eyes (N=45)	ACD <3.0 mm (N=15)	ACD ≥3.0 mm to 3.5 mm (N=24)	ACD >3.5 mm (N=6)
Mean	2.51	2.48	2.53	2.53
SD	0.33	0.35	0.31	0.38
Median	2.53	2.45	2.55	2.66

Mean peripheral clearance for left corneal measurements for 45 eyes with images was 2.17 mm (Table 57). Clearance for the left cornea increased from 2.13 mm for eyes with ACD <3.0 mm, 2.16 mm for ACD >3.0 to 3.5 mm, and 2.31 mm for eyes with ACD >3.5 mm. Mean clearance for the right peripheral cornea was 2.21 mm. Clearance measurements for the right cornea also increased slightly with increasing baseline anterior chamber depth.

TABLE 57
PERIPHERAL CLEARANCE FROM ANTERIOR SURFACE OF IMT
TO THE CORNEAL ENDOTHELIUM
ALL EYES WITH IMAGES VS EYES GROUPED BY BASELINE ACD
A013, VOL 1, PAGE 79, TABLE 37.3

	All Eyes Peripheral Clearance Left	Clearance Left ACD <3.0 mm	Clearance Left ACD ≥3.0 to 3.5 mm	Clearance Left ACD >3.5 mm	All Eyes Peripheral Clearance Right	Clearance Right ACD <3.0 mm	Clearance Right ACD ≥3.0 to 3.5 mm	Clearance Right ACD >3.5 mm
N	40	13	22	5	39	13	22	4
Mean	2.17	2.13	2.16	2.31	2.21	2.17	2.21	2.38
SD	0.29	0.32	0.30	0.12	0.35	0.34	2.22	0.26
Median	2.18	2.15	2.16	2.27	2.24	2.22	2.25	2.49

The clearance of 2.51 mm between the anterior surface of the IMT and the endothelium is substantial. While the IMT is not an anterior chamber device, it does protrude slightly into the anterior chamber; however, the minimum clearance of 1.00 mm required for anterior chamber intraocular lenses per ISO 11979-3 is significantly exceeded.

Central clearance was very similar for the three baseline ACD categories. Measurements made in the peripheral cornea, both right and left, increased slightly with increasing preoperative ACD. Because of the curvature of the cornea in the periphery, with narrowing of the anterior chamber toward the angle, this finding is not unanticipated, and does not represent a safety concern given the magnitude of clearance found both in the central cornea and in the periphery.

The absence of any clinically meaningful differences in central clearance for the three baseline ACD categories (<3.0 mm, 3.0 to 3.5 mm, >3.5 mm) is unanticipated, since baseline ACD would be expected to translate directly into postoperative clearance. This absence of a direct relationship between baseline ACD and postoperative clearance was further explored by comparing clearance in a subset of 13 IMT-implanted subjects who had an intraocular lens in the fellow eye, and underwent imaging of the anterior segment. In this cohort of 13 eyes, baseline ACD for the IMT-implanted eyes was 3.21 mm, while baseline ACD for the IOL-implanted fellow eyes was 3.79 mm. This deepening of the anterior chamber was not observed in phakic fellow eyes (Table 58).

TABLE 58
COMPARISON OF ACD IN IMT-IMPLANTED EYES AND
IOL-IMPLANTED FELLOW EYES AT ENTRY INTO PROTOCOL IMT-002
A013, VOL 1, PAGE 80, TABLE 37.4

Baseline ACD (mm) in IMT vs Fellow Eyes with IOL at Entry into Protocol IMT-002 N=13		Baseline ACD (mm) in IMT vs Phakic Fellow Eyes (without IOL) at Entry into Protocol IMT-002 N=32	
IMT-Implanted Eyes	IOL-Implanted Fellow Eyes	IMT-Implanted Eyes	Phakic Fellow Eyes
3.21	3.79	3.12	3.26

This finding of increased ACD following cataract removal is consistent with published literature on increased depth of the ACD after cataract removal. A series of studies has shown that extraction of the cataractous crystalline lens extraction results in an increase in ACD as well as in the irido-corneal angle (Kurimoto et al, 1997; Periera et al, 2003; Altan et al, 2004; Olsen et al, 2006).

