

P050034
Vision Care Ophthalmic Technologies, Inc.
Implantable Miniature Telescope

Safety and Efficacy Primary Review

I. STUDY POPULATION

- A. Background
 - 1. Guidance Document: “Accountability Analysis for Clinical Studies for Ophthalmic Devices” (4 AUG 99)¹
- B. Accountability²
 - 1. Accountability > 95% at all time intervals with the exception of 92% at Month 18
- C. Discontinued Subjects
 - 1. 16 subjects were discontinued from the study
 - a. 10 died
 - b. 6 subjects had the IMT device explanted prior to study completion
- D. Demographics³
 - 1. Gender = 47.6% female; 52.4% male
 - 2. Race = 96.1% Caucasian
 - 3. Implanted eye = 47.6% right; 52.4% left
 - 4. Age = 75.4 mean +/- 7.2; Range = 55 to 93 years
- E. Comment

Accountability is acceptable. The mean age in the study is consistent with the expected age of patients needing cataract surgery. The age of implantation of this device will be a critical factor when considering annual endothelial cell loss rates following device implantation in conjunction with the expected life span of the subject.

II. SAFETY ISSUES

- A. Best Spectacle Corrected Visual Acuity (BSCVA)
 - 1. Background Information
 - a. Definition of clinically meaningful change in vision
 - i. A loss of two or more Snellen lines of vision (i.e. 10 letters) has been recognized as being clinically meaningful because a gain or loss of one line can occur from one examination to another in unoperated eyes, particularly in individuals who can see 20/10, 20/12, and 20/16.⁴
 - b. Magnification or minification effects on BSCVA
 - i. For past PMA deliberations, the Ophthalmic Devices Panel has considered the effect of magnification or minification of the retinal image when interpreting visual acuity gains or losses.⁵ However, since most refractive surgery corrections at the corneal plane result only in very small magnification or minification gains or losses (i.e. only a few letters on a Snellen chart), great emphasis has not been previously given to readjusting the preoperative baseline. For example, a relative retinal minification of

¹ <http://www.fda.gov/cdrh/ode/1350.pdf>

² Volume I, page 30, table 9-3

³ Volume I, page 28, table 9-1

⁴ Waring GO, Lynn MJ, Culbertson W, Laibson PR, Lindstrom RD, McDonald MB, Myers WD, Obstbaum SA, Rowsey JJ, Schanzlin DJ, The PERK Study Group. Three-year results of the Prospective Evaluation of Radial Keratotomy (PERK) study. *Ophthalmology* 1987;94:1339-1354.

⁵ Written review of Refractec ViewPoint CK™ System (PMA P010018) dated 11 AUG 01, among others

- approximately 0.95 results from moving three diopters of hyperopic spectacle correction (vertex distance of 14 mm) to the corneal plane – that is, about a one letter loss in the postoperative visual acuity measurements.⁶
- c. Luminance effects on visual performance – normal and AMD eyes
 - i. Patients with macular degeneration have diminished contrast sensitivity.⁷ Patients with age related macular degeneration generally require increased illumination for best reading performance.⁸
 - ii. For normal subjects with a best-corrected visual acuity of 20/20 or better, the BSCVA and fusion begins to decrease significantly when the value of a neutral density filter reaches 2.0 (1% light transmission); and Titmus stereoacuity begins to decline significantly at a 1.4 ND filter (4% light transmission).⁹ Presumably, patients with age related macular degeneration will experience a decline in BSCVA, fusion, and stereoacuity at some unspecified light transmission threshold higher than 1% – likely dependent upon the degree of macular disease present. One study of 12 macular degeneration subjects reported maintenance of mean log contrast sensitivity with light filters which reduced photopic light transmission up to 75% (i.e. 0.6 ND filter or 25% light transmission).¹⁰
 2. Retinal Illumination & Magnification with the IMT device
 - a. 2.2X IMT device
 - i. The 2.2X IMT device reduces illumination by a factor of 4.8;¹¹ or 0.8 log units (16% light transmission)¹²
 - ii. The 2.2X IMT device expands the central 24 degrees of field to 52.8 degrees on the retina¹³ – a FDA predicted visual acuity improvement of 3.4 lines (0.34 logMAR), and a sponsor predicted visual acuity improvement of 2 to 3 lines.¹⁴
 - b. 3.0X IMT device
 - i. The 3.0X IMT device reduces illumination by a factor of 7.3;¹⁵ or 1.0 log units (10% light transmission)¹⁶
 - ii. The 3.0X IMT device expands the central 20 degrees of field to 54 degrees on the retina¹⁷ – a FDA predicted visual acuity improvement of 4.3 lines (0.43 logMAR), and a sponsor predicted visual acuity improvement of 3 lines.¹⁸

⁶ Applegate RA, Howland HC. Magnification and visual acuity in refractive surgery. *Arch Ophthalmol* 1993;111:1335-1342.

⁷ Langagergaard U, Ganer HJ, Baggesen. Age-related macular degeneration: filter lenses help in certain situations. *Acta Ophthalmologica Scandinavica* 2003;81:455-458.

⁸ Bowers AR, Meek C, Steward N. Illumination and reading performance in age-related macular degeneration. *Clin Exp Optom* 2001;84:139-147.

⁹ Chang YH, Lee JB, Kim NS, Lee DW, Chang JH, Han SH. The effects of interocular differences in retinal illuminance on vision and binocularity. *Graefes Arch Clin Exp Ophthalmol*. 2006 Jan 13:1-6.

¹⁰ Leguire LE, Suh S. Effect of light filters on contrast sensitivity function in normal and retinal degeneration patients. *Ophthalmic Physiol Opt*. 1993;13(2):124-128.

¹¹ Volume 2, page 142, Item 16 – Sponsor estimate

¹² Volume 2, page 142, Item 16 – FDA estimate

¹³ Volume 1, page 10 and page 24

¹⁴ Volume 2, pages 143 - 145, Item 17

¹⁵ Volume 2, page 142, Item 16 – Sponsor estimate

¹⁶ Volume 2, page 142, Item 16 – FDA estimate

¹⁷ Volume 1, page 10 and page 24

¹⁸ Volume 2, pages 143-145, Item 17.

3. Magnification Adjustment to Baseline Preoperative Visual Acuity
 - a. **FDA QUESTION:** Is preoperative acuity acceptable as a baseline for safety and effectiveness evaluations of acuity, or should an adjusted baseline be used that takes into account the magnification of the retinal image?
 - b. **Comment:**

In principle, I agree that the preoperative baseline visual acuity should be adjusted for device induced magnification or minification when calculating losses of BSCVA – a safety factor. This approach does have prior precedent in past Panel deliberations with excimer laser devices used for corneal refractive surgery. Adjusting for the induced magnification or minification following refractive surgery tends to “unmask” losses in BSCVA due to corneal irregular astigmatism. Unlike a corneal refractive surgical procedure, however, IMT implantation causes different competing effects that impact BSCVA gains or losses: (1) increased retinal magnification from the IMT device;(2) reduced retinal illumination from the IMT device; and (3) removal of a visually significant cataract, notwithstanding (4) device-induced optical aberrations.

The IMT device itself has two primary competing effects on macular performance, and therefore BSCVA: (a) reduced brightness which may cause reduced BSCVA – particularly in macular degeneration patients; and (b) increased magnification which should cause improved BSCVA. Given that both of these factors are occurring simultaneously, I do not believe that the preoperative BSCVA baseline should be “adjusted” solely on the basis of predicted magnification improvements in BSCVA. It seems to me that adjusting the baseline in this fashion would overestimate visual loss in the study since it ignores the compensatory BSCVA baseline “adjustment” that would be necessary on the basis of device-induced reduced luminance – whatever that “adjustment” is in an eye with macular degeneration. And, we mustn’t forget that these patients didn’t undergo clear lens extraction – visually significant cataracts were removed which should lead to improved contrast sensitivity and increased luminance to some unspecified degree. Certainly, I agree with the Sponsor that the IMT device will likely cause a reduction in contrast sensitivity and visual acuity in low lighting situations.¹⁹ However, since an ETDRS chart has near 100% contrast targets, I’m unsure how much the study BSCVA measurements are impacted (i.e. lowered) by the altered retinal illumination, if at all. Chang and colleagues report that normal eyes manifest BSCVA loss when light transmission reaches 1%.²⁰ However, the IMT device doesn’t lower light transmission to that degree – the FDA estimates 10% to 16% light transmission. The problem is that we are dealing with a cohort of macular degeneration eyes – not normal eyes – and the amount or degree of macular degeneration in this cohort is likely heterogeneous (e.g. preop BCDVA ranged from 20/120 to 20/328).²¹ Hence, we don’t know the exact light transmission threshold that will lead to BSCVA loss in a given macular degeneration patient. We can probably only

¹⁹ Volume 2, page 142, Item 16.

²⁰ Chang YH, Lee JB, Kim NS, Lee DW, Chang JH, Han SH. The effects of interocular differences in retinal illuminance on vision and binocularity. Graefes Arch Clin Exp Ophthalmol. 2006 Jan 13:1-6.

²¹ Volume 1, page 188, Table 4

say that some of the macular degeneration patients may be impacted by the reduced light transmission despite being presented with 100% contrast ETDRS letters, and some of the macular degeneration patients may not be impacted by that same reduced light transmission.

Based upon the foregoing, I'm not in favor of a magnification "adjustment" to the preoperative BSCVA baseline for two reasons: (1) the adjustment won't "unmask" a single deleterious vision factor (e.g. like corneal irregular astigmatism in corneal refractive surgery) to help us with our safety analysis (i.e. loss of BSCVA); and (2) a magnification "adjustment" would downgrade all of the effectiveness BSCVA data and eliminate the primary mechanism of visual improvement that the IMT device offers to a macular degeneration patient – magnification. If the magnification "adjustment" is performed, we'd be left evaluating the effectiveness of cataract surgery in macular degeneration patients with an implantable telescope that reduces illumination – that's not the goal!

4. Loss of BSCVA
 - a. About 5% (4.5% to 6.1%) lost 2 or more lines of vision in either near or distance BSCVA at all time intervals without a corresponding improvement (gain of 2 or more lines) in either near or distance BSCVA.²²
 - b. Slightly more than 1% (1.0% to 2.1%) lost 2 or more lines of BCDVA and BCNVA at all time intervals.²³
 - c. **Comment:**

An important indicator of the safety of a refractive surgical procedure is no change in the best spectacle corrected visual acuity following surgery. The rates of loss in the IMT study met the $\leq 10\%$ rate defined in the protocol – no untoward safety concern.

5. Corneal Endothelial Cell Loss
 - a. Background Information on Endothelial Cell Loss from Anterior Chamber Phakic IOLs²⁴
 - i. General Issues
 - 1) Phakic Intraocular Lens (IOL) Peer-reviewed Literature Review
 - A) Numerous limitations in published reports
 - i. mostly retrospective in design
 - ii. non-randomized case series
 - iii. low N
 - iv. poor accountability for longer follow-up intervals
 - v. morphometric endothelial analyses (i.e. coefficient of variation & percent hexagonality) generally not reported
 - ii. Phakic IOL Types
 - 1) Anterior Chamber
 - A) Angle supported

²² Volume 1, page 193, Table 6

²³ Volume 1, page 193, Table 6

²⁴ Adapted from a FDA presentation entitled "Phakic IOLs & Endothelial Considerations" to the FDA Ophthalmic Devices Panel on 8/2/02

- i. Baikoff ZB lens (Domiles SA, Lyon, France, 1987 – first generation)
 - negative 4.5 mm biconcave lens (high myopia), effective optical zone of 4.0 mm
 - 25 degree angulated haptics
 - distance between IOL and crystalline lens = 1.12 mm
 - distance between the IOL edge and endothelium = 1.16 mm
 - High endothelial cell loss secondary to excessive contact between IOL optic edge and endothelium²⁵
 - 16% to 18.8% loss at 1 year (Jimenez-Alfaro, op. cit., 2001)
 - 20% to 28% loss at 2 years (Jimenez-Alfaro, op. cit., 2001)
 - up to 56% loss²⁶
 - 6/16 (37.5%) with morphologic or cell density changes (Saragoussi, op. cit., 1991)
 - “We have stopped doing this surgical procedure”²⁷
 - “Further implantation of this IOL (is) unacceptable” (Saragoussi, op. cit., 1991)
- ii. Baikoff ZB5M lens (1991 – Chiron-Domilens, Chiron Vision, Lyon, France – second generation lens – manufactured until 1997)
 - haptic angulation = 20 degrees
 - optic edge thinned
 - total optic diameter = 5.0 mm; effective optical diameter = 4.0 mm
 - biconcave
 - distance between IOL and crystalline lens = 0.59 mm
 - distance between IOL edge and endothelium = 1.56 mm
 - endothelial cell loss (Jimenez-Alfaro, op. cit., 2001)
 - 4.5% to 5.5% cell loss at 1 year
 - 5.6% to 6.8% cell loss at 2 years
 - 5.5% to 7.5% cell loss at 3 years
 - endothelial cell loss (N=30)²⁸
 - 7.5% at 3 months
 - 10.94% at 6 months
 - 12.33% at 1 year
 - 12.3% at 2 years

²⁵ Jimenez-Alfaro I, Garcia-Feijoo J, Perez-Santonja JJ, Cuina R. Ultrasound biomicroscopy of ZSAL-4 anterior chamber phakic intraocular lens for high myopia. *J Cataract Refract Surg* 2001;27:1567-73.

