P050034

Vision Care Ophthalmic Technologies
Implantable Miniature Telescope

March 27, 2009

Regulatory History

IDE Phase

May 2000 – IDE application approved to begin clinical study

Oct. 2002 – IMT-002 protocol approved

Feb. 2006 – IMT-002-LTM protocol approved

Regulatory History

PMA Phase (Modular PMA)

Jan. 2005 – Module 0 submitted (PMA shell)

Feb. 2005 – Module 1 submitted (biocompatibility and chemistry)

Aug. 2005 – Module 2 submitted (engineering and sterilization)

June 2005 – Module 3 submitted (manufacturing)

Sept. 2005 – Module 4 submitted (clinical) converted to PMA

Regulatory History

July 14, 2006 Ophthalmic Panel meeting –

Reviewed PMA P050034

On a 10-3 vote, voted "Not Approvable" due to safety and effectiveness concerns with the device

Regulatory History

Post 2006 Ophthalmic Panel meeting –

Sponsor submitted Amendments 6-19 to address outstanding issues with their device.

FDA Review Team

Team Leader/ Eng. -	Don Calogero
Biocompatibility –	Susanna Jones
Microbiology –	Sara Thornton
Statistical –	T.C. Lu, Yao Huang, Ning Li, Gene Hilmantel
Clinical –	Bernard Lepri, Gene Hilmantel
Vision Science –	Bruce Drum
Epidemiology –	Michele Bonhomme, Youlin Qi

FDA Presentation

FDA presenters:

1. Bernard Lepri – General clinical summary

2. Gene Hilmantel – Specular microscopy summary

3. Yao Huang – Statistical summary

4. Michele Bonhomme – Post-market approval summary

Clinical Issues

Bernard P. Lepri, OD, MS, MEd
FDA/CDRH/ODE/DOED
March 27, 2009

IMT Protocols & Cohorts

IMT – 002

N = 218

Enrolled

→

IMT-002

N = 206

All IMT Implanted Eyes

→

IMT-002-LTM

N = 129

Long Term Monitoring Study

Accountability: IMT 002

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

Accountability: IMT-002-LTM

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

Modifications to the Statement of Indications

Proposed Indications

The Implantable Miniature Telescope (IMT) is indicated to improve vision by monocular implantation in patients 65 years of age or older with stable moderate (distance BCVA of 20/80 or poorer) to profound (distance BCVA 20/800 or better) vision impairment caused by bilateral central scotomas associated with end-stage age-related macular degeneration. Subjects selected for implantation should meet the following criteria:

Indications continued

- retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography;
- evidence of cataract;
- at least a five-letter improvement on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart with an external telescope;
- adequate peripheral vision in the eye not scheduled for surgery;
- willingness to participate in a postoperative visual training/rehabilitation program.

Proposed Contraindications

Proposed Patient Population

2006	2009
Minimum age 55	Minimum age 65
Stable central vision disorders resulting from AMD determined by fluorescein angiography	Stable, moderate, to profound central vision impairment, i.e. distance BCVA of 20/80 or poorer to 20/800 or better, due to bilateral central scotomas associated with end-stage macular degeneration, defined as retinal findings of geographic atrophy or disciform scar, with foveal involvement as determined by fluorescein angiography;
Show interest in rehabilitation	…are willing to participate in rehabilitation

Proposed Patient Population (*cont'.)*

2006	2009
No contraindications for Guttata	Guttata contraindicated
No contraindications for specific ACD	ACD < 3.0 mm contraindicated
Contraindicated: Endothelial cell density < 1600 cells/mm2	Contraindicated in patients who do not meet the Minimum ECD grid values - based on statistical modeling

Effectiveness
Mean BCVA at Baseline, 12 Months, and 24 Months
All IMT-Implanted Eyes

	Baseline		**12 months**		**24 months**	
	N	Mean	N	Mean	N	Mean
Mean BCDVA	206	20/312	196	20/141	174	20/149
Mean BCNVA 8″	206	20/315	196	20/181	174	20/190
Mean BCNVA 16″	206	20/262	196	20/149	174	20/157

Effectiveness Degree of Visual Impairment @ 12months Compared to Baseline All IMT-Implanted Eyes

Baseline VA	Improved	Unchanged	Worse
Mod. Impairment 0.6 to 0.9 20/80 - 20/160	3.6%	4.7%	2.1%
Sev. Impairment >0.9 to 1.3 20/160 - 20/400	41.0%	15.5%	0.5%
Profound Impairment >1.3 < 20/400	31.1%	1.6%	0.0%
Total	**75.7%**	**21.8%**	**2.6%**

Effectiveness
VA based on whether the operated eye was the better or worse eye at baseline

All IMT-implanted eyes and a 24-month consistent cohort,

- difference between IMT-implanted eyes that were worse vs. those that were better or the same at baseline was constant throughout the study.
- difference was largest at baseline and smaller at follow-up visits, with relatively small between-group differences observed.

Explants and Corneal Transplants up to and beyond the 24 month follow up period

Summary of IMT Explants

Adverse Event	N	% of All Operated Eyes (N=217)	% of All Implanted Eyes (N=206)
Intraoperative IMT Placement and Removal (Attempted Implantation)	6	2.8%	NA
IMT Explantation within 24-Month Study Follow-up	8	3.7%	3.9%
Total IMTs Explanted (Attempted Implantation and Postoperative Removal within 24-Month Study Follow-up)	14	6.5%	NA
IMT Explant Post-24 months*	4	1.4%	1.5%
Total IMT Removals Post Implant (all available data)	12	NA	5.3%
Total IMT removals intraoperatively and postoperatively (all available data)	18	8.3%	NA

Unresolved Corneal Edema

- 9 IMT-Implanted Eyes with Unresolved Corneal Edema (at last available visit)
  - 4 Decompensation with Transplant
  - 2 Decompensations without Transplant
  - 3 Additional Unresolved Edema Cases

Corneal Edema (*cont'*.)

- 19 total eyes with ECD <750 at final visit
  - » 9.22% of original PMA cohort of 206
- 31 total eyes with ECD <1000 at final visit
  - » 15% of original PMA cohort of 206

Panel Question

The Implantable Miniature Telescope (IMT) is indicated to improve vision by monocular implantation in patients 65 years of age or older with stable moderate (distance BCVA of 20/80 or poorer) to profound (distance BCVA 20/800 or better) vision impairment caused by bilateral central scotomas associated with end-stage age-related macular degeneration.

Panel Question (*cont'.)*

Patients must have:

- Retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography,
- Evidence of cataract
- At least a five-letter improvement on the ETDRS chart with an external telescope
- Adequate peripheral vision in the eye not scheduled for surgery

Panel Question (*cont'*.)

- Willingness to participate in a postoperative visual training/rehabilitation program

<u>Contraindications</u>

- Evidence of corneal guttata
- Anterior chamber depth <3.0 mm
- The IMT is contraindicated in patients who do not meet the minimum age and endothelial cell density as specified in the proposed grid.
- Additional contraindications as proposed by the sponsor in the labeling (Vol II, Amendment #13)

Panel Question (cont'.)

Please discuss whether the sponsor has provided reasonable assurance of safety and effectiveness of the device for the proposed indications and contraindications. What, if any, modifications to the proposed patient population do you recommend?