6.6 INTRAOCULAR PRESSURE

Intraocular pressure (IOP) and change in IOP from baseline for eyes implanted with the IMT is displayed in Table 59. Mean IOP was 16 mm Hg at baseline, increased to 22 mm Hg at Day 1, then returned to within 1 mm of baseline and was generally stable for the remainder of the study.

TABLE 59
INTRAOCULAR PRESSURE (IOP) AND CHANGE IN IOP FROM BASELINE
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 81, TABLE 38

IOP	Baseline n (%)	1 Day n (%)	7 Day n (%)	1 Month n (%)	3 Months n (%)	6 Months n (%)	9 Months n (%)	12 Months n (%)
N	206	206	205	203	199	198	195	194
Mean	16	22	16	16	15	14	14	14
95% CI	15, 16	21, 23	15, 17	15, 16	14, 15	14, 15	14, 15	14, 14
Change from Baseline								
N		206	205	203	199	198	195	194
Mean		6	0	-0	-1	-1	-1	-2
95% CI		5, 8	-0, 1	-1, 0	-2, -1	-2, -1	-2, -1	-2, -1
Decrease > 10 mm Hg		1 (0%)	6 (3%)	1 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Decrease 6 - 10 mm Hg		11 (5%)	22 (11%)	15 (7%)	23 (12%)	26 (13%)	21 (11%)	30 (15%)
Decrease 1 - 5 mm Hg		39 (19%)	67 (33%)	76 (37%)	95 (48%)	96 (48%)	100 (51%)	86 (44%)
No Change		12 (6%)	19 (9%)	25 (12%)	14 (7%)	21 (11%)	14 (7%)	23 (12%)
Increase 1 - 5 mmHg		49 (24%)	56 (27%)	73 (36%)	58 (29%)	49 (25%)	55 (28%)	50 (26%)
Increase 6 - 10 mm Hg		33 (16%)	24 (12%)	11 (5%)	8 (4%)	6 (3%)	4 (2%)	4 (2%)
Increase > 10 mm Hg		61 (30%)	11 (5%)	2 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)

TABLE 59 (CONTINUED)
INTRAOCULAR PRESSURE (IOP) AND CHANGE IN IOP FROM BASELINE
IMT-002 AND IMT-002-LTM
A013, VOL 1, PAGE 81, TABLE 38

IOP	18 Months n (%)	24 Months n (%)	36 Months n (%)	42 Months n (%)	48 Months n (%)	54 Months n (%)	60 Months n (%)
N	179	174	74	104	96	34	6
Mean	15	15	14	16	15	14	17
95% CI	14, 15	14, 15	14, 15	15, 16	15, 16	13, 15	13, 20
Change from Baseline							
N	179	174	74	104	96	34	6
Mean	-1	-1	-1	-0	-1	-1	2
95% CI	-1, -0	-1, -0	-2, -0	-1, 0	-1, 0	-2, 0	-2, 5
Decrease > 10 mm Hg	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Decrease 6 - 10 mm Hg	14 (8%)	17 (10%)	6 (8%)	5 (5%)	4 (4%)	2 (6%)	0 (0%)
Decrease 1 - 5 mm Hg	78 (44%)	77 (44%)	36 (49%)	54 (52%)	43 (45%)	19 (56%)	2 (33%)
No Change	27 (15%)	25 (14%)	10 (14%)	6 (6%)	17 (18%)	2 (6%)	1 (17%)
Increase 1 - 5 mmHg	51 (28%)	49 (28%)	17 (23%)	33 (32%)	29 (30%)	10 (29%)	1 (17%)
Increase 6 - 10 mm Hg	7 (4%)	5 (3%)	4 (5%)	5 (5%)	3 (3%)	1 (3%)	2 (33%)
Increase > 10 mm Hg	1 (1%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)