²⁶ Saragoussi JJ, Cotinat J, Renard G, Savoldelli M, Abenhaim A, Pouliquen Y. Damage to the corneal endothelium by minus power anterior chamber intraocular lenses. *Refract Corneal Surg* 1991;7:282-85.

²⁷ Mimouni F, Colin J, Doffi V, Bonnet P. Damage to the corneal endothelium from anterior chamber intraocular lenses in phakic myopic eyes. *Refract Corneal Surg* 1991;7:277-81.

²⁸ Perez-Santonja JJ, Iradier MT, Sanz-Iglesias L, Serrano JM, Zato MA. Endothelial changes in phakic eyes with anterior chamber intraocular lenses to correct high myopia. *J Cataract Refract Surg* 1996;22:1017-22.

- endothelial cell loss²⁹ (pooled data ZB5M & ZB5MF & ZSAL-4)
 - 3.76% loss at 3 months (N = 263)
 - 5.53% loss at 1 year (N = 251)
 - 6.83% loss at 2 years (N = 216)
 - 7.5% loss at 3 years (N = 157)
 - 7.78% loss at 4 years (N = 49)
 - 8.33% loss at 5 years (N = 41)
 - 8.7% loss at 6 years (N = 33)
 - 9.26% loss at 7 years (N = 33)
 - overall loss approximates normal aging loss following year 2: preop to year one 5.53% loss; year one to two 1.37% loss; year two to three 0.72% loss; year three to four 0.28% loss; year four to five 0.55% loss; year five to six 0.37% loss; year six to seven 0.56% loss.
- iii. Perez-Santonja ZSAL-4 (fourth generation lens) (Morcher GmbH)
 - plano-concave lens; PMMA; Z-shaped haptics; Kelman Multiflex style
 - effective optical zone = 5.0 mm; total optic zone = 5.5 mm
 - haptic angulation = 19 degrees
 - distance from crystalline lens = 0.80 mm
 - distance from central cornea = 2.36 mm
 - distance from IOL edge to peripheral cornea = 1.65 mm
 - distance from iris = 0.35 mm
 - endothelial cell loss (Jimenez-Alfaro, op. cit., 2001)
 - 3.5% at 1 year (n=18)
 - 4.18% at 2 years (n=18)
- iv. Perez-Santonja ZSAL-4/Plus lens (fifth generation) (Morcher GmbH)
 - modifications include larger optic diameter and increased haptic flexibility: effective optical zone 5.3 mm (total optical zone = 5.8 mm)
 - published data?
- v. Nuvita (Bausch & Lomb Surgical, Monrovia, GA – 1997)
 - total optical zone = 5.0 mm; effective optical zone = 4.5 mm
 - single piece PMMA IOL; Z-shaped angle supported haptics
 - Central endothelial cell loss (N= 21 eyes)³⁰

²⁹ Alio JL, de la Hoz F, Perez-Santonja JJ, Ruiz-Moreno JM, Quesada JA. Phakic anterior chamber lenses for the correction of myopia. A 7-year cumulative analysis of complications in 263 cases. *Ophthalmology* 1999;106(3):458-66.

³⁰ Allemann N, Chamon W, Tanaka HM, Mori ES, Campos M, Schor P, Baikoff G. Myopic angle-supported intraocular lenses. Two-year follow-up. *Ophthalmology* 2000;107(8):1549-54.

- 10% loss from preop to 12 month visit
 - 14.3 % loss from preop to 24 month visit
- B) Iris fixation
- i. Worst-Fechner Lens (1989)
 - Endothelial cell loss³¹ (N=62 eyes)
 - no mean cell density analyses provided
 - no morphometric analyses provided
 - 2 eyes with > 50% cell loss
 - mean follow-up 11.9 months
 - Endothelial cell loss (Perez-Santonja, op. cit., 1996) (N = 30)
 - 7.26% loss at 3 months
 - 10.64 % loss at 6 months
 - 13.0% loss at 12 months
 - 17.6% loss at 24 months
 - conclusion: central endothelial cell loss did not stabilize over 2 years
 - ii. Artisan or Iris-Claw lens (Ophtec, Boca Raton, FL) (a.k.a. Worst Iris-Claw Lens)
 - convex-concave profile; PMMA lens
 - optic zone = 5.0 mm
 - - 15.0 D lens in 3.2 mm anterior chamber leaves 1.97 mm from corneal endothelium
 - -20.0 D lens in 3.2 mm anterior chamber leaves 1.86 mm from corneal endothelium
 - Central endothelial cell density (pooled data from 48 Worst-Fechner lens and 63 Worst lens; N = 111)³²
 - 3.85% loss at 6 months (maximum = 30.53% loss) (N = 111)
 - 6.59% loss at 12 months (maximum = 32.41% loss) (N = 109)
 - 9.22% loss at 2 years (maximum = 33.17% loss) (N = 97)
 - 11.68% loss at 3 years (maximum = 34.82% loss) (N= 94)
 - 13.42% loss at 4 years (maximum = 35.81% loss) (N = 88)
 - conclusion: reduction in cell density is progressive → 6.6% preop to one year, 2.63% year one to two, 2.46% year two to three, 1.74% year three to four. Cell loss correlated to increased power of IOL (i.e. thicker) and shallower anterior chamber depth
 - Central % hexagonality (Menezo JL, op. cit., 1998)
 - 64.05% preop

³¹ Fechner PU, Van Der Heijde GL, Worst JGF. The correction of myopia by lens implantation into phakic eyes. *Am J Ophthalmol* 1989;107:659-63.

³² Menezo JL, Cisneros AL, Rodriguez-Salvador V. Endothelial study of iris-claw phakic lens: Four year follow-up. *J Cataract Refract Surg* 1998;24:1039-49.

- 62.57% at 6 months (statistically significant decrease)
 - 62.89% at 12 months
 - 63.58% at 2 years (statistically significant increase)
 - 63.97% at 3 years
 - 63.52% at 4 years
 - Coefficient of variation in cell area (Menezo JL, op. cit., 1998)
 - 0.320 preop
 - 0.354 at 6 months (statistically significant increase)
 - 0.346 at 12 months
 - 0.342 at 2 years (statistically significant decrease)
 - 0.329 at 3 years
 - 0.311 at 4 years
- iii. Normative Data
- 1) Rates of Endothelial Cell Density Loss
- A) Unoperated “normal” eyes – longitudinal studies
- i. 0.3 % cell loss per year (Numa 1993 per Bourne 1994)³³
 - ii. 0.6% cell loss per year (Bourne 1997 per Azar 2001)^{34,35}
 - iii. 0.59% central cell loss per year, 0.45% paracentral cell loss per year, and 0.40% peripheral cell loss per year³⁶
 - “it has been substantiated that the normal decrease in human ECD is about 0.6% per year from age 15 to 85 years.” (Edelhauser 2006)
 - v. 0.75% cell loss per year (Bourne 1996)³⁷
 - *exponential* cell loss rate over a 10.5 year interval in 47 normal subjects with an average age of 53 years +/- 22 years
 - coefficient of variation increased from 0.25 to 0.28
 - percentage of hexagonal cells decreased from 69.2 to 65.2
 - vi. 0.8% cell loss per year (Werblin 1993)³⁸
 - vii. 1.0% cell loss per year (Cheng 1985 per Bourne 1994)
- B) Surgical Procedures
- i. Cataract Surgery

³³ Bourne WM, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. *Ophthalmology* 1994;101(6):1014-22.

³⁴ Azar RG, Holdbrook MJ, Lemp M, Edelhauser HF, KeraVision Study Group. Two-year corneal endothelial cell assessment following INTACS implantation. *J Refract Surg* 2001;17:542-8.

³⁵ Bourne WM, Nelson LF, Hodge DO. Central corneal endothelial cell changes over a ten-year period. *IOVS*. 1997;38:779-782.

³⁶ Edelhauser HF. The balance between corneal transparency and edema. The Proctor Lecture. *IOVS*. 2006 May;47(5):1755-1767.

³⁷ Bourne WM, Nelson LR, Hodge DO. Morphologic changes in human corneal endothelium over a ten-year period. *Investigative Ophthalmology & Visual Science* 1996;37(3):S702.

³⁸ Werblin TP. Long-term endothelial cell loss following phacoemulsification: Model for evaluating endothelial damage after intraocular surgery. *Refract Corneal Surg* 1993;9:29-35.

- after cataract surgery the rapid component of the ECD loss – surgical trauma – becomes negligible after 6 months.³⁹
- After ICCE, the effect of surgical trauma on the endothelium seems to be complete by 3 months (Galini 1979 per Kraff 1980).⁴⁰
- After ICCE (n=4), ECCE (n=5), & ECCE/IOL (n=13) (i.e. large incision surgery), the endothelial cell density stabilized, and the morphometric changes resolved within 3 months in all regions of the cornea.⁴¹ After cataract surgery, endothelial damage and cell loss is greatest in the superior cornea because the incision is placed superiorly and the lens extraction itself is most traumatic to the superior endothelium.
- mean 2.5% ECD loss per year from one to 10 years post cataract surgery in eyes with lens implants, or aphakic status (Bourne 1994)⁴²
 - lens styles: medallion iris suture (n=15), transiridectomy clip (n=27), posterior chamber (n=7), or aphakic (n=15)
 - intracapsular and extracapsular surgery 1976 to 1982
 - Capsulotomy doesn't affect ECD loss
 - About a 40% increase in the mean ECD standard deviation from baseline post cataract surgery with an IOL (n=50)
 - 2 months: + 40.33%
 - 1 year: + 43.44%
 - 5 years: +45.58%
 - 10 years: +30.79%
- 1.1% exponential cell loss rate per year (Numa 1993 per Bourne 1994) for 15 eyes with posterior chamber lenses
- 8.8% ECD loss at one year following uncomplicated phacoemulsification with posterior chamber lenses (Werblin 1993)
- 12.6% ECD loss after ICCE (no IOL) 3 to 6 months postop, 15.2% after phacoemulsification (no IOL) 3 to 6 months postop (Kraff 1980).⁴³

³⁹ Armitage WJ, Dick AD, Bourne WM. Predicting endothelial cell loss and long-term corneal graft survival. IOVS. 2003 Aug;44(8):3326-3331.

⁴⁰ Kraff MC, Sanders DR, Lieberman HL. Specular microscopy in cataract and intraocular lens patients. A report of 564 cases. Arch Ophthalmol. 1980;98:1782-1784.

⁴¹ Schultz RO, Glasser DB, Matsuda M, Yee RW, Edelhauser HF. Response of the corneal endothelium to cataract surgery. Arch Ophthalmol. 1986 Aug;104:1164-1169.

⁴² Bourne WM, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. Ophthalmology. 1994;101(6):1014-1023.

⁴³ Kraff MC, Sanders DR, Lieberman HL. Specular microscopy in cataract and intraocular lens patients. A report of 564 cases. Arch Ophthalmol. 1980;98:1782-1784.

- Central ECD loss 3 months post phacoemulsification cataract surgery ranged from 8.5%, 11.8%, 12.03%, 18.3% in various studies (Beltrame 2002)
 - Surgically induced endothelial damage greatest at the 12 o'clock position than at the center in clear corneal cataract surgery (Beltrame 2002)
 - Morphometric changes (pleomorphism & polymegathism) are transient after phacoemulsification
 - Normalization at one month postop (Beltrame 2002)⁴⁴
 - Normalization at 3 months postop (Kosrirukvongs 1997 & Kiaz-Valle 1998 per Beltrame 2002)
- ii. Penetrating Keratoplasty
- 34% cell loss per year from baseline to 1 year post keratoplasty⁴⁵
 - 7.8% cell loss per year from 3 to 5 years post keratoplasty⁴⁶
 - 4.2% cell loss per year from 5 to 10 years post keratoplasty.⁴⁷
 - 0.2% +/- 5.7% cell loss per year from 10 to 15 years post keratoplasty.⁴⁸
 - 2.6% per year beyond 15 years post keratoplasty (Zacks 1990)⁴⁹
- C) Endothelial “Remodeling” versus Chronic Endothelial Cell Loss
- i. Acute surgical trauma to the cornea can cause several year declines (i.e. up to three years with the Star ICL) in ECD due to endothelial cell migration, but this doesn't necessarily reflect an increased rate of ongoing endothelial cell loss.⁵⁰
- ii. “With chronic cell loss or a stressed endothelium (contact lens use or diabetics), the coefficient of

⁴⁴ Beltrame G, Salvetat, Driussi G, Chizzolini M. Effect of incision size and site on corneal endothelial changes in cataract surgery. *J Cataract Refract Surg.* 2002 Jan;28:118-125.