Fundus Visualization through the IMT

- 1,821 fundus examinations were performed on 194 patients using:
  - diagnostic photography,
  - OCT (Optical Coherence Tomography) and/or B scan ultrasonography.
  - slit lamp with a 90 D hand-held lens;
  - fluorescein angiography,
  - indirect ophthalmoscopy; 50 – 60 degrees of retina visible when fully dilated; limited when full dilation is not possible

Examination and treatment of the posterior segment

- Uncertainty reported in 9 of over 1,821 examinations (rate of 0.5%)
- 90 D lens; 4% failure rate
- Direct visualization with contact/non-contact viewing lenses rated best

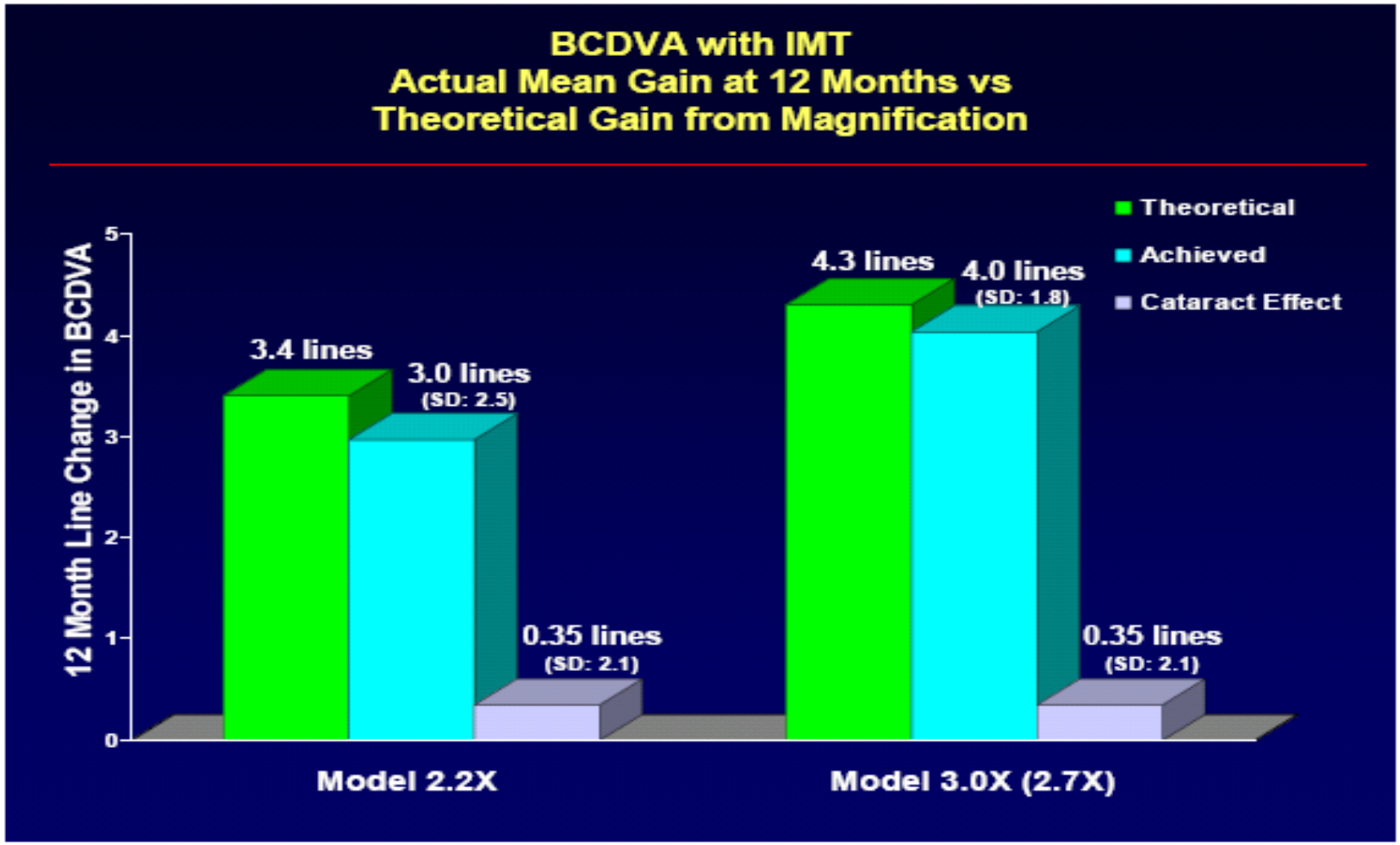
Panel Question

The sponsor has provided fundus images and investigator reports of fundus visualization performed by various techniques. Does this information support adequate visualization and treatment of the posterior segment of eyes implanted with the IMT? If not, please provide your rationale.

Effect of Cataract Removal
BCDVA IMT vs BCDVA Cataract Removal

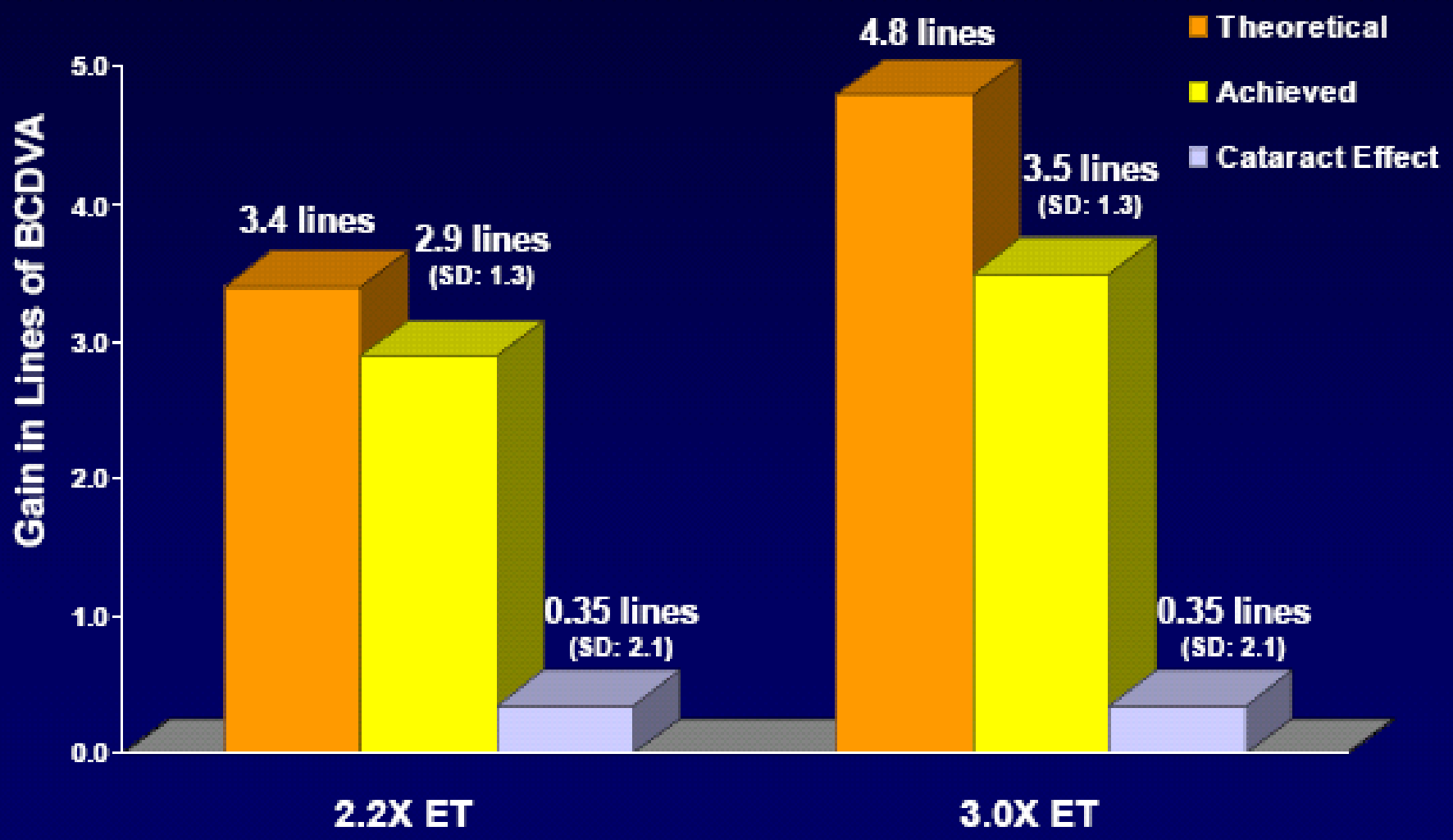
- control group of 22 IMT patients with visual acuity outcomes following cataract surgery and IOL implant of the fellow eye
- the IMT-implanted population at 12 months had a mean change of 3.43 lines (SD 2.31)
- 22 fellow eyes having cataract extraction and IOL implantation had a mean change from baseline of 0.35 lines (SD 2.14)