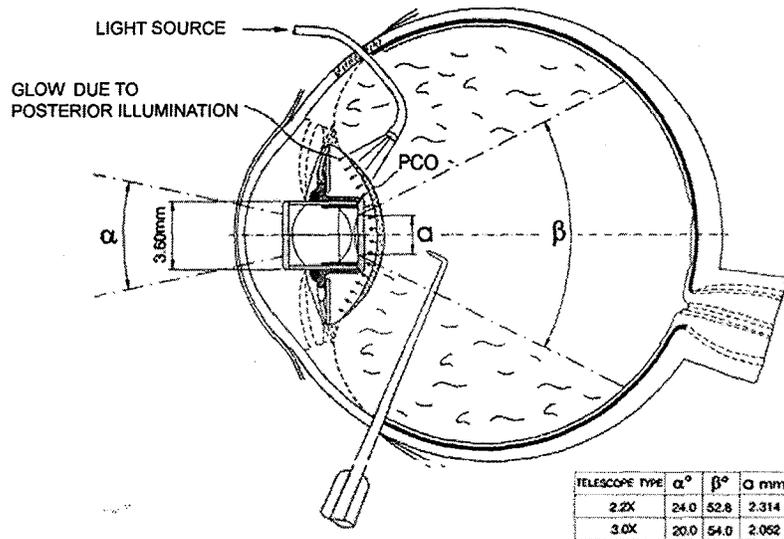
6.7 POSTERIOR CAPSULE OPACIFICATION

There were 8 reports of posterior capsule opacification (PCO) during the 24-month clinical trial (Protocol IMT-002). Six of these were graded minimal, 2 were graded moderate and none was reported as vision-impairing.

PCO was reported in an additional eye during Protocol IMT-002-LTM, and surgical capsulotomy was successfully performed using needling. In this eye, a combination of coaxial and retroillumination was used to identify the posterior capsule and a 25-gauge vitrector was used to engage the posterior capsule. A capsulotomy was performed using a combination of peeling and direct vitrectomy. Following capsulotomy, the patient's visual acuity improved by approximately 4 lines, allowing the eye to regain the initial improvement in vision from preoperative baseline BCDVA of 20/726 to 20/320 at 42 months.

The pars plana approach utilized in the needling procedure is shown schematically in Figure 29.

FIGURE 29
PARS PLANA CAPSULOTOMY
A013, VOL 1, PAGE 82, FIGURE 25



One case of visually significant PCO was observed during the Phase 1 clinical trial, which employed a slightly different IMT design.

Although Nd:YAG laser treatment of PCO has not been undertaken in any IMT-implanted subjects, the feasibility of utilizing the Nd:YAG laser for posterior capsulotomy in IMT-implanted patients has been evaluated in a rabbit study. In this study,

Nd:YAG laser capsulotomy was successfully performed in rabbit eyes implanted with the IMT by focusing the laser beam on the posterior capsule, aiming and firing the laser beam through the periphery of the telescope while carefully avoiding contact with the glass optical element of the telescope (Rosner et al, 2003). 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.

On the basis of these study findings, VisionCare has developed instructions for performing Nd:YAG laser capsulotomy in IMT-implanted patients with posterior capsular opacification (PCO). These instructions are included in physician labeling for the IMT.

The low incidence of PCO reported in the IMT-002 and IMT-002-LTM clinical trials reflect the design considerations implemented during development of the IMT with the specific objective of minimizing the occurrence of posterior capsular haze. These design activities included a review, analysis and implementation of the relevant parameters identified in the published literature as well as from consultation with experts in the field, including David Apple, M.D (Apple et al, 2000).

6.8 RETINAL EXAMINATION AND FINDINGS

The presence of the IMT does not preclude examination or treatment of retinal pathology. The study investigators routinely performed fundus examinations as part of the standard of care for patients with retinal disease.

Protocol IMT-002 did not require fundus photographs or imaging with other methods. However, at the request of FDA, fundus photographs were requested from clinical sites that had obtained these from IMT-implanted eyes. Investigators were also asked to participate in a survey asking whether fundus examinations had been routinely and successfully performed, and whether there had been difficulties in visualizing the fundus.

The available photographs showed that fluorescein angiography of the fundus could be successfully performed and recorded. Standard fundus photographs were also obtained. Responses to the survey were received from 33 of the 38 principal investigators, representing 25 of the 28 clinical sites enrolling 194 of the 206 IMT-implanted study subjects. The majority of respondents, accounting for a majority of study investigators, performed fundus examinations routinely, and of the 1,800 fundus examinations attempted, examinations could not be performed in only 4% of eyes. Fluorescein angiography, diagnostic photography, OCT and/or B scan ultrasonography was successfully performed in nearly all of the subjects who could not be examined with direct visualization. The macula was imaged through an IMT using fluorescein angiography and posterior segment OCT. The image took longer to obtain (15 minutes rather than the 5 minutes required for a normal eye), but allowed identification of a membrane and hemorrhage.