⁴⁵ Patel SV, Hodge DO, Bourne WM. Corneal endothelium and postoperative outcomes 15 years after penetrating keratoplasty. *Trans Am Ophthalmol Soc.* 2004;102:57-66.

⁴⁶ Bourne WM, Hodge DO, Nelson LR. Corneal endothelium five years after transplantation. *Am J Ophthalmol.* 1994;118:185-196.

⁴⁷ Ing JJ, Ing HH, Nelson LR, Hodge DO, Bourne WM. Ten-year post-operative results of penetrating keratoplasty. *Ophthalmology.* 1998;105:1855-65.

⁴⁸ Patel SV, Hodge DO, Bourne WM. Corneal endothelium and postoperative outcomes 15 years after penetrating keratoplasty. *Trans Am Ophthalmol Soc.* 2004;102:57-66.

⁴⁹ Patel SV, Hodge DO, Bourne WM. Corneal endothelium and postoperative outcomes 15 years after penetrating keratoplasty. *Trans Am Ophthalmol Soc.* 2004;102:57-66.

⁵⁰ Edelhauser HF, Sanders DR, Azar R, Lamielle H, ICL in Treatment of Myopia Study Group. Corneal endothelial assessment after ICL implantation. *J Cataract Refract Surg.* 2004 March;30:576-583.

variation increases over time and there is a decrease in hexagonality.”⁵¹

- N.B. – Implies that morphometric data are required to tell the difference between an increased rate of chronic cell loss versus cellular migration.
- iii. analysis of cell size and shape provides a more sensitive indication of endothelial cell damage than cell density alone.^{52,53} Alterations may indicate an unstable endothelium or low functional reserves, or they may be an early sign of continuing cell loss.
 - One year after ICCE and ACLs, 13 eyes had a significant increase in CV and a significant decrease in the percentage of hexagonal cells when compared with age-matched controls.⁵⁴ This may represent continued insult to the corneal endothelium. Similar morphologic changes in the corneal endothelium have been associated with a low functional reserve and an unstable endothelial monolayer, which may lead to progressive cell loss or corneal decompensation.
 - iv. “If the corneal endothelium is exposed to a continued insult, wound healing will not progress normally. Continued cell loss may occur and morphologic abnormalities will persist.”⁵⁵
- 2) Age Stratified “Normal” Endothelial Cell Density Values
- A) Central Cornea (cells/mm²) (Yee, op. cit., 1985) – specular microscopy *in vivo*
 - i. Age 20 – 29: 2942 +/- 116 (n=11)
 - ii. Age 30 – 39: 2787 +/- 58 (n=6)
 - iii. Age 40 – 49: 2640 +/- 133 (n=6)
 - iv. Age 50 – 59: 2685 +/- 94 (n=7)
 - v. Age 60 – 69: 2711 +/- 121 (n=9)
 - vi. Age 70 – 79: 2630 +/- 60 (n=9)
 - vii. Age 80 – 89: 2316 +/- 154 (n=9)
 - B) Central Cornea (cells/mm²) (Moller-Pedersen 1997)⁵⁶ – pathologic analysis
 - i. Age 21 – 30: 2970 +/- 250 (n=10)
 - ii. Age 31 – 40: 2730 +/- 320 (n=15)
 - iii. Age 41 – 50: 2880 +/-270 (n=13)

⁵¹ Edelhauser HF, Sanders DR, Azar R, Lamielle H, ICL in Treatment of Myopia Study Group. Corneal endothelial assessment after ICL implantation. J Cataract Refract Surg. 2004 March;30:576-583.

⁵² Yee RW, Matsuda M, Schultz RO, Edelhauser HF. Changes in the normal corneal endothelial cellular pattern as a function of age. Current Eye Research 1985;4(6):671-8.

⁵³ Glasser DB, Matsuda M, Gager WE, Edelhauser HF. Corneal endothelial morphology after anterior chamber lens implantation. Arch Ophthalmol. 1985 Sept;103:1347-1349.

⁵⁴ Glasser DB, Matsuda M, Gager WE, Edelhauser HF. Corneal endothelial morphology after anterior chamber lens implantation. Arch Ophthalmol. 1985 Sept;103:1347-1349.

⁵⁵ Schultz RO, Glasser DB, Matsuda M, Yee RW, Edelhauser HF. Response of the corneal endothelium to cataract surgery. Arch Ophthalmol. 1986 Aug;104:1164-1169.

⁵⁶ Moller-Pedersen T. A comparative study of human corneal keratocyte and endothelial cell density during aging. Cornea 1997;16(3):333-8.

- iv. Age 51 – 60: 2800 +/- 450 (n=11)
 - v. Age 61 – 70: 2690 +/- 220 (n=7)
 - vi. Age 71 – 80: 2400 +/- 500 (n= 8)
 - vii. Age 81 – 90: 2370 +/- 690 (n=7)
- C) Peripheral Cornea⁵⁷
- i. 5.8% increase in cell density in paracentral region (2.7 mm from center)
 - ii. 9.8% increase in cell density in peripheral cornea (4.7 mm from center)
 - iii. Superior peripheral ECD was increased compared with the other three peripheral quadrants (nasal 7.8%, inferior 6.7%, temporal 9.6%) and was 15.9% higher than central ECD
 - iv. % hexagonals = 65% +/- 5%
 - v. coefficient of variation = 0.31 +/- 0.03
- D) Morphometric Data
- i. Analysis of cell shape and pattern is a more sensitive indicator of endothelial damage than cell density alone.^{58,59,60,61,62}
 - ii. Percent hexagonality (pleomorphism)
 - iii. Coefficient of variation (polymegethism)
- E) The mean ECD in a Japanese population was significantly higher than that of an age-matched U.S. cohort.⁶³
- F) Other states that alter corneal endothelial cell density⁶⁴
- i. Glaucoma: after age 40, there is a significant decrease in ECD compared to a normal population
 - ii. Contact lens wear: increased pleomorphism and increased coefficient of variation⁶⁵
 - iii. Diabetics: type I diabetics have higher coefficient of variation, decrease in percentage of hexagonal cells, and decrease in ECD in 4th and 5th decades of life. Type II diabetics have higher C.V. and decreased hexagonals without ECD difference.

⁵⁷ Amann J, Holley GP, Lee SB, Edelhauser HF. Increased endothelial cell density in the paracentral and peripheral regions of the human cornea. *American Journal of Ophthalmology*. 2003 May;135(5):584-590.

⁵⁸ Matsuda M, Suda T, Manabe R. Serial alterations in endothelial shape and pattern after intraocular surgery. *Am J Ophthalmol*. 1984;98:313-319.

⁵⁹ Werblin TP. Long-term endothelial cell loss following phacoemulsification: model for evaluating endothelial damage after intraocular surgery. *Refract Corneal Surg*. 1993;9:29-35.

⁶⁰ Mishima S. Clinical investigations on the corneal endothelium. *Am J Ophthalmol*. 1982;93:1-29.

⁶¹ Matsuda M, Miyake K, Inaba M. Long-term corneal endothelial changes after intraocular lens implantation. *Am J Ophthalmol*. 1988;105:248-252.

⁶² Beltrame G, Salvetat, Driussi G, Chizzolini M. Effect of incision size and site on corneal endothelial changes in cataract surgery. *J Cataract Refract Surg*. 2002 Jan;28:118-125.

⁶³ Matsuda M, Yee RW, Edelhauser HF. Comparison of the corneal endothelium in an American and a Japanese population. *Arch Ophthalmol*. 1985;103:68-70.

⁶⁴ Edelhauser HF. The resiliency of the corneal endothelium to refractive and intraocular surgery. *Cornea*. 2000;19(3):263-273.

⁶⁵ McCarey, B. Clinical Specular Microscopy. *Corneal Endothelial Cell Morphology*. Presentation to the FDA Ophthalmic Devices Panel, 2 AUG 02.

- iv. Unilateral ptosis with unilateral increased coefficient of variation (i.e. potential hypoxic stress).⁶⁶
- 3) Life Expectancy Data⁶⁷
 - A) RP-2000 Mortality Table⁶⁸
 - i. Life expectancy for a 21 year-old male is 58 future years (i.e. age of death of 79)
 - ii. Life expectancy for a 21 year-old female is 62 future years (i.e. age of death of 83)
 - B) United States Life Tables 2002⁶⁹
 - i. Life expectancy for a person 60 years old is 22 future years (i.e. age of death 82).⁷⁰
 - ii. Life expectancy for a person 90 years old is 5 future years (i.e. age of death 95 years old).⁷¹
- 4) “Minimum Acceptable” Corneal Endothelial Cell Density Value
 - A) “Minimal acceptable” = 1500 cells/mm² (McCarey, FDA presentation of 2 AUG 02)
 - i. A 1500 endothelial cell density may allow a future intraocular surgical procedure without causing imminent corneal edema
 - B) “Potential corneal edema” = 800 cells/mm² (McCarey, FDA presentation of 2 AUG 02)
 - i. An 800 endothelial cell density will not allow a future intraocular surgical procedure without causing corneal edema
 - C) “Imminent corneal decompensation”
 - i. 500 cells/mm² (Bates 1986 per Bourne 1994)^{72,73}
 - ii. chronic corneal endothelial cell decompensation typically occurs when the central ECD declines to 700 to 400 cells/mm².^{74,75}

⁶⁶ McCarey, B. Clinical Specular Microscopy. Corneal Endothelial Cell Morphology. Presentation to the FDA Ophthalmic Devices Panel, 2 AUG 02.

⁶⁷ N.B. – life expectancy will differ slightly depending upon the entry age

⁶⁸ N.B. – The RP-2000 mortality table is based on a study of the mortality experience of pension plans conducted by the Society of Actuaries. This was in response to pension legislation (Retirement Protection Act of 1994) that directed the Secretary of Treasury to promulgate the use of updated mortality tables for various pension calculation purposes.

⁶⁹ Arias E. United States Life Tables, 2002. National Vital Statistics Reports, Vol. 53, No. 6. Hyattsville, Maryland: National Center for Health Statistics, 2004.

⁷⁰ Lane SS, Kuppermann BD. The implantable miniature telescope for macular degeneration. Current Opinion in Ophthalmology. 2006;17:94-98.

⁷¹ Lane SS, Kuppermann BD. The implantable miniature telescope for macular degeneration. Current Opinion in Ophthalmology. 2006;17:94-98.

⁷² Bates AK, Cheng H, Hiorns RW. Pseudophakic bullous keratopathy: relationship with endothelial cell density and use of a predictive cell loss model. A preliminary report. Curr eye Res. 1986;5:363-6.

⁷³ Bourne WM, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. Ophthalmology. 1994;101(6):1014-1023.

⁷⁴ Edelhauser HF. The balance between corneal transparency and edema. The Proctor Lecture. IOVS. 2006 May;47(5):1755-1767.

⁷⁵ Mishima S. Clinical investigations on the corneal endothelium. XXXVIII Edward Jackson Memorial Lecture. Am J Ophthalmol. 1982;93:1-29.

- iv. Conclusions / Recommendations for studies of the corneal endothelium based upon experience with phakic IOLs
- 1) General Issues For All Phakic IOL Studies
 - A) Endothelial cell density measurements mandatory
 - i. central count
 - ii. peripheral count
 - especially if anterior chamber lens – want cell density in region near IOL edge, or in area of minimum distance between IOL and endothelium
 - B) Morphometric analyses mandatory
 - i. pleomorphism (i.e. variation in cell shape -- % hexagons)
 - ii. polymegethism (coefficient of variation of cell area)
 - iii. conclusion: analysis of cell size and shape provides a more sensitive indication of endothelial cell damage than cell density alone.⁷⁶ Alterations may indicate an unstable endothelium or low functional reserves, or they may be an early sign of continuing cell loss.
 - C) Corneal pachymetry (i.e. corneal functional analysis) suggested
 - D) Duration of Study
 - i. 3 years probably represents sufficient follow-up interval for corneal endothelial studies of phakic IOLs, *especially for posterior chamber phakic IOLs*, although some data indicate that it may take 4 years to see morphometric data return to baseline levels and ensure stability (e.g. Menezo, op. cit., 1998; anterior chamber iris-claw lens)
 - E) Recommendation⁷⁷
 - i. I favor 4 year endothelial study duration for higher risk factors:
 - angle supported IOL > iris fixation IOL > posterior chamber IOL (i.e. closer to the endothelium = greater concern)
 - thicker anterior chamber IOLs > thinner anterior chamber IOLs (i.e. thicker lens closer to the corneal endothelium)
 - shallower anterior chamber depth > deeper anterior chamber depth (i.e. IOL closer to the endothelium with shallower anterior chamber)
 - chronic anterior chamber inflammation > quiet anterior chamber
 - ii. Phakic IOL study duration recommended by Drews (1991)⁷⁸ was 5 years

⁷⁶ Yee RW, Matsuda M, Schultz RO, Edelhauser HF. Changes in the normal corneal endothelial cellular pattern as a function of age. *Current Eye Research* 1985;4(6):671-8.