Effectiveness
Predicted visual acuity of IMT with cataract removal



BCDVA with External Telescope at Baseline

Theoretical Gain from Magnification of External Telescope, Achieved Mean Gain at Baseline, and Achieved Mean Gain at Baseline + Cataract Effect



Panel Question

Please discuss whether the sponsor has adequately demonstrated the effectiveness of the IMT taking into account the analyses of visual acuity (VA) improvement in eyes with cataract removal without IMT implantation.

Thank you!

Specular Microscopy

Gene Hilmantel, O.D., M.S.
FDA/CDRH/ODE
Division of Ophthalmic and ENT Devices
March 27, 2009

Topics

- Brief Background
- Endothelial Cell Density (ECD) Loss (Acute and Chronic)
- Morphometric Analysis
- Risk of Corneal Decompensation and Late Edema
- Risk of ECD Decline to Low Levels

Brief Background

2006 Panel Meeting

- At the 2006 Panel meeting, endothelial cell density (ECD) data from preop to 2 years postop was presented.
- The Panel expressed concerns about the ECD decline presented.
- The Panel and FDA recommended:
  - Analyses of morphometric data in order to help characterize endothelial changes.
  - Analysis of longer term follow-up data to estimate the acute and chronic rates of ECD loss.
  - Analysis to further identify cofactors that might be used to help mitigate the risk of decreased ECD.

Sub-Group Analyses

- Sponsor has analyzed the effect of cofactors in an attempt to mitigate the risk of loss
- Multiple post-hoc tests for the significance of
  - Anterior chamber depth
  - Surgical specialty
  - Surgical order
  - Glaucoma
  - Chronic inflammation
  - Diabetes
  - Guttata

Sponsor has suggested that the following are "risk factors" for endothelial cell loss

- Baseline presence of *corneal guttata*
  (Now a proposed Contraindication)
- Baseline *Anterior Chamber Depth < 3.0 mm*
  (Now a proposed Contraindication)
- Implantation by a *non-cornea-trained surgeon,**
  (Now part of a proposed Warning)
- Being among the first five eyes implanted by a given surgeon

Baseline ECD has also been shown to have some relationship to low postop ECD (Now part of a proposed Contraindication)

* "Cornea-trained" defined as: "had completed training in surgery of the cornea as part of a post residency fellowship training, and were experienced in and currently performing corneal transplantation."

Sponsor has presented results from various sub-groups

- **"All IMT-Implanted" Cohort**: Eyes that had surgery and had the IMT implanted and not removed intraoperatively (**n=206 at preop**)
  - » **"Guttata-Free, Large ACD" Sub-Cohort**: no guttata and anterior chamber depth (ACD) ≥ 3.0 mm at baseline (**n=112 at preop**) [Similar to Indicated Population, but without age restriction of ≥ 65]
    - **"Sub-Cohort A":** no guttata and ACD ≥ 3.0 mm at baseline AND

      ≥ 65 years of age, and implanted by a "cornea specialist" (**n=33 at preop**)

["Sub-Cohort A" represents approximately the Indicated Population PLUS restriction concerning surgical specialty from a WARNING]

Number of Eyes with ECD Measurements for Key Cohorts

	IMT-002 baseline to 24 months					IMT-002-LTM 24+ to 60 months					
	Preop	6 mos	12 mos	18 mos	24 mos		36 mos	42 mos	48 mos	54 mos	60 mos
"All IMT-Implanted" Cohort	206	198	186	180	171		70	101	88	60	17
"Guttata-Free Large ACD" Subcohort	112	107	103	100	95		36	50	45	3	1
"Sub-Cohort A"	33	33	30	28	27		9	12	12	0	0

ECD Loss

Safety Endpoint for Specular Microscopy

- Endpoint: Mean % Loss of Endothelial Cell Density (ECD) at 12 months Postop. (Average of Individual % Loss)
- Analysis: Demonstrate that for the population, the mean % ECD loss was no greater than 17%.
  - » H_0: $\mu \geq 17\%$ vs.
  - » H_a: $\mu < 17\%$;
- Why was 17% chosen?
  - » Based on a review of the literature, a mean ECD loss of 10 – 17% within 1 year postop was observed for large incision surgeries.

Observed Surgery-Related Decline at 12 months Postop

- **"All IMT-Implanted" Cohort: 25%** (Failed Hypothesis Test)

Decline at 12 Months Postop for the Sub-Cohorts:

- "Guttata-Free Large ACD" Sub-Cohort: 24%
- "Sub-Cohort A": 19%

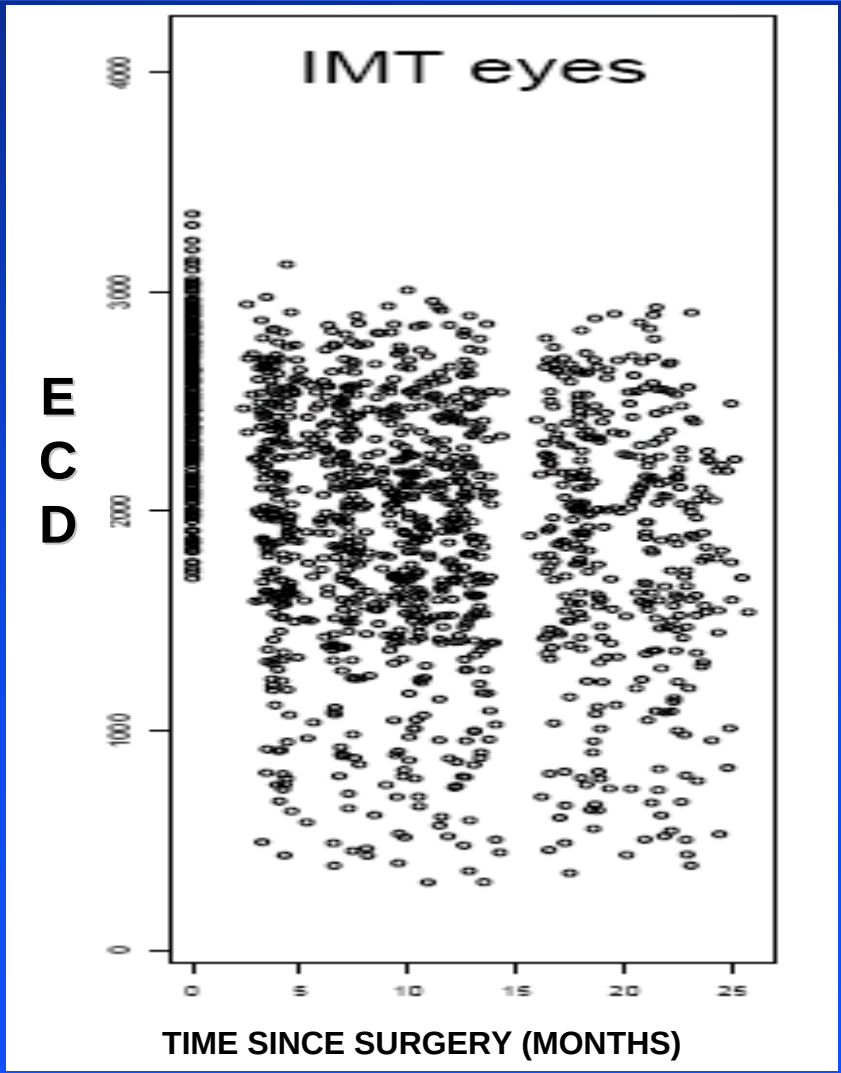
Changes in ECD distribution from preop

- Lowering of the mean ECD
- Skewing of the distribution toward lower values
- Increase in variance