IMT labeling and the surgeon training program describe techniques for visualization and treatment of the posterior segment of the eye. Since use of a contact lens facilitates direct visualization of the fundus, labeling for the IMT recommends use of a contact lens in appropriate cases.

Importantly, no retinal detachments have been reported to date in the IMT-implanted eyes in the IMT-002 and IMT-002-LTM trials.

7.0 LABELING FOR RISK MITIGATION

According to the applicable law, a PMA will be approved when there is a reasonable assurance of efficacy and safety under the conditions of use prescribed, recommended, or suggested in the labeling for the device, and also specifically for the persons for whose use the device is represented (i.e., labeled for) or intended.

As the legal standards state, regulatory decisions about both safety and effectiveness are based on the labeling for the device. If effectiveness can be enhanced by proper use of the device and the labeling includes information about proper use, then a decision that the device is effective if used in accordance with the labeling can be more readily made. Similarly, if the risks of a device can be mitigated (i.e., if the safety can be improved) by labeling that includes warnings, contraindications, precautions, or other information that will aid safe use, and the labeling includes such information, then a decision that the device is safe if used in accordance with the labeling can also be more readily made. Also, it follows that as effectiveness is improved by proper labeling or risk is reduced by proper labeling, the benefit to risk ratio will likewise be enhanced in favor of approvability.

The proposed labeling for the IMT addresses both enhancement of effectiveness and mitigation of risk.

The proposed indication for the IMT is:

To improve vision by monocular implantation in patients 65 or older with stable moderate (distance BCVA of $\leq 20/80$) to profound (distance BCVA $\geq 20/800$) vision impairment caused by bilateral central scotomas associated with end-stage age-related macular degeneration. Patients must have:

- *retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography*
- *evidence of cataract*
- *at least a five-letter improvement on the ETDRS chart with an external telescope*
- *adequate peripheral vision in the eye not scheduled for surgery*
- *willingness to participate in a post-operative training program in use of the IMT.*

(Because only 6 subjects with Stargardt's disease were included in the IMT-002 study, there is insufficient information on these subjects to support efficacy. Accordingly, the proposed indication does not include patients with Stargardt's disease.)

The proposed professional use information provides detailed instructions for performing the surgery. In addition, if FDA agrees, the device will be restricted for use by physicians who have completed the training offered by VisionCare. Both measures will improve the likelihood that the device will be implanted in a manner that allows it to function effectively.

As discussed in the safety section of this executive summary, several steps can be taken to reduce the risk that endothelial cell density (ECD) will, over time, fall to levels inconsistent with corneal stability. These steps will be incorporated into the labeling for the IMT as restrictions, contraindications, precautions, warnings, and other safety information.

1. The presence of corneal guttata is associated with greater loss of ECD as a result of the implantation surgery. Accordingly, the proposed labeling states that corneal guttata are a contraindication.
2. Anterior chamber depth less than 3.0 mm is a contraindication.
3. In order to minimize the risk that patients will, over time, lose so many corneal endothelial cells that their corneas will decompensate and require a corneal transplant, a grid utilizing age, preoperative life expectancy, and preoperative ECD together with expected rates of ECD loss as predicted by the biexponential model will be presented as a contraindication. If patients lack sufficient ECD at baseline to predict ECD of at least 750 cells/mm² at the end of their life span, implantation of an IMT will be contraindicated. The grid of preoperative ECD required for IMT implantation is shown on the following page.