⁷⁷ N.B.—tacit assumption that manufacturers will use knowledge gained from peer-reviewed literature, and not repeat the same phakic IOL design errors as in the past (e.g. Baikoff ZB lens)

⁷⁸ Drews RC. Risk benefit analysis of anterior chamber intraocular lenses for the correction of myopia in phakic patients. *Eur J Implant Ref Surg* 1991;3:171-94.

- 2) Anterior Chamber Phakic IOLs
 - A) Optic-Endothelium distance plays an important role in potential endothelial damage
 - i. Recommendations for future studies
 - high resolution ultrasound biomicroscopy *mandatory* to disclose optic-endothelial distance (central and peripheral) (Jimenez-Alfaro, op. cit., 2001), and distances between other eye structures & IOL
 - peripheral endothelial cell density, *and morphometric*, measurements mandatory in region of IOL optic edge, in addition to central endothelial cell analysis (Saragoussi, op. cit., 1991)
 - examination limited to central cornea may fail to detect significant endothelial injury (Saragoussi, op. cit., 1991)⁷⁹
 - specular images can show significant morphologic changes over the edge of the IOL in the absence of central cell density changes (Saragoussi, op. cit., 1991)
 - preop history of eye rubbing a contraindication for entry into study (e.g. allergic eye disease, etc.)
 - depending upon IOL design, the manufacturer must specify a minimum anterior chamber depth that contraindicates IOL insertion
 - 3) Chronic inflammation a known factor in ongoing endothelial damage^{80,81}
 - A) Some studies disclose chronic anterior segment inflammation after phakic IOL implantation using a laser flare-cell meter (Worst-Fechner iris-fixated & ZB5M angle-supported lenses) (Perez-Santonja 2000)
 - B) Recommendations for future studies
 - i. laser flare fluorophotometry may be a useful test to evaluate chronic anterior chamber inflammation (i.e. breakdown of blood aqueous barrier)
 - ii. consider iris fluorescein angiography in a subset to rule out iris leakage (especially in iris fixated lenses)
- b. Background Information on the Implantable Miniature Telescope
- i. Corneal Endothelium – IMT distance by Anterior Segment Ultrasound Biomicroscopy in two patients with the IMT⁸²
 - 1) Patient One: IMT implantation for age related macular degeneration

⁷⁹ Saragoussi JJ, Cotinat J, Renard G, Savoldelli M, Abenhaim A, Pouliquen Y. Damage to the corneal endothelium by minus power anterior chamber intraocular lenses. *Refractive and Corneal Surgery*. 1991 July/Aug;7:282-285.

⁸⁰ Perez-Santonja JJ, Alio JL, Jimenez-Alfaro IJ, Zato MA. Surgical correction of severe myopia with an angle-supported phakic intraocular lens. *J Cataract Refract Surg* 2000;26:1288-1302.

⁸¹ Edelhauser HF, Sanders DR, Azar R, Lamielle H, ICL in treatment of myopia study group. Corneal endothelial assessment after ICL implantation. *J Cataract Refract Surg*. 2004 March;30:576-583.

⁸² Garcia-Feijoo J, Duran-Poveda S, Cuina-Sardina R, Mendez-Hernandez C, Garcia-Sanchez J, Gomez de Liano MZ. Ultrasound biomicroscopy of an implantable miniaturized telescope. *Arch Ophthalmol* 2001 Oct;119(10):1544-6.

- A) preoperative anterior chamber depth = 3.22 mm
- B) one haptic in the bag, one in the sulcus
 - i. localized angle closure in the region of the sulcus placed haptic
 - ii. 1.2 mm distance between optic edge and corneal endothelium in the meridian of the sulcus placed haptic
 - iii. 1.4 mm distance between the optic edge and corneal endothelium in the meridian of the bag-fixated haptic
 - iv. 1.5 mm distance between the central lens surface and the corneal endothelium
 - v. 1.1 mm was the minimum distance found between the lens optic and the corneal endothelium
- 2) Patient Two: IMT implantation for age related macular degeneration
 - A) preoperative anterior chamber depth = 3.47 mm
 - B) one haptic in the bag, one in the sulcus
 - i. partial localized angle closure in the region of the sulcus placed haptic
 - ii. 0.967 mm distance between the optic edge and the corneal endothelium in the region of the sulcus placed haptic
 - iii. 1.6 mm distance between the central lens surface and the corneal endothelium
 - iv. slight tilt of the intraocular lens due to misplaced haptic
- 3) “. . .the small distance between the IMT and the cornea could affect the endothelium in the long term . . . one of the most important preoperative factors should be the depth of the anterior chamber. Therefore, because of the IMT morphologic features, we not only should select patients who present a wide anterior chamber but also must make sure that the implantation of the lens is intracapsular to try to increase the distance between the IMT and the endothelium as much as possible. For these reasons, and regardless of their possible functional effectiveness, these implantations present significant surgical challenges and risks, even in the hands of an experienced surgeon.”
- ii. Corneal Endothelium – IMT (3.0X) Distance by Slit-Lamp Biomicroscopy⁸³
 - 1) slit-lamp biomicroscopy estimate: the mean value = 1.71 mm +/- 0.2 mm with the range as low as 1.0 mm – central measurement or near optic edge not specified in the study.
 - 2) the IMT device didn’t move at 1, 6, & 12 month intervals – no significant differences in the slit-lamp measurements with time.
 - 3) 3/40 IMT devices not in the bag (i.e. closer to the endothelium)
- iii. Mean ECD loss in 10 of 40 eyes over 1 year⁸⁴
 - 1) 3 months = 14.5% loss; 6 months = 30.8% loss; 12 months = 34.5% loss

⁸³ Alio JL, Mulet EM, Ruiz-Moreno JM, Sanchez MJ, Galal A. Intraocular telescopic lens evaluation in patients with age-related macular degeneration. J Cataract Refract Surg 2004;30:1177-1189.

⁸⁴ Alio JL, Mulet EM, Ruiz-Moreno JM, Sanchez MJ, Galal A. Intraocular telescopic lens evaluation in patients with age-related macular degeneration. J Cataract Refract Surg 2004;30:1177-1189.

- iv. Clinical Examination Limitations after IMT Implantation
 - 1) Argon Laser Photocoagulation
 - i. Not possible to carry out effective argon laser treatment of the retina through the IMTs optic⁸⁵ (rabbits). Only a small area of the retina was visible when the retina was viewed through the telescope, and no retinal landmarks could be seen. Neither posterior capsulotomy nor peripheral retinal photocoagulation could be performed when adhesions between the pupil margin and IMT were present.
 - ii. very small image size in patients. 300 to 400 mW of argon energy with exposure of 0.1 to 0.2 seconds did not damage the IMT in one patient. “Challenging” although treatment was completed.⁸⁶
 - 2) YAG capsulotomy
 - i. (around the optic) required 100 to 138 bursts, and could crack the PMMA carrier plate, haptics, or the cap (rabbits)⁸⁷
 - ii. the laser beam should be directed through the clear part of the haptic and not the glass optic of the IMT.⁸⁸
 - 3) Retinal Examination
 - i. the implanted telescope did not permit detailed fundus examination – AMD evaluation and CME evaluation difficult⁸⁹
 - ii. poor magnification to view microscopic changes in the fovea (i.e. CME diagnosis or progression of AMD).⁹⁰
 - iii. Fluorescein angiography is “burdensome” due to the small image and the inherent glare of the telescope tube.⁹¹
- v. Chronic inflammation is a known factor in endothelial decompensation⁹²
 - 1) Phase I IMT trial reports late intraocular inflammation observed 1 month or more postoperatively in 6/14 eyes(43%) consisting of anterior chamber cells, fibrin, conjunctival injection, iritis, and anterior uveitis. There were several reports of inflammatory deposits on the IMT as well as posterior synechiae.⁹³

⁸⁵ Rosner M, Ben-Simon G, Sachs. Feasibility and safety of laser treatments in eyes with an intraocular implantable miniature telescope. *J Cataract Refract Surg.* 2003 May;29:1005-1010.

⁸⁶ Garfinkel RA, Berinstein DM, Frantz R. Treatment of choroidal neovascularization through the implantable miniature telescope. *Am J Ophthalmol.* 2006;141(4):766-767.

⁸⁷ Rosner M, Ben-Simon G, Sachs. Feasibility and safety of laser treatments in eyes with an intraocular implantable miniature telescope. *J Cataract Refract Surg.* 2003 May;29:1005-1010.

⁸⁸ Alio JL, Mulet EM, Ruiz-Moreno JM, Sanchez MJ, Galal A. Intraocular telescopic lens evaluation in patients with age-related macular degeneration. *J Cataract Refract Surg.* 2004;30:1177-1189.

⁸⁹ Alio JL, Mulet EM, Ruiz-Moreno JM, Sanchez MJ, Galal A. Intraocular telescopic lens evaluation in patients with age-related macular degeneration. *J Cataract Refract Surg.* 2004;30:1177-1189.

⁹⁰ Kaskaloglu M, Uretmen O, Yagci A. Medium-term results of implantable miniaturized telescopes in eyes with age-related macular degeneration. *J Cataract Refract Surg.* 2001;27:1751-1755.

⁹¹ Garfinkel RA, Berinstein DM, Frantz R. Treatment of choroidal neovascularization through the implantable miniature telescope. *Am J Ophthalmol.* 2006;141(4):766-767.

⁹² Perez-Santonja JJ, Alio JL, Jimenez-Alfaro IJ, Zato MA. Surgical correction of severe myopia with an angle-supported phakic intraocular lens. *J Cataract Refract Surg.* 2000;26:1288-1302.

⁹³ Lane SS, Kuppermann BD, Fine IH, Hamill MB, Gordon JF, Chuck RS, Hoffman RS, Packer M, Koch DD. A prospective multicenter clinical trial to evaluate the safety and effectiveness of the implantable miniature telescope. *Am J Ophthalmol.* 2004;137(6):993-1001.

- 2) Following implantation of the IMT, the device requires higher dose steroids than conventional cataract surgery to include routine intraoperative corticosteroid injections along with intensive topical steroids postop.⁹⁴
- c. IMT Endothelial Cell Data

TABLE A28
ENDOTHELIAL CELL DENSITY (MEAN, SD)⁹⁵
24-MONTH CONSISTENT COHORT OF EYES IMPLANTED WITH IMT

ECD	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	130	130	130	130	130	130	130
Mean	2499.73	1998.44	1929.71	1878.74	1832.09	1845.62	1789.71
Standard Deviation	354.39	562.04	571.77	568.47	579.83	604.28	601.95
Median	2506.8	2026.3	2024.2	1953.3	1917.2	1943.2	1873.3
Range	1695.0, 3356.0	492.3, 2907.3	431.0, 2935.7	309.0, 2931.3	310.7, 2786.7	434.0, 2825.7	385.7, 2930.0
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥3000	7 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2500 to <3000	59 (45.4%)	29 (22.3%)	22 (16.9%)	17 (13.1%)	18 (13.8%)	18 (13.8%)	15 (11.5%)
2000 to <2500	52 (40.0%)	38 (29.2%)	45 (34.6%)	45 (34.6%)	39 (30.0%)	44 (33.8%)	39 (30.0%)
1500 to <2000	12 (9.2%)	41 (31.5%)	36 (27.7%)	40 (30.8%)	43 (33.1%)	32 (24.6%)	42 (32.3%)
1000 to <1500	0 (0.0%)	12 (9.2%)	15 (11.5%)	16 (12.3%)	12 (9.2%)	21 (16.2%)	18 (13.8%)
<1000	0 (0.0%)	10 (7.7%)	12 (9.2%)	12 (9.2%)	18 (13.8%)	15 (11.5%)	16 (12.3%)
95% CI for % of eyes with ECD<1000	0.0%, 2.8%	3.8%, 13.7%	4.9%, 15.6%	4.9%, 15.6%	8.4%, 21.0%	6.6%, 18.3%	7.2%, 19.2%

N = number of successful IMT implanted eyes with ECD at all visits.