Mean ECD Over Time
(All IMT-Implanted Cohort)

	IMT-002 Protocol					IMT-002-LTM Protocol				
	Pre-op	6 mos	12 mos	18 mos	24 mos	36 mos	42 mos	48 mos	54 mos	60 mos
N	206	198	186	180	171	70	101	88	60	17
Mean ECD	2496	1937	1871	1878	1808	1713	1595	1620	1572	1616
%change in mean from 6 mos prior		-22.4%	-3.4%	0.4%	-3.7%		-6.9%	1.6%	-3.0%	2.8%

Increase in Variance



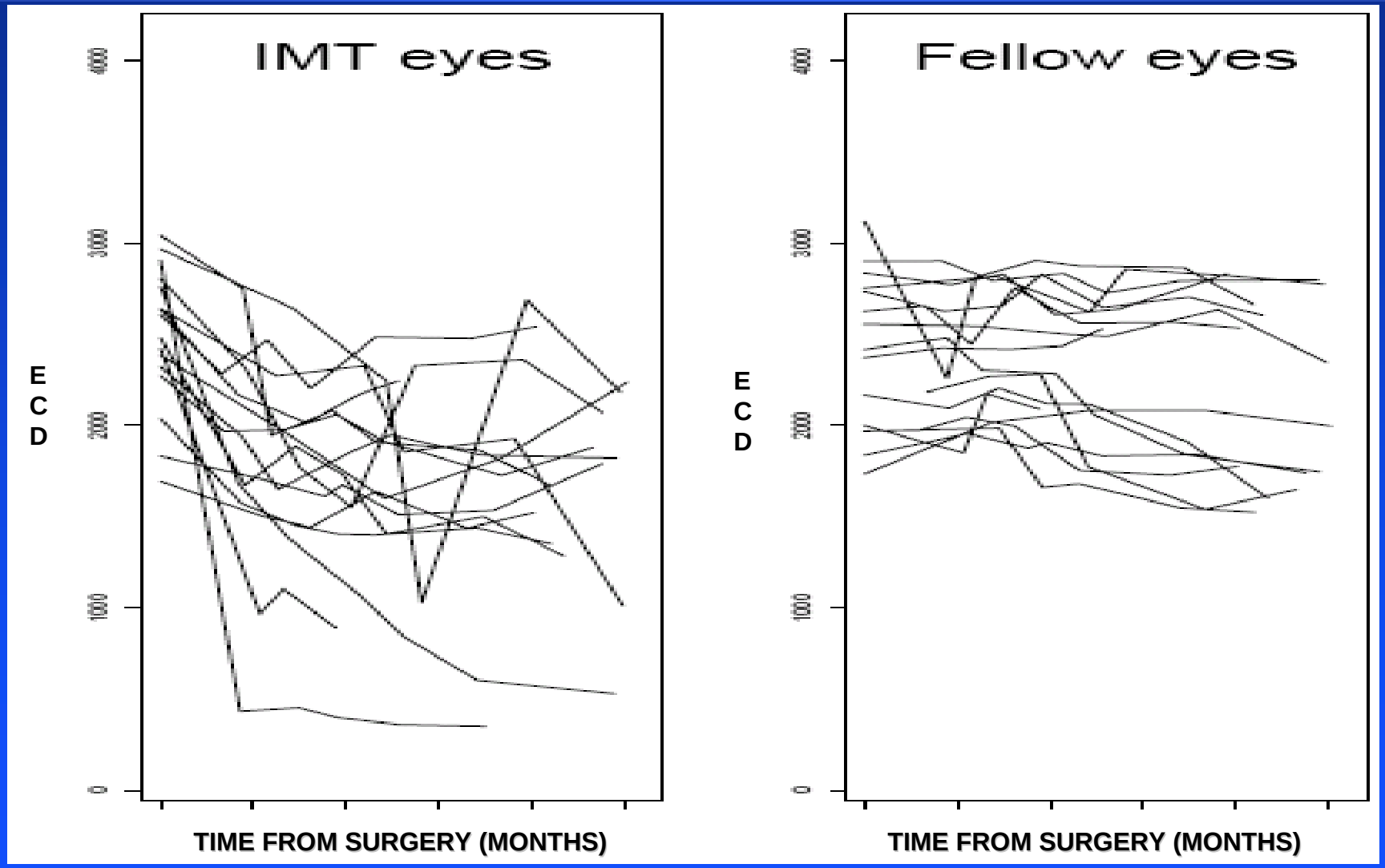
- Because of the skewing toward lower values and increased variance, it is important not to look <u>only</u> at the mean changes.

A Number of Eyes Had Very Low Postop Cell Counts (All IMT-Implanted Cohort)

Months Postop:	Base line	3	6	9	12	18	24	36	42	48
N	206	193	198	190	186	180	171	70	101	88
# of eyes ECD<1000	0 (0%)	16 (8%)	17 (9%)	16 (8%)	21 (11%)	21 (12%)	19 (11%)	8 (11%)	21 (21%)	15 (17%)

Significant changes in counts from visit to visit partly because of …

Low Precision in the ECD Measurement



Chronic ECD Loss

Why Use a Statistical Model?

- Smooths out bumps in ECD data
- Reduces problem of different sub-sets of patients available at different visits. (Does not eliminate problem.)
- Permits simple estimation of a constant chronic loss rate using <u>all</u> of the data
- <u>However</u>, modeling only estimates an <u>average</u> rate of decline – and is based upon certain artificial mathematical assumptions

Biexponential model

- Introduced by sponsor subsequent to 2006 Panel
- Previously published in the literature
- Does not require establishing a “break point” between surgical loss and chronic loss.

Chronic Loss
Biexponential Model

- Used by the sponsor to estimate the chronic rate of loss (using baseline to 48 months data)

Group	Chronic Annual Rate	90% Conf Interval
All IMT-Implanted Cohort	4.8%	(3.2%, 6.2%)
"Guttata-free, Large ACD" Sub-Cohort	3.8%	(2.0%, 5.5%)
"Sub-Cohort A"	3.4%	(0.3%, 6.4%)

Sponsor-Proposed Grid Based On Biexponential Model

- Contraindication for preop ECD below minimum baseline values for each age (and gender) group
  - » Assumes need for end-of-life ECD of 750 cells/mm^2
  - » Back-Calculated using upper 90% confidence limit on rate of loss
  - » Assumes an average life span, stratified by sex

Assumptions Used By Sponsor in Calculating Proposed Grid (Minimum Preop ECD)

- Used results from Biexponential Modeling of "Guttata-Free Large ACD" Sub-Cohort (n=112)
  - 12-month ECD loss of 24.6% (the lower 90% confidence limit for the 12 month estimate of mean ECD)
  - Annual chronic ECD loss of 5.5% (i.e., the upper 90% confidence limit for annual loss [3.8% per year])