FIGURE 26
PROPOSED GRID OF PREOPERATIVE ECD REQUIRED FOR IMT IMPLANTATION
BASED ON IMT-IMPLANTED EYES WITHOUTH GUTTATA AND WITH ACD ≥ 3.0 MM
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Age Range	65-69		70-74		75-79		80-84		85-89		90 or Greater	
Gender	Male	Female	Male	Female								
Avg. Life Span	16.6	19.5	13.2	15.8	10.3	12.4	7.8	9.4	5.7	6.9	4.2	5.0
Minimum Cell Density	2460	2755	2000	2325	2000	2000	2000	2000	1800	1800	1800	1800
EDC at year	1	1855	2077	1508	1753	1508	1508	1508	1357	1357	1357	1357
	2	1753	1963	1425	1657	1425	1425	1425	1283	1283	1283	1283
	3	1657	1855	1347	1566	1347	1347	1347	1212	1212	1212	1212
	4	1565	1753	1273	1480	1273	1273	1273	1145	1145	1145	1145
	5	1479	1657	1203	1398	1203	1203	1203	1082	1082	1082	1082
	6	1398	1566	1137	1321	1137	1137	1137	1023	1023	1023	1023
	7	1321	1480	1074	1249	1074	1074	1074	967	967	967	967
	8	1248	1398	1015	1180	1015	1015	1015	913	913	913	913
	9	1180	1321	959	1115	959	959	959	863	863	863	863
	10	1115	1249	906	1054	906	906	906	816	816	816	816
	11	1054	1180	857	996	857	857	857	771	771	771	771
	12	996	1115	809	941	809	809	809	728	728	728	728
	13	941	1054	765	889	765	765	765	688	688	688	688
	14	889	996	723	840	723	723	723	651	651	651	651
	15	840	941	683	794	683	683	683	615	615	615	615
	16	794	889	646	750	646	646	646	581	581	581	581
	17	750	840	610	709	610	610	610	549	549	549	549
	18	709	794	576	670	576	576	576	519	519	519	519
	19	670	750	545	633	545	545	545				
	20	633	709	515	598	515	515	515				
	21	598	670		566							
	22	565	633		534							
	23	534	598		505							
	24	505	566									
	25		534									
	26		505									

Life expectancy -- National Vital Statistics Reports, Vol. 53, No. 6, November 10, 2004

Cell density at end of life

Years post implant when cell density reaches 500 cell per mm²

4. Because prospective patients should receive full and accurate information before deciding whether the potential benefits and risks of IMT implantation are appropriate for them, a legend beneath the grid will read: See Precautions for information to provide to prospective patients about the risk of loss of endothelial cell density. The following appears as a Precaution:

Patients should be advised of the potential risk of loss of endothelial cell density, and further advised that additional ECD may be lost over time. They should also be told that sufficiently large loss of endothelial cell density could cause corneal edema leading to cornea decompensation possibly requiring corneal transplantation. Patients should be advised that it is important to have a pre-operative assessment of their corneal endothelium. Patients should be given sufficient information about the benefits and risks, including ECD loss, of the procedure to make a judgment together with their physician about whether to undergo the procedure.

5. A "cornea specialist" is defined as an ophthalmologist who had fellowship or other specialty training in diseases and surgery of the cornea and who regularly performs corneal surgical procedures such as penetrating keratoplasty. In IMT-002, patients whose surgeries were performed by cornea specialists incurred less loss of endothelial cell density. Accordingly, the labeling includes a warning stating that implantation of the IMT should be performed only by cornea specialists.

6. VisionCare believes that patients will have less risk of endothelial cell density loss if physicians are trained in use of the IMT before implanting it in patients. VisionCare asks FDA to restrict use of the device to those who have completed in a training session provided to the physician before shipping the device to that physician. If FDA agrees, this restriction will be included in the labeling.

Table 60 on the following page shows the currently-proposed Indication, Contraindications, Warnings, Precautions, Restrictions, and other labeling information compared to those proposed at the time of the Ophthalmic Devices Advisory Panel meeting in 2006 to highlight modifications introduced into the currently proposed labeling.

TABLE 60
KEY CURRENT VERSUS PREVIOUS PROPOSED LABELING ELEMENTS
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CURRENT	PREVIOUS
<p>Proposed indication</p> <p>The Implantable Miniature Telescope (Implantable Miniature Telescope (IMT™_{by Dr. Isaac Lipshitz}))</p> <p>is indicated to improve vision by monocular implantation in patients 65 or older with stable moderate (distance BCVA of ≤ 20/80) to profound (distance BCVA ≥ 20/800) vision impairment caused by bilateral central scotomas associated with end-stage age-related macular degeneration. Patients must have:</p> <ul style="list-style-type: none"> • retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography, • evidence of cataract, • at least a five-letter improvement on the ETDRS chart with an external telescope, <hr/> <ul style="list-style-type: none"> • <i>adequate peripheral vision in the eye not scheduled for surgery</i> <hr/> <ul style="list-style-type: none"> • <i>willingness</i> to participate in a postoperative visual training/rehabilitation program. 	<p>Proposed indication</p> <p>The Implantable Miniature Telescope (Implantable Miniature Telescope (IMT™_{by Dr. Isaac Lipshitz})) is indicated for monocular implantation in patients ≥55 years of age with:</p> <ul style="list-style-type: none"> • bilateral, stable, untreatable moderate to profound central vision disorders resulting from age-related macular degeneration as determined by fluorescein angiography, • evidence of cataract • who achieve a five-letter improvement on the ETDRS chart in the eye scheduled for surgery using an external telescope, <hr/> <ul style="list-style-type: none"> • anterior chamber depth < 2.5 mm • who show interest in participating in postoperative visual rehabilitation program.
CONTRAINDICATIONS*	CONTRAINDICATIONS
<ul style="list-style-type: none"> • <i>evidence of corneal guttata</i> <hr/> <ul style="list-style-type: none"> • <i>anterior chamber depth <3.0 mm</i> 	<ul style="list-style-type: none"> • <i>corneal endothelial dystrophies contraindicated</i> <hr/> <ul style="list-style-type: none"> • The IMT is contraindicated in patients with <i>endothelial cell density less than 1,600 cell/mm²</i>
<ul style="list-style-type: none"> • <i>The IMT is contraindicated in patients who do not meet the minimum age and endothelial cell density, as shown in the grid below:</i> 	