% = $n \div N \times 100$

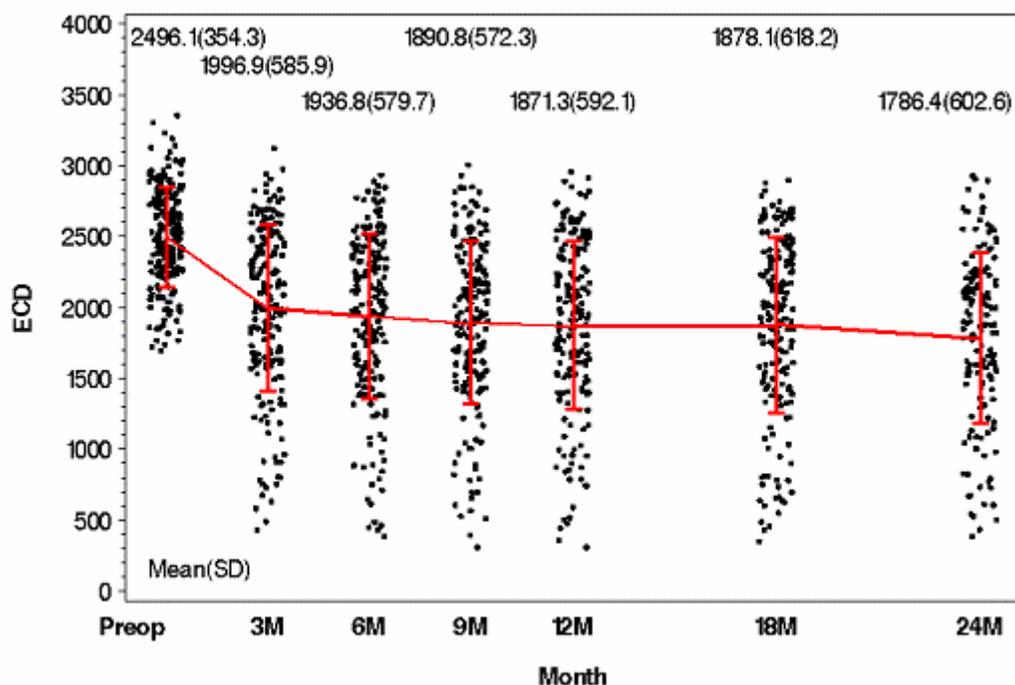
95% CI was calculated based on Clopper Pearson method.

- i. Endothelial cell count drops from 2,500 (preop) to 1,832 at one year (i.e. loss of 668 cells) and 1,790 at 2 years (i.e. loss of 710 cells).
- ii. The spread of the data (i.e. the standard deviation) increased from 354 preop to approximately 600 – almost doubles.
- iii. 18 eyes (14%) at the one year interval with an endothelial cell count < 1000 (i.e. imminent clinically significant corneal edema)

⁹⁴ Lane SS, Kuppermann BD, Fine IH, Hamill MB, Gordon JF, Chuck RS, Hoffman RS, Packer M, Koch DD. A prospective multicenter clinical trial to evaluate the safety and effectiveness of the implantable miniature telescope. *Am J Ophthalmol.* 2004;137(6):993-1001.

⁹⁵ Volume 1, page 243

FIGURE 11: ENDOTHELIAL CELL DENSITY IN ALL EYES IMPLANTED WITH IMT⁹⁶



- iv. The spread of the data (i.e. the standard deviation) noticeably increases after the procedure

Percentage Change in ECD, SD, & Median from Baseline Using Table 28 Values:

	3 months	6 months	9 months	12 months	18 months	24 months
Mean	- 20.05%	- 22.80%	- 24.84%	- 26.71%	- 26.17%	- 28.40%
S.D.	+ 58.59%	+ 61.34%	+ 60.41%	+ 63.61%	+ 70.51%	+ 69.86%
Median	- 19.17%	- 19.25%	- 22.08%	- 23.52%	- 22.48%	- 25.27%

- v. Early Endothelial Loss
 - 1) Mean 20% loss of endothelial cell density at 3 months (i.e. most of the cell loss is early) – probable surgical insult.
- vi. Ongoing rate of decline after the 3 month interval
 - 1) 20% mean loss at 3 month interval increases to 28% mean loss at 24 month interval.
 - 2) FDA states that annual endothelial cell loss using 3 – 24 month data is 5.4%.⁹⁷
 - 3) The annual endothelial cell loss is 5.97% using 3 – 24 month endothelial data from Table 28 (130 eye consistent cohort) when using Sponsor’s formula⁹⁸ to calculate the annual percentage change in ECD between intervals.

⁹⁶ Volume 1, page 243

⁹⁷ FDA Executive Summary, page 28

⁹⁸ Formula to calculate the annual percentage change in ECD based upon a visit period is from Table 38 (Volume 1 page 253): $(\text{later postop ECD} - \text{previous postop ECD}) \div \text{previous postop ECD} \times 100 \div \text{number of months} \times 12$

- 4) The standard deviation of the ECD increases by 70% at the 24 month interval compared to the baseline preoperative ECD standard deviation (i.e. larger spread of the data).
- vii. FDA model for ECD loss over time
 - 1) FDA model using all ECD data:⁹⁹ (1) baseline to 3 months = -20.65%; and (2) annual loss from 3 months to 24 months = - 6.02% per year.
 - 2) FDA model using all ECD data: operated eyes lose -9.83 cells per month while fellow eyes lose -3.03 cells per month – about a 3.25 fold increased rate of loss from 3 to 24 months comparing IMT eyes to all fellow eyes (phakic & pseudophakic).
 - 3) FDA model to determine the percentage of subjects with predicted ECD \leq 1000 at the end of year 2, 3, & 4: 11.1% (24/216) at year 2;¹⁰⁰ 17.6% (38/216) at year 3; and 22.7% (49/216) at year 4 – about 5.8% more eyes per year.

Table B: Predicted Probability of ECD <1000 cells/mm² Mixed Effect 3-Piece Piecewise Regression Model with Break Points at 3 and 9 Months¹⁰¹

Baseline ECD	ACD			
	2.5	3.0	3.5	4.0
Month 3				
2500	0.010	0.006	0.003	0.001
2000	0.125	0.084	0.055	0.034
1600	0.413	0.328	0.251	0.185
2 Years (Month 24)				
2500	0.051	0.033	0.021	0.013
2000	0.269	0.208	0.156	0.114
1600	0.579	0.501	0.423	0.348
3 Years (Month 36)				
2500	0.093	0.068	0.048	0.033
2000	0.337	0.276	0.221	0.173
1600	0.618	0.550	0.481	0.413
4 Years (Month 48)				
2500	0.149	0.116	0.089	0.067
2000	0.398	0.341	0.288	0.238
1600	0.644	0.587	0.527	0.467

⁹⁹ FDA Executive Summary, page 32.

¹⁰⁰ N.B. – the actual figure in the study for patients with ECD \leq 1,000 at 24 months was 18/144 or 12.5% (Table 27, Volume 1, page 242), a close match to the predicted value from the FDA model

¹⁰¹ Sponsor's Amendment 5 dated June 23, 2006.

- viii. Probability of ECD < 1,000 with Sponsor's Model (table above): Worse with Shallower Anterior Chamber Depth
- 1) Two years
 - A) If enter with 1,600 ECD, 35% to 58% will have final ECD < 1000 @ 2 years following the procedure
 - B) If enter with 2,000 ECD, 11% to 27% will have final ECD < 1000 @ 2 years following the procedure
 - C) If enter with 2,500 ECD, 1% to 5% will have final ECD < 1000 @ 2 years following the procedure
 - 2) Three years
 - A) If enter with 1,600 ECD, 41% to 62% will have final ECD < 1000 @ 3 years following the procedure
 - B) If enter with 2,000 ECD, 17% to 34% will have final ECD < 1000 @ 3 years following the procedure
 - C) If enter with 2,500 ECD, 3% to 9% will have final ECD < 1000 @ 3 years following the procedure
 - 3) Four years
 - A) If enter with 1,600 ECD, 47% to 64% will have final ECD < 1000 @ 4 years following the procedure
 - B) If enter with 2,000 ECD, 24% to 40% will have final ECD < 1000 @ 4 years following the procedure
 - C) If enter with 2,500 ECD, 7% to 15% will have final ECD < 1000 @ 4 years following the procedure
- ix. Sponsor's model for ECD loss over time
- 1) statistically significant difference between IMT implanted eyes and phakic fellow eyes for 3 to 24 month interval and 6 to 24 month interval. Phakic fellow eyes lost about 1.06% per year.
 - 2) ECD loss rates are all significantly different than zero ($p < 0.001$) from baseline to 3 months, 3 months to 9 months, and 9 months to 24 months.¹⁰²
 - 3) no statistically significant difference between IMT implanted eyes and pseudophakic eyes, but only about 30 pseudophakic eyes. Pseudophakic fellow eyes lost about 2.44% per year.
 - 4) If surgeon performed less than 3 surgical cases, more ECD loss with anterior chamber depth < 3.0 mm
- x. Other Sponsor Factors Related to Endothelial Cell Density Loss in IMT Study
- 1) increased corneal edema on postop day one
 - 2) larger incision sizes ≥ 12.0 mm
 - 3) For all time intervals, shallower anterior chamber depth ≤ 3.0 mm has more ECD loss than > 3.00 mm to 3.50 mm group, and > 3.0 mm to 3.50 mm anterior chamber depth group has more ECD loss than > 3.50 mm anterior chamber depth.¹⁰³
 - 4) corneal subspecialists had a statistically lower ECD change from baseline to 3 months.
- xi. Anterior segment inflammation with the IMT @ 18 months following implantation
- 1) "Standard" Anti-Inflammatory Regimen High: sub-tenon's steroid injection at time of surgery + Voltaren + topical prednisolone acetate

¹⁰² FDA Executive Summary – Addendum: FDA Review of Sponsor Amendments 4 & 5.

¹⁰³ FDA Executive Summary, page 21

tapering over 3 months starting at every 2 hours for 2 weeks + homatropine for 4 to 6 weeks¹⁰⁴

- 2) Anterior chamber inflammation = 1.7% (3/180)
- 3) Inflammatory deposits on IMT = 13.3% (24/180)
- 4) Inflammatory membrane = 0.6% (1/180)
- 5) Iritis = 2.2% (4/180)
- 6) Pigment deposits on IMT = 7.2% (13/180)

d. **Comment**

Proximity to the Corneal Endothelium

Purely from a corneal endothelial proximity standpoint, the IMT device is analogous to an angle-supported phakic IOL.

Published data regarding phakic IOLs suggest that an optic-endothelial distance of 1.16 mm leads to an unacceptable rate of endothelial cell loss due to excessive contact between the IOL optic edge and endothelium. In contradistinction, published reports suggest that a central IOL-endothelial distance of 2.36 mm and a peripheral IOL-endothelial distance of 1.56 mm to 1.65 mm may be acceptable, albeit there is a paucity of data in this regard. In general, the greater the distance from the endothelium, the better.

Much to my surprise, the PMA materials do not contain any data regarding the IMT-endothelial distance following implantation – a critical factor known to be a risk factor for endothelial cell loss. I couldn't locate either slit-lamp estimates of the IMT-endothelial distance – central and peripheral – or ultrasound biomicroscopic measurements of the IMT-endothelial distance in a representative sample of eyes stratified across the various anterior chamber depths. The lack of these particular data in the PMA is disturbing and represents a deficiency for this study.

Published ultrasound biomicroscopic data on two IMT implanted eyes – anterior chamber depths of 3.22 mm and 3.47 mm – disclosed peripheral IMT-endothelial distances as small as 0.967 mm in one eye and 1.1 mm in the other eye, albeit these small distances were likely due to a sulcus-fixated haptic in each eye which moved the implant anteriorly in dangerous proximity of the corneal endothelium.¹⁰⁵ Central IMT-endothelial distances for these two eyes were 1.5 mm to 1.6 mm. At least for these two eyes, the IMT-endothelial distances are unacceptable and will likely to lead to progressive endothelial cell loss, particularly for patients who rub their eyes. The fact that an experienced surgeon couldn't properly bag fixate both haptics is concerning – perhaps the haptics are excessively stiff by design in order to properly support the increased mass of this device in the eye. A different study of slit-lamp estimates for 40 IMT-implanted eyes disclosed a mean IMT-endothelial distance of 1.71 mm +/- 0.2 mm with a minimum value of 1.0 mm – central or peripheral distance not specified. Regrettably, the measurements were not stratified by preoperative anterior chamber depth, nor by axial length. Based

¹⁰⁴ Sponsor's Volume 1, page 165, Section 7.4 Postoperative Treatment Regimen

¹⁰⁵ Garcia-Feijoo J, Duran-Poveda S, Cuina-Sardina R, Mendez-Hernandez C, Garcia-Sanchez J, Gomez de Liano MZ. Ultrasound biomicroscopy of an implantable miniaturized telescope. Arch Ophthalmol 2001 Oct;119(10):1544-6.

upon this particular study, the IMT-endothelial distance is barely sufficient, and there may be some cases of dangerous proximity of the IMT optic to the corneal endothelium.