	Age Range→	**65 - 69**
	Gender→	**Male**
	Avg Life Span→	**16.6**
	Minimum ECD→	**2460**
Years Postop→	**1**	1855
	2	1753
	3	1657
		…
	13	…
	14	908
	15	840
	16	794
Average End of Life	**17**	**750**

Assumptions Used By in Calculating Alternative Grid (Minimum Preop ECD)

- Used results from Biexponential Modeling of "All IMT-Implanted" Cohort (n=206)
  - 12-month ECD loss of 26.3% (the lower 90% confidence limit for the 12 month estimate of mean ECD)
  - Annual chronic ECD loss of 6.2% (i.e., the upper 90% confidence limit for annual loss [4.8% per year])

Grid Comparison

A. Proposed by Sponsor:

Age Range	65-69		70-74		75-79		80-84		85 or Greater	
Gender	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Minimum Cell Density	2460	2755	2000	2325	2000	2000	2000	2000	1800	1800

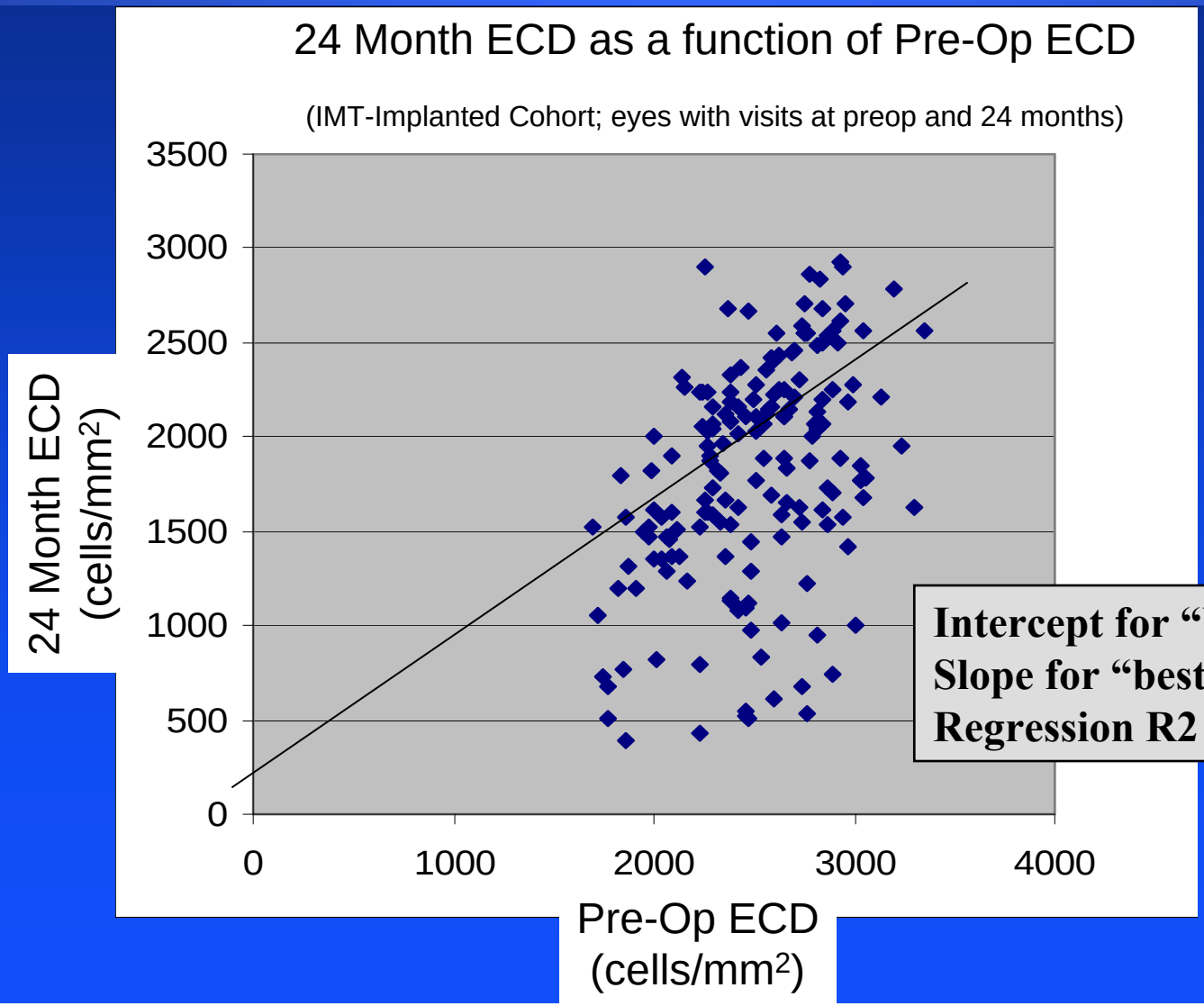
B. Requested Alternative:

Age Range	65-69		70-74		75-79		80-84		85 or Greater	
Gender	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Minimum Cell Density	2834	3223	2195	2659	2000	2058	2000	2000	1800	1800

Panel Input

- Adequacy of 750 cells/mm^2 at end of life?
- Consider:
  - » Whether sufficient to prevent decompensation?
  - » IMT patients will not routinely require another intraocular surgery
  - » IMT removal, if needed, may cause significant surgical trauma
  - » The grid is based upon estimates of <u>average</u> rates of cell loss. (Poor predictability of postop ECD from baseline measurement)

Poor Predictability of ECD Loss from baseline measurement



Intercept for "best fit" line: 64.2
Slope for "best fit" line: 0.70
Regression R2 = 0.18

Panel Question

- The sponsor has constructed two "grids" for determination of minimum preoperative ECD (for various age and gender groups). Both "grids" are based upon calculations assuming an end of life ECD of 750 cells/mm^2.

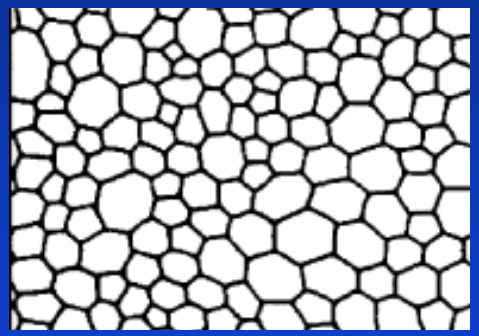
Panel Question (*cont'*.)

- Is the assumption of an end of life ECD of 750 cells/mm^2 acceptable? If not, what do you believe is appropriate?
- One grid is based on the ECD changes in a sub-cohort of 112 eyes (guttata-free eyes with anterior chamber depth ≥ 3.0 mm). The other is based upon the ECD changes seen in the full cohort of 206 IMT-Implanted eyes. Please discuss which grid is appropriate as a contraindication for the proposed patient population.