Age Range	65-69		70-74		75-79		80-84		85-89		90 or Greater	
Gender	Male	Female	Male	Female								
Avg. Life Span	16.6	19.5	13.2	15.8	10.3	12.4	7.8	9.4	5.7	6.9	4.2	5.0
Minimum Cell Density	2460	2755	2000	2325	2000	2000	2000	2000	1800	1800	1800	1800

*Additional contraindications, consistent with the exclusion criteria found in Protocol IMT-002, have been included in labeling for the IMT

TABLE 60 (continued)
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WARNINGS AND OTHER RELEVANT LABELING INFORMATION	WARNINGS AND OTHER RELEVANT LABELING INFORMATION
<i>Surgery to implant the IMT should be performed only by cornea specialists.</i>	Not specified
<i>This device is restricted to use only by physicians who have participated in the training provided by VisionCare</i> Precaution	Not specified
<i>Patients should be advised of the potential risk of loss of endothelial cell density, and further advised that additional ECD may be lost over time. They should also be told that sufficiently large loss of endothelial cell density could cause corneal edema leading to cornea decompensation possibly requiring corneal transplantation. Patients should be advised that it is important to have a pre-operative assessment of their corneal endothelium. Patients should be given sufficient information about the benefits and risks, including ECD loss, of the procedure to make a judgment together with their physician about whether to undergo the procedure.</i>	Not specified

With a targeted, focused indication for use, and warnings, precautions, contraindications, restrictions, and other information included in the labeling to provide information about effective strategies for risk mitigation, the IMT will be effective and safe under the conditions of use prescribed, suggested, or recommended in the labeling.

8.0 CONCLUSION

VisionCare respectfully requests that CDRH approve P050034 as amended for the Implantable Miniature Telescope.

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October 1, 2008

PMA Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, MD 20850

RE: P050034 – Amendment 14
VisionCare Ophthalmic Technologies Implantable Miniature Telescope
IMT (by Dr. Isaac Lipshitz)TM

Dear Sir or Madam,

Please find enclosed six (6) copies of Amendment 15 to P050034, for the Implantable Miniature Telescope (IMT).

This amendment provides two sets of information requested by the Division of Ophthalmic and ENT Devices (DOENTD):

1. A tabulation (or data line listing) of adverse events that have occurred in the IDE protocols for the IMT (IMT-002 and IMT-002-LTM), by site. DOENTD requested the dates each AE was reported to the sponsor, the IRB, and FDA. Because there is no requirement to make such reports other than for UADEs (of which there have been none), no such reports were made and that information is not available.
2. A data line listing for key clinical endpoints, by site. The format used for the data line listing of key clinical outcomes was reviewed and agreed upon with DOENTD.

The study records for the two IDE clinical trials are maintained at the company's contract research organization:

DataMed Devices, Inc.
Kathryn Tsang, President
25042 Castlewood
Lake Forest, CA 92630
Phone: 949-458-6330
Fax: 949-581-8106

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Thank you for your consideration of this PMA P050034 as amended. If you have any questions or need any additional information during your review, please contact me at (949) 715-0609 (phone), or by fax at (949) 715-0610, or by email at judy@clinregconsulting.com.

Sincerely,

Judy F. Gordon, D.V.M.
Regulatory Consultant to VisionCare Ophthalmic Technologies, Inc.