Ideally, the Sponsor should supply additional data to the FDA regarding the IMT-endothelial distance across representative anterior chamber depth groups – central and peripheral measurements – especially since the endothelial cell density loss appears excessive and further justification for safety appears prudent. Let’s not repeat what has already been learned with the first generation Baikoff ZB lens – it was too close to the corneal endothelium and led to an unacceptable rate of cell loss.

FDA Endothelial Cell Loss Model versus Sponsor Endothelial Cell Loss Model

The FDA model for ECD loss in IMT-implanted eyes is a two slope linear model (i.e. from baseline to 3 months and from 3 to 24 months) with a 20.65% ECD loss by month 3 and a 6.02% annual ECD loss thereafter. From a clinical standpoint, the choice of a break-point at 3 months is in general agreement with published literature regarding ECD loss after large incision cataract surgery (i.e. ICCE & ECCE), albeit one article noted that the rapid component of the ECD loss – surgical trauma – becomes negligible after a 6 month time period.¹⁰⁶ Of note, the IMT procedure utilized a large incision analogous to ICCE or ECCE procedures. Prior studies of ICCE or ECCE disclose that the effect of acute surgical trauma on the endothelium seems to be complete by 3 months with return of morphometric endothelial parameters (e.g. coefficient of variation and percent hexagonals) to baseline status following the three month interval.^{107,108} Hence, the FDA’s choice of an initial breakpoint time at 3 months is consistent with published clinical literature, and Sponsor agrees that the FDA model is “reasonable.”¹⁰⁹

The Sponsor’s model for ECD loss in IMT-implanted eyes is a three slope model (i.e. from baseline to 3 months, from 3 months to 9 months, and from 9 months to 24 months). According to FDA, the rationale or justification for this three piecewise linear model has not been provided by the Sponsor, and the three slope model has numerous unresolved problems (e.g. actual visit time vs. nominal visit time, among others).¹¹⁰ I’m currently unaware of published literature regarding ECD loss in large incision cataract surgery that analyzes ECD loss with a three slope model analogous to Sponsor’s model. In essence, for IMT eyes, the FDA model predicts a long-term chronic monthly endothelial loss of 9.83 cells¹¹¹ while the Sponsor model predicts a long-term chronic monthly endothelial loss of approximately 6 cells¹¹² (i.e. a 39% decreased rate of loss).

¹⁰⁶ Armitage WJ, Dick AD, Bourne WM. Predicting endothelial cell loss and long-term corneal graft survival. IOVS. 2003 Aug;(44(8):3326-3331.

¹⁰⁷ Kraff MC, Sanders DR, Lieberman HL. Specular microscopy in cataract and intraocular lens patients. A report of 564 cases. Arch Ophthalmol. 1980;98:1782-1784.

¹⁰⁸ Schultz RO, Glasser DB, Matsuda M, Yee RW, Edelhauser HF. Response of the corneal endothelium to cataract surgery. Arch Ophthalmol. 1986 Aug;104:1164-1169.

¹⁰⁹ Volume 9, Amendment 4, June 5, 2006, page 14.

¹¹⁰ FDA Executive Summary – Addendum to amendments 4 & 5 provided June 30, 2006, pages 2-3.

¹¹¹ FDA Executive Summary, page 32

¹¹² Amendment 5, page 1, June 23, 2006.

Regarding the initial breakpoint time, it stands to reason that Sponsor ran many ECD loss models using a multitude of breakpoints (e.g. 6 months, 9 months, others).¹¹³ With all due respect to Sponsor, common sense dictates that Sponsor would present the model most favorable to their position (i.e. the lowest chronic endothelial cell loss rate). I favor a different approach: utilize morphometric corneal endothelial data (e.g. coefficient of variation and percent hexagonals) to justify the selection of a breakpoint in Sponsor's model. Regrettably, I haven't been able to find morphometric endothelial data for the IMT study – a critical piece of safety information – in the PMA materials. In the absence of these morphometric endothelial data, I'm at a loss to justify Sponsor's model from a clinical perspective. Apparently, the FDA has no compelling statistical reason to independently support Sponsor's model.¹¹⁴

Endothelial Remodeling versus Chronic Endothelial Cell Density Loss

Regarding the ECD declines following IMT implantation, the Sponsor spoke with Henry Edelhauser, PhD at Emory University who suggested that “redistribution of cells in the corneal endothelium can continue for a number of months following the initial surgical insult.”¹¹⁵ In general, I agree with this statement.^{116,117,118,119} However, the key issue is whether the ongoing declines in the ECD following IMT implantation represents an unstable corneal endothelial cell layer or simply corneal remodeling/redistribution. In my mind, the answer to this question lies in the morphometric endothelial data (i.e. coefficient of variation and percent hexagonality). Regrettably, none were provided.

I searched the Sponsor's PMA and did not locate morphometric endothelial data anywhere in the application. This is a critical deficiency and must be supplied to the FDA in order to determine whether the ongoing ECD loss represents ongoing cell loss or redistribution of cells following an obviously substantial surgical insult. Regarding ongoing cell loss, it is conceivable that the proximity of the device to the endothelium could lead to an unstable endothelial cell layer and cause chronic endothelial loss – this would be reflected by a lower percentage of hexagonal cells and an increased coefficient of variation that do not return to baseline levels (i.e. a chronically stressed endothelium). The only way to know is to get the morphometric data from the existing endothelial specular photographs.

¹¹³ Volume 9, page 9, Amendment 4, June 5, 2006.

¹¹⁴ FDA Executive Summary Addendum, page 3.

¹¹⁵ Amendment 4, Volume 9, page 14.

¹¹⁶ Edelhauser HF, Sanders DR, Azar R, Lamielle H, ICL in Treatment of Myopia Study Group. Corneal endothelial assessment after ICL implantation. J Cataract Refract Surg. 2004 March;30:576-583.

¹¹⁷ Yee RW, Matsuda M, Schultz RO, Edelhauser HF. Changes in the normal corneal endothelial cellular pattern as a function of age. Current Eye Research 1985;4(6):671-8.

¹¹⁸ Glasser DB, Matsuda M, Gager WE, Edelhauser HF. Corneal endothelial morphology after anterior chamber lens implantation. Arch Ophthalmol. 1985 Sept;103:1347-1349.

¹¹⁹ Schultz RO, Glasser DB, Matsuda M, Yee RW, Edelhauser HF. Response of the corneal endothelium to cataract surgery. Arch Ophthalmol. 1986 Aug;104:1164-1169.

Central ECD Measurements versus Peripheral ECD Measurements

I am surprised that the study was designed with only central endothelial cell density measurements given that it has been long recognized that peripheral endothelial cell density measurements provide valuable information about corneal endothelial remodeling and health.^{120,121,122} Moreover, since the IMT optic edge may be in close proximity to the endothelium, peripheral endothelial measurements seem prudent given our knowledge of the poor endothelial results from first generation angle supported phakic IOLs (e.g. first generation Baikoff lenses date to 1987). Additionally, with the superior cornea acting as a reserve of endothelial cells for remodeling (i.e. a 15.9% increased ECD compared to central ECD), we can expect that the IMT procedure (i.e. a large superior incision and a bulky device to implant from a superior approach) will preferentially damage the largest corneal reserve for remodeling. In this light, peripheral endothelial cell counts are preferred to substantiate the safety of the IMT device. Apparently, these measurements were not obtained in the IMT study despite their relevance.

Pachymetry

Screening criteria for eligibility included pachymetry (Volume 1, page 162). Pachymetry reflects endothelial cell function by measuring corneal stromal hydration. Regrettably, pachymetry was not measured in the postoperative period (Volume 1, page 166), nor was it reported in the PMA materials despite its relevance to corneal endothelial function.

Preoperative States that Affect Endothelial Cell Density and Morphometric Data

Several clinical circumstances can affect endothelial cell density and endothelial morphometric data: (a) diabetes mellitus; (b) glaucoma; and (c) contact lens wear,¹²³ among others. In looking at the study's exclusion criteria (Volume 1, pages 155 to 156), diabetes mellitus wasn't an exclusion criterion (i.e. only patients with diabetic retinopathy were excluded). Additionally, controlled glaucoma was apparently allowed. Moreover, contact lens wear was not an exclusion criterion, albeit I certainly understand that a 75 year old cohort with macular degeneration and cataracts are not likely candidates for contact lens wear. Nonetheless, given the importance of monitoring corneal endothelial health following IMT implantation, I'm surprised that relevant confounding factors for endothelial compromise were not specifically excluded at the outset.

¹²⁰ Glasser DB, Matsuda M, Gager WE, Edelhauser HF. Corneal endothelial morphology after anterior chamber lens implantation. Arch Ophthalmol. 1985 Sept;103:1347-1349.

¹²¹ Schultz RO, Glasser DB, Matsuda M, Yee RW, Edelhauser HF. Response of the corneal endothelium to cataract surgery. Arch Ophthalmol. 1986 Aug;104:1164-1169.

¹²² Amann J, Holley GP, Lee SB, Edelhauser HF. Increased endothelial cell density in the paracentral and peripheral regions of the human cornea. American Journal of Ophthalmology. 2003 May;135(5):584-590.

¹²³ Edelhauser HF. The resiliency of the corneal endothelium to refractive and intraocular surgery. Cornea. 2000;19(3):263-273.

Chronic Inflammation and Endothelial Cell Loss

Chronic inflammation is a known factor in ongoing endothelial damage^{124,125}
Following implantation of the IMT device, a whopping amount of steroids is required to quiet things down, and the steroids are not routinely stopped until 3 months after the procedure. In contradistinction, modern routine cataract extraction generally requires a tapering dose of steroids over about a month and at much lower dose. Lane reported in the phase I trial of this device that the most notable complication following IMT implantation was late intraocular inflammation observed 1 month or more postoperatively, with varying clinical signs, including anterior chamber cells, fibrin, conjunctival injection, iritis, and anterior uveitis.¹²⁶ Tellingly, the PMA reported inflammatory deposits on IMT in 13.3% (24/180) at 18 months following the procedure. Additionally, pigment deposits on the IMT were identified in 7.2% (13/180) which may be a sign of chronic iris chafe with subsequent breakdown of the blood-aqueous barrier. Regrettably, laser flare fluorophotometry – a useful test to evaluate chronic anterior chamber inflammation (i.e. breakdown of blood aqueous barrier) – was not performed. Based upon these data, I'm unable to rule out chronic inflammation as a cause of potential ongoing endothelial cell damage in at least some of these IMT implanted eyes.

Mean Central ECD Loss

I found it reassuring that the IMT study¹²⁷ disclosed annual pseudophakic fellow eye ECD losses of 2.44%, and annual phakic fellow eye ECD losses of 1.06% per year – values that reasonably “match” known annual ECD loss rates for pseudophakic eyes (i.e. 2.5%) and unoperated eyes (i.e. 0.6% to 1.0%). In my mind, these findings validate the accuracy of Sponsor's central ECD measurements in this study – after all, the IMT study just matched known ECD loss findings for both unoperated and pseudophakic eyes. Given these data, I have no reason to doubt the IMT ECD loss rates reported in the study since the methodology for endothelial cell analysis – whatever it is – must have been identical across all eyes – phakic, pseudophakic, or IMT implanted. Sponsor's ECD image quality analysis also found no untoward bias.¹²⁸

The most notable feature of the IMT application is the central ECD losses over time – they are substantially more than standard large incision cataract surgery. There was a 20% mean loss at the 3 month interval that increased to a 28% mean ECD loss at the 24 month interval. Published literature¹²⁹ for mean ECD losses in 10 of 40 eyes implanted with the IMT are similarly high: (a) 14.5% loss at 3

¹²⁴ Perez-Santonja JJ, Alio JL, Jimenez-Alfaro IJ, Zato MA. Surgical correction of severe myopia with an angle-supported phakic intraocular lens. *J Cataract Refract Surg* 2000;26:1288-1302.

¹²⁵ Edelhauser HF, Sanders DR, Azar R, Lamielle H, ICL in treatment of myopia study group. Corneal endothelial assessment after ICL implantation. *J Cataract Refract Surg*. 2004 March;30:576-583.