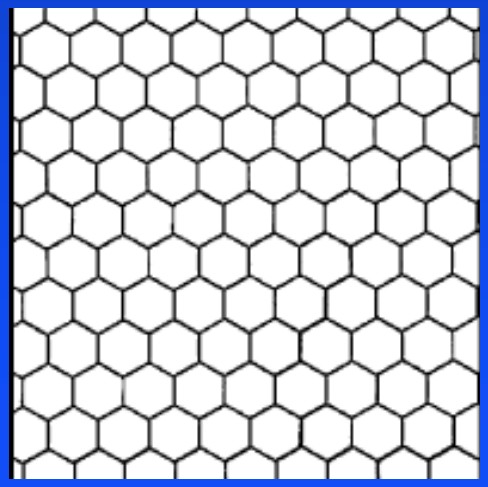
Morphometric Analysis

Morphometric Measures

- Coefficient of Variation (CV)
  - » A measure of variation in cell area
  - » High CV = "Polymegathism"



- Percent Hexagonality (%HEX)
  - » A measure of regularity of cell shape
  - » Low %HEX = "Pleomorphism"



Coefficient of Variation

24-Month Consistent Cohort of IMT-Implanted Eyes (n=153)

CV	Preop	3 Month	6 Month	9 Month	12 Month	18 Month	24 Month
Mean (SD)	34.23 (4.79)	33.21 (4.36)	33.66 (3.99)	33.26 (4.92)	33.19 (5.17)	33.38 (4.69)	33.50 (5.56)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≤ 45	147 (96.1%)	150 (98.0%)	151 (98.7%)	150 (98.0%)	149 (97.4%)	151 (98.7%)	150 (98.0%)
> 45 (Stress)	6 (3.9%)	3 (2.0%)	2 (1.3%)	3 (2.0%)	4 (2.6%)	2 (1.3%)	3 (2.0%)

Hexagonality

24-Month Consistent Cohort of IMT-Implanted Eyes (n=154)

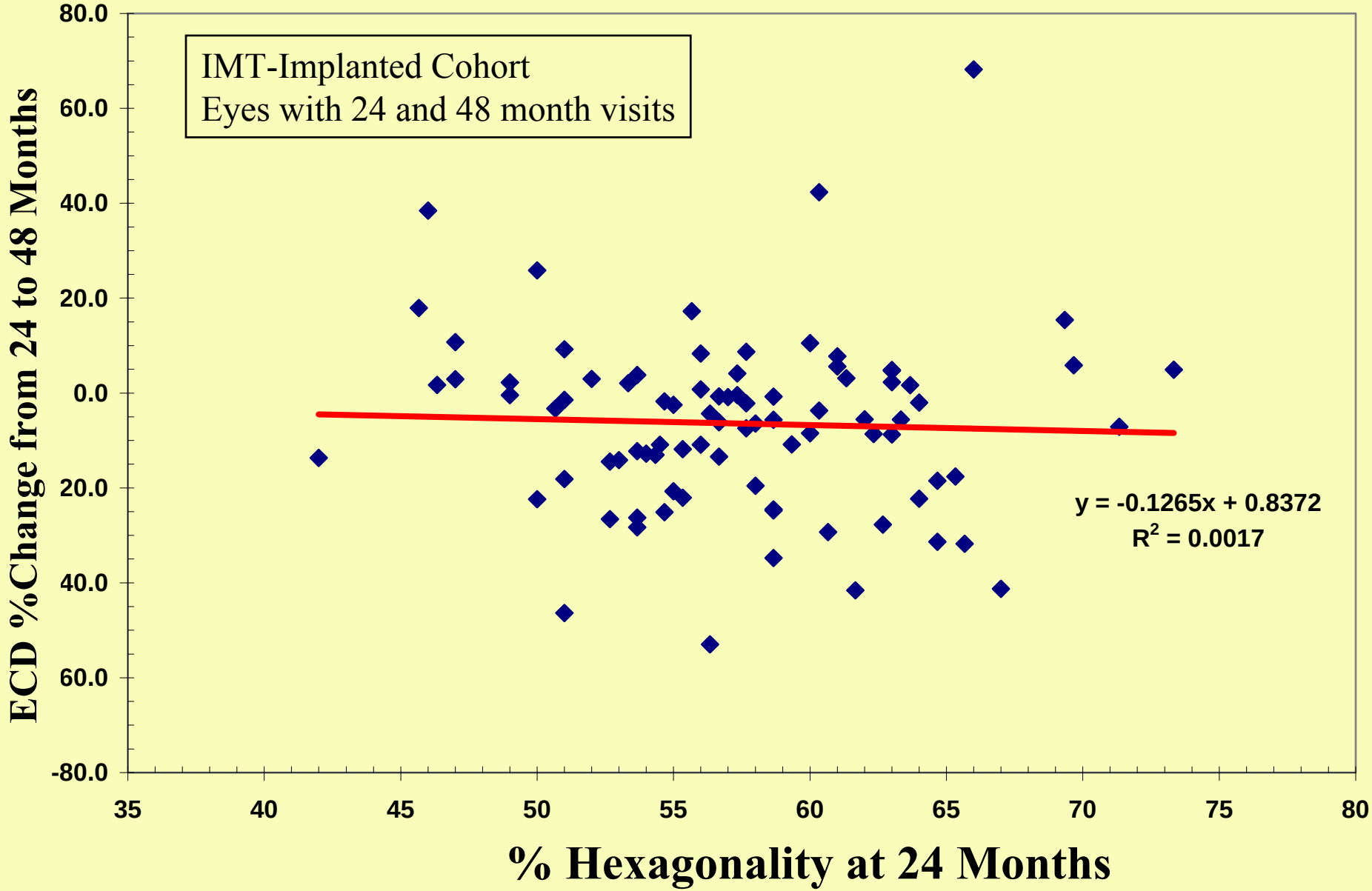
% Hexagonality	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Mean (SD)	59.67 (6.04)	56.57 (5.79)	56.61 (5.72)	57.60 (5.93)	58.52 (5.83)	57.48 (7.18)	57.10 (6.82)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 45	151 (98.1%)	147 (95.5%)	150 (97.4%)	153 (99.4%)	151 (98.1%)	149 (96.8%)	147 (95.5%)
< 45 (Stress)	3 (1.9%)	7 (4.5%)	4 (2.6%)	1 (0.6%)	3 (1.9%)	5 (3.2%)	7 (4.5%)

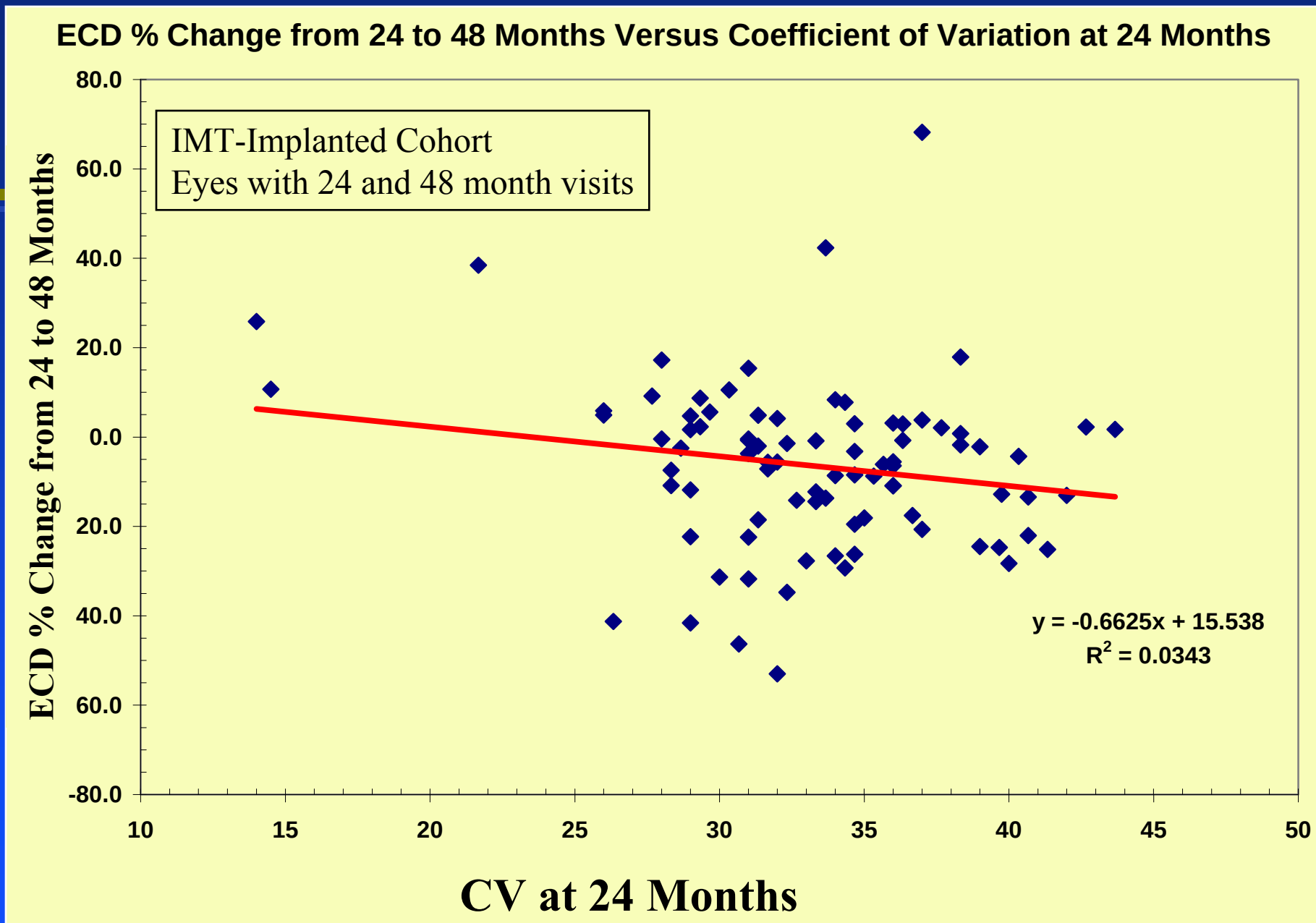
Morphometric Data and Stability of ECD in IMT Study