¹²⁶ Lane SS, Kuppermann BD, Fine IH, Hamill MB, Gordon JF, Chuck RS, Hoffman RS, Packer M, Koch DD. A prospective multicenter clinical trial to evaluate the safety and effectiveness of the implantable miniature telescope. *Am J Ophthalmol*. 2004;137(6):993-1001.

¹²⁷ FDA Table 1, 24 month data point, pages 28 - 29, FDA Executive Summary

¹²⁸ Volume 1, page 249-250.

¹²⁹ Alio JL, Mulet EM, Ruiz-Moreno JM, Sanchez MJ, Galal A. Intraocular telescopic lens evaluation in patients with age-related macular degeneration. *J Cataract Refract Surg* 2004;30:1177-1189.

months; (b) 30.8% loss at 6 months; and (c) 34.5% loss at 12 months. The endothelial losses in the FDA model using all ECD data disclose the following loss rates:¹³⁰ (1) baseline to 3 months = - 20.65%; and (2) annual ECD loss from 3 months to 24 months = - 6.02% per year. The study rates of ECD loss are quite a bit higher than the 12% ECD losses incurred with the acute trauma of standard cataract surgery and also about 2 ½ fold higher than the chronic rate of loss that occurs after standard cataract surgery (i.e. 2.5%). Comparing to the normal 0.6% ECD loss rate for unoperated eyes, IMT implanted eyes have a 10 fold higher rate of chronic ECD loss.

Using the aforementioned mean ECD loss rates along with United States life expectancy data,¹³¹ entry endothelial cell density values can be derived and then compared to normative endothelial cell densities. The table that follows (Table 1) shows the needed ECD at a given age in order to live the projected average lifespan as predicted by U.S. Life Tables. The endothelial cell loss rates reflect an initial 20.65% decline at 3 months (i.e. the surgical insult) followed by a 6.02% instantaneous annual endothelial loss rate (i.e. exponential). Fractions have been rounded down to the next integer since partial cells are not viable. The target endothelial cell density was set at 800 cells/mm² – the cutoff for “potential corneal edema” as presented by Bernard McCarey, PhD to the FDA Ophthalmic Devices Panel on 2 AUG 02. Obviously, a cell density of 800 cells/mm² would not allow any future intraocular surgical procedures without a high likelihood of causing postoperative corneal edema.

¹³⁰ FDA Executive Summary, page 32.

¹³¹ Arias E. United States Life Tables, 2002. National Vital Statistics Reports, Vol. 53, No. 6. Hyattsville, Maryland: National Center for Health Statistics, 2004.

Table 1: Required Beginning ECD at Projected FDA Model Runoff

Age	ECD										
60.00	3,984	65.00	3,106	70.00	2,577	75.00	2,137	80.00	1,771	85.00	1,563
60.25	3,161	65.25	2,464	70.25	2,044	75.25	1,695	80.25	1,405	85.25	1,240
61.25	2,970	66.25	2,315	71.25	1,920	76.25	1,592	81.25	1,320	86.25	1,165
62.25	2,791	67.25	2,175	72.25	1,804	77.25	1,496	82.25	1,240	87.25	1,094
63.25	2,622	68.25	2,044	73.25	1,695	78.25	1,405	83.25	1,165	88.25	1,028
64.25	2,464	69.25	1,920	74.25	1,592	79.25	1,320	84.25	1,094	89.25	966
65.25	2,315	70.25	1,804	75.25	1,496	80.25	1,240	85.25	1,028	90.25	907
66.25	2,175	71.25	1,695	76.25	1,405	81.25	1,165	86.25	966	91.25	852
67.25	2,044	72.25	1,592	77.25	1,320	82.25	1,094	87.25	907	92.25	<u>800</u>
68.25	1,920	73.25	1,496	78.25	1,240	83.25	1,028	88.25	852		
69.25	1,804	74.25	1,405	79.25	1,165	84.25	966	89.25	<u>800</u>		
70.25	1,695	75.25	1,320	80.25	1,094	85.25	907				
71.25	1,592	76.25	1,240	81.25	1,028	86.25	852				
72.25	1,496	77.25	1,165	82.25	966	87.25	<u>800</u>				
73.25	1,405	78.25	1,094	83.25	907						
74.25	1,320	79.25	1,028	84.25	852						
75.25	1,240	80.25	966	85.25	<u>800</u>						
76.25	1,165	81.25	907								
77.25	1,094	82.25	852								
78.25	1,028	83.25	<u>800</u>								
79.25	966										
80.25	907										
81.25	852										
82.25	<u>800</u>										

The table discloses that a 60 year-old patient must have an entry endothelial cell count of 3,984 cells/mm² in order to live the projected average lifespan with a clear cornea; an ECD value that far exceeds the normative mean ECD for patients aged 60 to 69: 2711 +/- 121 cells/ mm². In other words, we are not likely to find a 60 year old with an ECD more than 10 standard deviations above the mean – it’s exceedingly unlikely. It is similarly unlikely that a 65 year old will have an entry ECD of 3,106 cells/ mm². After the age of 70, however, it is possible that patients

can have the necessary entry ECD to live the projected average lifespan with a clear cornea. However, we must be cognizant of the fact that viewing things only from the point of view of the mean ECD loss does not adequately describe the high number of corneal casualties that occur with increasing time following this procedure – that is the distribution of endothelial cell densities increases quite a bit after IMT implantation.

Anterior Chamber Depth and ECD Loss

The average anterior chamber depth was 3.15 mm +/- 0.37 (range 2.48 to 4.74 mm). Sponsor reports that a preoperative anterior chamber depth (ACD) \leq 3.0 mm led to more ECD loss at 3 months than those subjects with a preoperative ACD $>$ 3.0 mm – but only for subjects who underwent surgery by a less experienced surgeon (i.e. surgical order \leq 3).¹³² From 3 to 24 months, Sponsor reports that ACD and surgical order are not predictive of the ECD percent change.¹³³ Further, Sponsor concludes that the “ACD has very low predictive power for the ECD percent loss from baseline to 3 months.”¹³⁴

In contradistinction, FDA evaluated the Sponsor’s data and states that “the relationship between ACD and ECD loss was found to be highly significant.”¹³⁵ For all time intervals, FDA reports that a shallower anterior chamber depth \leq 3.0 mm has more ECD loss than the $>$ 3.00 mm to 3.50 mm group, and that the $>$ 3.0 mm to 3.50 mm anterior chamber depth group has more ECD loss than $>$ 3.50 mm anterior chamber depth.¹³⁶ In other words, shallower chambers lead to more ECD loss irrespective of the time interval analyzed.

These two opposing opinions interpreting the identical data set present a conundrum to the Primary Reviewer. Which analysis is correct? As a clinician, I’m leaning toward the FDA viewpoint because common sense tells me that shallower anterior chambers are likely to impact endothelial cell loss through two mechanisms: (a) increased chance to harm the endothelium during insertion of the IMT device; and (b) increased proximity of the IMT optic to the endothelium once the device is implanted potentially leading to chronic ECD loss. In support of this stance are the following: (a) Garcia-Feijoo’s published comments that “. . . the small distance between the IMT and the cornea could affect the endothelium in the long term . . . one of the most important preoperative factors should be the depth of the anterior chamber. Therefore, because of the IMT morphologic features, we not only should select patients who present a wide anterior chamber but also must make sure that the implantation of the lens is intracapsular to try to increase the distance between the IMT and the endothelium as much as possible.”¹³⁷; and (b) published literature on angle supported IOLs discloses that intraocular devices that are closer to the endothelium present an increasing risk for ECD loss.

¹³² FDA Executive Summary, page 29.

¹³³ Volume 8, Amendment dated April 25, 2006, page 27, Item 3

¹³⁴ Volume 8, Amendment dated April 25, 2006, page 27, Item 3

¹³⁵ FDA Executive Summary, page 21

¹³⁶ FDA Executive Summary, page 21

¹³⁷ Garcia-Feijoo J, Duran-Poveda S, Cuina-Sardina R, Mendez-Hernandez C, Garcia-Sanchez J, Gomez de Liano MZ. Ultrasound biomicroscopy of an implantable miniaturized telescope. Arch Ophthalmol 2001 Oct;119(10):1544-6.

In order to mitigate against the high ECD losses caused by the IMT device, I wouldn't oppose limiting the preoperative ACD to 3.0 mm, or even perhaps 3.50 mm in light of Sponsor's Table B (above). Additionally, recall the published cases where an inadvertent sulcus-placed haptic moved this device dangerously close to the corneal endothelium (0.967 to 1.1 mm) in two eyes with preoperative anterior chamber depths of 3.22 mm to 3.47 mm – moderate chamber depths.¹³⁸ In this study, the two patients that required corneal transplants as a consequence of the IMT device had sulcus placed IMTs (i.e. patients 31-205 & 013-209) – I haven't been able to locate the anterior chamber depth for these two patients as of the date of this writing. If a haptic is placed in the sulcus, a deep anterior chamber becomes even more important since the device is shifted anteriorly toward the corneal endothelium.

And, we mustn't forget that the Sponsor presumably hand picked highly trained and highly experienced surgeons representing the best in their respective fields. In this light, how is this device going to fare in the hands of an average ophthalmologist?

Increased ECD Standard Deviation in IMT Implanted Eyes

For all eyes implanted with the IMT device, it only takes a cursory review of Figure 11 to disclose that the spread of the central ECD measurements substantially increases for this cohort. Indeed, many eyes are pushed below an ECD of 1000 cells/mm². Said another way, the standard deviation of the mean ECD increases from a baseline of 354.39 to 601.95 at the 24 month interval – almost a 70% increase. For comparison, following large incision cataract surgery Bourne reported about a 40% increase in the standard deviation of the mean ECD as compared to baseline.¹³⁹ The increased spread of the data tells us that simply following the mean ECD likely does not describe many serious adverse corneal outcomes that may impact a significant proportion of patients following IMT implantation.

Overall, the FDA model disclosed that 11.1% (24/216) of IMT eyes ended up with an ECD < 1,000 cells/mm² at 2 years, 17.6% (38/216) of IMT eyes ended up with an ECD < 1,000 cells/mm² at 3 years, and 22.7% (49/216) of IMT eyes ended up with an ECD < 1,000 cells/mm² at 4 years¹⁴⁰ – not trivial percentages. Those IMT eyes with a preoperative ECD in the lowest quartile fared the worst: 20.4% (11/54) ended up with an ECD < 1,000 cells/mm² at 2 years, 31.5% (17/54) ended up with an ECD < 1,000 cells/mm² at 3 years, and 38.9% (21/54) ended up with an ECD < 1,000 cells/mm² at 4 years. Yikes! Since a 75 year-old – the average entry age in this study – has a projected 11 ½ future years of life, we could be seeing an epidemic of Pseudophakic Bullous Keratopathy in a short time after the implantation of this device in a substantial proportion of eyes – that is, unless the

¹³⁸ Garcia-Feijoo J, Duran-Poveda S, Cuina-Sardina R, Mendez-Hernandez C, Garcia-Sanchez J, Gomez de Liano MZ. Ultrasound biomicroscopy of an implantable miniaturized telescope. Arch Ophthalmol 2001 Oct;119(10):1544-6.

¹³⁹ Bourne WM, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. Ophthalmology. 1994;101(6):1014-1023.

¹⁴⁰ FDA Executive Summary, page 33

rate of chronic cell loss slows down substantially to standard cataract surgery rates (i.e. 2.5% per year).

The Sponsor performed calculations using their three slope model to predict the proportion of eyes ending up with an ECD < 1,000 cells/mm² at 2, 3, and 4 years. I do agree with Sponsor's concerns that a linear model does not reflect the normal exponential decline of endothelial cells and that loss projections become more inaccurate the further one looks into the future. With little doubt, however, Sponsor's three slope model presents the ECD data in their best light as the final slope after 9 months time reduces the average endothelial cell loss to 6 cells per month (i.e. approximately 39% lower cell loss rate than the corresponding FDA model). It must also be recognized that FDA found numerous problems with Sponsor's model (e.g. actual visit time versus nominal visit time, among others). Nonetheless, Sponsor's model predicts that the proportion of eyes ending up with an ECD < 1,000 cells/mm² at 2, 3, and 4 years is very high, and worrisome for the long-term clarity of corneas in patients who may live for another decade or more.