In interpretation of the morphometric analyses, the following should be considered:

- No morphometric data are available for the corneal periphery
- Mean ECD continued to drop significantly after 24 months postoperatively. (e.g., 6% in 86 IMT eyes with visits available at 24 and 48 months)
- Several new incidents of corneal edema continued to occur well after the initial surgery
- CV and %Hexagonality seem to show little predictive value

ECD % Change from 24 to 48 Months Versus Percent of Hexagonality at 24 Months




ECD % Change from 24 to 48 Months Versus Coefficient of Variation at 24 Months
IMT-Implanted Cohort
Eyes with 24 and 48 month visits
y = -0.6625x + 15.538
R2 = 0.0343
ECD % Change from 24 to 48 Months
CV at 24 Months
80.0
60.0
40.0
20.0
0.0
20.0
40.0
60.0
-80.0
10
15
20
25
30
35
40
45
50

Risk of Corneal Edema

Late Corneal Edema (≥ 3 months postop)

- Late corneal edema: observed in 13 eyes
  - 1 case in non-implanted eye (related to choroidal hemorrhage during surgery)
- 12 cases in IMT-Implanted: 10 of the 12 were observed at 24 months or later.
  - 3 of the 12 in IMT-Implanted were Reported Resolved:
    - **026-202, 11-203** : Etiology believed by medical monitor to be inflammatory in nature.
    - **012-212**: Reported "resolved" after duration of 196 days. However, CCT remains increased from baseline (unresolved at last report)

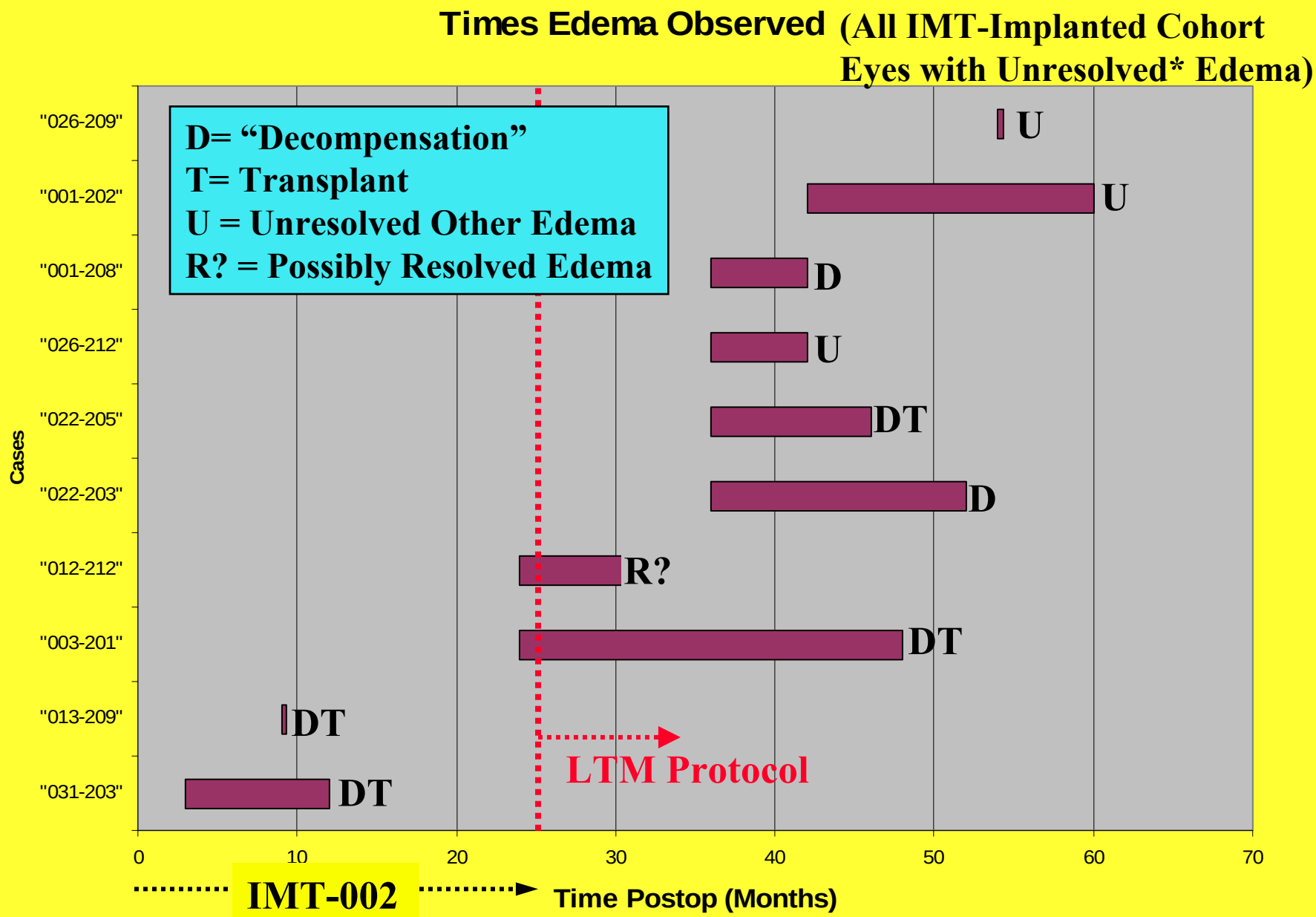
Unresolved Corneal Edema

- 9 IMT-Implanted Eyes with Unresolved Corneal Edema (at last available visit)
  - 6 cases reported as "decompensations"
    - 4 of these had transplants (2 of these had the device explanted)
  - 3 additional cases reported as unresolved corneal edema (all with low ECDs)

Proportion of Eyes with Unresolved Corneal Edema (or Decompensation) at Last Available Observation

Subset	Total Number of Eyes At Preop	Number of Eyes with Unresolved Edema	% of Eyes with Unresolved Edema	95% Confidence Interval
All IMT-Implanted Eyes	206	**9‡**	**4.4%‡**	(2.0% - **8.1**%)
"Guttata-Free, Large ACD" Sub-Cohort	112	2 (1Decomp)	1.8%	(2.2% - **6.3**%)
"Sub-Cohort A" (≥65 yrs; cornea-trained; Guttata-free, ACD≥3)	33	2 (1Decomp)	6.1%	(0.7% - **20.2**%)

‡Does not count 012-212 reported with resolution of edema, but CCT remained increased



* Includes case 012-212: reported with resolution of edema, but CCT remained increased.