Here's my take on Table B (above): (a) the proportion of eyes entering corneal edema territory is higher with narrower anterior chamber depths across all categories; (b) eyes with a baseline ECD of 1600 cells/mm² have an unreasonably high risk of entering corneal edema territory – a risk that increases with time; (c) about 1/3 of eyes (range 24% to 40%) – too many in my book – with a baseline ECD of 2000 cells/mm² cross over into corneal edema territory at year 4; (d) the best circumstance of a preoperative ECD of 2500 cells/mm² still leads to about 10% of eyes (range 7% to 15%) entering corneal edema territory by year 4 – not to mention the inexorable ECD decline that is expected if the patient continues to live. Based upon these data, I'm very concerned about the safety of this device from a corneal endothelial standpoint. A large proportion of patients can be expected to develop corneal stromal edema during their lifetimes if the entry criteria are not limited to some extent, or if the chronic ECD loss doesn't decrease with time.

Overall Recommendations for Sponsor Based Solely Upon Endothelial Analysis

- ✓ Due to the very high rate of both early and late central ECD loss, we must know whether this device causes a chronically unstable endothelium OR whether this device leads to prolonged endothelial remodeling. Which is it? The current PMA does not include the relevant information to make this determination: morphometric endothelial data. Therefore, in the absence of endothelial morphometric data, the study is not approvable in its current form. The Sponsor must submit to the FDA morphometric endothelial data (e.g. coefficient of variation and percent hexagonal cells) derived from existing endothelial photographs to determine whether the high rate of chronic endothelial cell loss following IMT implantation represents an unstable endothelial cell layer (i.e. chronically stressed endothelium) or simply redistribution/remodeling of the endothelial cell layer following the initial surgical trauma. If the morphometric data are consistent with ongoing corneal remodeling, then the device may be approvable with conditions that limit entry criteria to mitigate against the development of pseudophakic bullous keratopathy during patient's lifetimes. For example: (a) limit ACD to ≥ 3.5 mm; (b) limit baseline ECD to ≥ 2500 ; and (c) limit

entry age to ≥ 75 ; or (d) develop a sliding scale of required baseline endothelial cell densities for given ages consistent with life expectancy tables. If, however, the existing morphometric data disclose an unstable endothelium over the entire duration of the IMT study, the device is not approvable purely from a safety standpoint. In that circumstance, implanted eyes should be followed for additional year(s) with new specular photographs at various time intervals until the morphometric data stabilize, if ever.

- ✓ **Assuming that the morphometric data do not show a chronically unstable endothelial cell layer over the entire 2-year study period (i.e. the coefficient of variation and percent hexagonality return to near baseline levels), the aforementioned entry limits may be altered if supported by additional ECD data regarding central ECD losses through year three.**
- ✓ **While peripheral ECD counts would be nice, it's too late to gather this information.**
- ✓ **Sponsor should submit Ultrasound Biomicroscopy images for several eyes within each anterior chamber depth group to ascertain the distance of the optic to the corneal endothelium – central and peripheral distances. These data may be most relevant for the narrow anterior chamber depths that seem to have the most risk of endothelial loss.**
- ✓ **At a minimum, new surgeons should perform IMT implantation only upon eyes with deep anterior chambers.**
- ✓ **Surgeons must be extraordinarily vigilant to implant both IMT haptics within the capsular bag since sulcus fixation is likely to bring this device dangerously close to the corneal endothelium. The two corneal transplant patients in the IMT study had sulcus fixated haptics, and the two published cases in the literature with sulcus fixation had unacceptably close optic-endothelial distances. Appropriate labeling must reflect this circumstance.**

6. Intraocular Pressure
 - a. Transient IOP elevations (50 cases = 24.3% on day 1) likely related to Healon V.
 - b. Was gonioscopy performed at least in the eyes that had a transient pressure elevation?
7. Explants
 - a. 8 explants
 - i. 4 patients dissatisfied with the device
 - ii. 2 removed due to condensation within the tube
 - iii. 2 removed at the time of penetrating keratoplasty

III. EFFECTIVENESS ISSUES

A. Vision

1. Improvement of ≥ 2 lines BCDVA or BSNVA = 85% to 90%
2. Improvement of ≥ 2 lines BCDVA and BSNVA = 67% to 73%
3. 52.8% (102/193) gained ≥ 3 lines BCDVA and BCNVA
3. The mean increase in lines of BCDVA was 3.1 lines +/- 2.2 lines at 24 months
4. Patients with profound impairment gained considerably more lines of BCDVA and BCNVA than subjects with moderate impairment

B. Comment:

Since a cataract was removed and the device induces significant magnification, I suppose I'm not surprised that a high percentage of patients had improvement in lines of vision. After all, that's what the device is supposed to do. If anything, the lines of vision gained aren't as large as I would expect if estimating the combination of the magnification (i.e. expect a 3 to 4 line gain) plus removal of a lens opacity – but then again, these patients have altered macular function due to macular degeneration.

Table Q17 disclosed that about 50% of IMT eyes achieved at least the predicted improvement from the induced magnification (i.e. 3.4 lines from the 2.2X IMT & 4.3 lines from the 3.0 X IMT). I agree with Sponsor that less than the theoretical improvement should be expected clinically because of the central scotoma from macular degeneration.

C. Quality of Life Surveys

1. VFQ-25 subscales improved
 - a. general vision by 14 points, near activities by 11.2 points, and distance activities by 7.9 points.
 - b. clinically significant improvements across all vision specific subscales (social functioning, mental health, role difficulties, and dependency) were observed.
 - c. Subjects reporting extreme difficulty with the items pertaining to visual function generally showed a lessening of this difficulty by one year postop.
2. ADL outcomes at 12 months
 - a. the mean improvement from baseline was 14.1 points.
 - b. the mobility subscale improved by 12 points.
 - c. the distance subscale improved by 13.4 points
 - d. the near activities subscale improved by 17 points
3. **Comment**

It appears that the VFQ and ADL scores improved – I'll defer to Panel & FDA expertise regarding the clinical significance of these scores.

D. Postoperative Vision Rehabilitation

1. In the IMT trial, the patient was responsible for implementing the rehabilitation program with assistance from the family.¹⁴¹
 - a. no validated methods for measuring the outcome
 - b. no professional rehabilitation included in Sponsor's training program
2. **Comment**

The FDA will ask the Ophthalmic Devices Panel to consider a vision training rehabilitation program as a requirement for IMT implantation. Published comments by physicians who have implanted this device include the following:

Following implantation of the IMT in 40 eyes of 40 patients, Alio and colleagues¹⁴² stated: "Adequate postoperative visual rehabilitation is also mandatory and should be performed by trained low-vision specialists." Following implantation of

¹⁴¹ FDA Executive Summary, page 22

¹⁴² Alio JL, Mulet EM, Ruiz-Moreno JM, Sanchez MJ, Galal A. Intraocular telescopic lens evaluation in patients with age-related macular degeneration. J Cataract Refract Surg. 2004;30:1177-1189.

the IMT in 3 patients, Kaskaloglu and colleagues¹⁴³ stated: “patients must be willing to participate in low-vision training postoperatively.” Commenting upon the 6 month results of the IMT study, Lane and Kuppermann¹⁴⁴ recommended a team of specialists to “realize the benefits” of the IMT device to include a retina specialist, an anterior segment surgeon, and finally “a visual rehabilitation program led by a visual rehabilitation specialist.” Lane and Kuppermann also state: “The visual rehabilitation program is a key factor to a successful outcome, as it allows the patients to leverage their improved visual acuity into performance of everyday activities.” Another IMT study investigator, G. Robert Lesser, MD, stated: “Patients must work with a low-vision specialist because it’s like learning to write with your left hand if you’re right handed.”¹⁴⁵

Based upon these comments – to include the Medical Monitor of this IMT study (i.e. Stephen Lane, MD) – it seems unanimous that a visual rehabilitation program led by a trained professional is a key component for success with this device. Accordingly, it is my opinion that a vision training rehabilitation program should be a requirement, not just a recommendation.

- E. Binocular Visual Performance Considerations
1. potential problems with binocular rivalry, suppression, and magnification differences
 2. **Comment**

FDA has succinctly outlined the issue on page 24 of their Executive Summary. I’ll look to Panel expertise – Dr. Brilliant and others – in this regard.

IV. OTHER ISSUES

- A. Posterior Capsular Opacification
1. 8 eyes had PCO – 6 minimal and 2 moderate: No visual sequelae in these 8 eyes
 2. Tight apposition of telescope with posterior capsule seems to inhibit PCO
 3. Needling procedures performed in 2 eyes
 3. **Comment**

The Sponsor’s proposed mechanism for decreased PCO rates seems reasonable. We know that square edge IOLs in close proximity to the posterior capsule do inhibit posterior cellular migration. The low rates of PCO are comforting since a YAG capsulotomy appears to be a significant challenge in patients implanted with the IMT.

In rabbits, a YAG capsulotomy required 100 to 138 bursts around the optic, and could crack the PMMA carrier plate, haptics, or the cap.¹⁴⁶ Given that a YAG capsulotomy must be done in a circular fashion, it will require an excessive number of shots which may increase the risk of retinal detachment. Published evidence shows that eyes following YAG capsulotomy have a 4 fold increased

¹⁴³ Kaskaloglu M, Uretmen O, Yagci A. Medium-term results of implantable miniaturized telescopes in eyes with age-related macular degeneration. J. Cataract Refract Surg. 2001;27:1751-1755.

¹⁴⁴ Lane SS, Kuppermann BD. The implantable miniature telescope for macular degeneration. Current Opinion in Ophthalmology. 2006;17:94-98.

¹⁴⁵ Article from USA Today dated 12/8/03; http://www.usatoday.com/tech/news/techinnovations/2003-12-08-bionic-eye_x.htm

¹⁴⁶ Rosner M, Ben-Simon G, Sachs. Feasibility and safety of laser treatments in eyes with an intraocular implantable miniature telescope. J Cataract Refract Surg. 2003 May;29:1005-1010.

incidence of retinal detachment as compared to eyes that haven't undergone a YAG capsulotomy. For diamond pattern YAG capsulotomies, I generally expect 25 to 30 or so bursts from the laser – the circular pattern increases the number of shots. A circular capsulotomy may also lead to a large floater since the cut piece of capsule will be free floating – that is if it detaches from the posterior aspect of the optic in the first instance.

The Sponsor indicates that a needling procedure may also be done to complete a YAG capsulotomy. I wish to point out that most ophthalmologists in practice today have never performed a needling procedure given that the first YAG laser indicated for capsulotomy procedures was approved in 1984 (Coherent Laser). Since all procedures, however simple, require a learning curve, I would expect that a needling procedure is no exception to that rule. I doubt that needling procedures are currently taught in ophthalmology residency programs. I've never done one and I've never seen one done – I completed my ophthalmic training from 1989 to 1993. It is my experience that there are always tricks and tips that make procedures easier and safer to perform – I don't currently know those tricks and tips for a needling procedure.

I was wondering if progressive capsular contraction can put pressure on this device and move it anteriorly toward the cornea. Similarly, does a successful YAG capsulotomy move the device posteriorly in any way since posterior capsular tension on the device is removed?

B. Device Design

1. Question:

The telescope tube is drawn as 4.40 mm in length. Is it 50% in front of the IOL holder and 50% behind the IOL holder? Or is it moved anteriorly toward the cornea?

C. Angle Narrowing

- 1. Comment: Sulcus placed haptics can close or narrow the anterior chamber angle.¹⁴⁷ While I noted that narrow angles (less than Shaffer grade 2) was an exclusion criteria in the study, I wasn't able to find any gonioscopy data in the PMA materials. Was it performed? After IMT implantation, is the angle narrowed due to the size of this device, or due to capsular tension pushing things anteriorly? Why wasn't this factor evaluated? 3% to 4% of eyes in this study had haptics out of the bag – what was the angle status in the meridian of the sulcus haptic in those eyes?**

D. Retinoscopy

- 1. Is it possible to perform retinoscopy on these eyes?**

E. Routine Clinical Care that may be Impacted by the IMT Device

- 1. Fluorescein Angiogram for Macular Disease**
- a. small image size and glare from telescope – “burdensome”¹⁴⁸
- 2. Peripheral Retinal Examination**
- a. may be difficult due to poor view, especially if pupil-optic adhesions
- 3. Macular Laser / Peripheral Retinal Laser**

¹⁴⁷ Garcia-Feijoo J, Duran-Poveda S, Cuina-Sardina R, Mendez-Hernandez C, Garcia-Sanchez J, Gomez de Liano MZ. Ultrasound biomicroscopy of an implantable miniaturized telescope. Arch Ophthalmol 2001 Oct;119(10):1544-6.

¹⁴⁸ Garfinkel RA, Berinstein DM, Frantz R. Treatment of choroidal neovascularization through the implantable miniature telescope. Am J Ophthalmol. 2006;141(4):766-767.

- a. possible with Argon laser in one case report. Challenging due to small size of image.
- 4. Ocular Coherence Tomography (OCT)
 - a. Is it possible to perform an OCT for macular disease?

July 6, 2006