Risk of Low Endothelial Cell Density at Last Observation

Observed Proportion of Eyes with "Last Visit ECD" < 750 cells/mm^2 (Last Visit Carried Forward Analysis)

Subset	Total Number of Eyes At Prop	Number of Eyes with Final ECD ≤ 750 cells/mm^2	% of Eyes with Final ECD ≤ 750 cells/mm^2	95% Confidence Interval
All IMT-Implanted Eyes	206	**19***	**9.2%**	5.6% – **14.0%**
"Guttata-Free, Large ACD" Sub-Cohort	112	7	6.3%	2.5% – **12.5%**
"Sub-Cohort A" (≥65 yrs; cornea-trained; Guttata-free, ACD≥3)	33	2	6.1%	0.7% – **20.2%**

* 1 Eye had ECD < 750 only AFTER IMT Explantation

*Fellow Eyes had 2 of 206 (1%) with final ECD ≤ 750 cells/mm^2

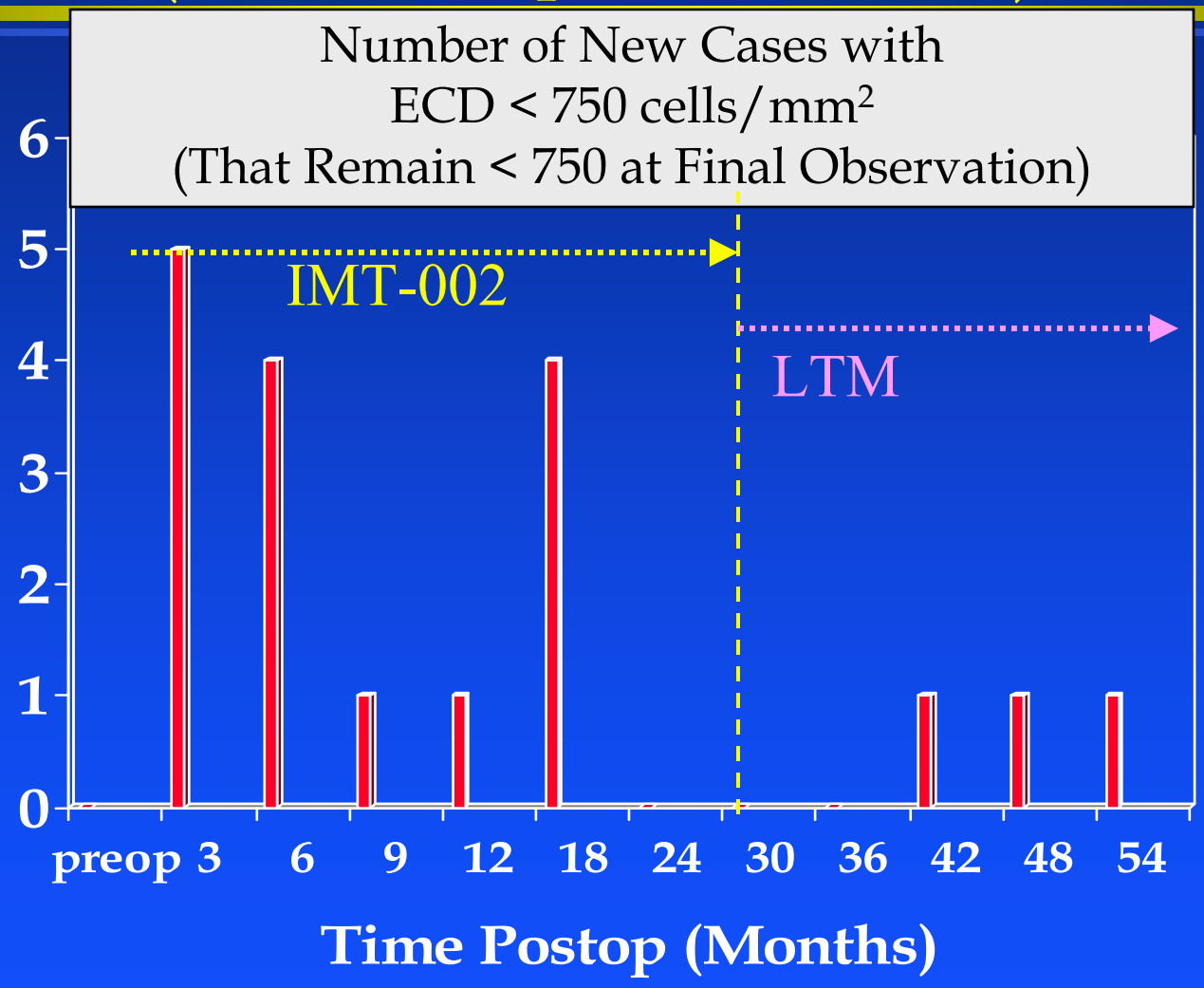
Observed Proportion of Eyes with "Last Visit ECD" < 1000 cells/mm2 (Last Visit Carried Forward Analysis)

Subset	Total Number of Eyes at Preop	Number of Eyes with Final ECD ≤ 1000 cells/mm^2	% of Eyes with Final ECD ≤ 1000 cells/mm^2	95% Confidence Interval
All IMT-Implanted Eyes	206	**31***	**15.0%**	10.5% – **20.7%**
"Guttata-Free, Large ACD" Sub-Cohort	112	11	9.8%	5.0 – **16.9%**
"Sub-Cohort A" (≥65 yrs; cornea-trained; Guttata-free, ACD≥3)	33	2	6.1%	0.7% – **20.2%**

* 1 Eye had ECD < 1000 only AFTER IMT Explantation

*Fellow Eyes had 5 of 206 (2%) with final ECD ≤ 1000 cells/mm^2

Times When Cases Dropped to ECD < 750 cells/mm^2 (All IMT-Implanted Cohort)



*Does not include 1 case with final ECD <750 that appeared only AFTER IMT explantation.

Relationship Between Low ECD and Some Serious Adverse Events (All IMT-Implanted Cohort; n=206)

SUBJECT (Total Cases: 41)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	…	…	40	41
Unresolved Edema/Decomp (Total Cases: 9)	X	X	X	X	X	X	X	X	X																
Explants (Total Cases: 12)				X	X					X	X	X	X	X	X	X	X	X	X						
Final ECD < 1000 (Total Cases: 31)	X	X	X	X	X		X	X	X								X			X	X	…	…	X	X

Panel Question

The sponsor has presented specular microscopy data from IMT-002 and IMT-002-LTM. Morphometric analyses were collected under both protocols. Considering the surgery related decline in ECD, the chronic rate of ECD loss, the morphometric analyses, the proportion of eyes that declined to low ECD levels, and the number of cases of decompensation and late corneal edema, please address the following:

Panel Question (*cont'*.)

a. Please discuss whether the ECD and morphometric data provide reasonable assurance that the long term risk of corneal decompensation will be acceptable for the intended population.

b. Please discuss whether the specular microscopy data provide sufficient characterization of long term ECD trends.

Thank You

Statistical Comments for Implantable Miniature Telescope

Yao Huang
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Center for Devices and Radiological Health

Outline

- Analysis of the safety endpoint
- Caveats about data extrapolation
- Issues on post hoc subgroup analysis
- Summary

Analysis of Safety Endpoint

- Mean percentage ECD loss at 12 months:

  H0: % ECD Loss $\geq$ 17%

  - All IMT-implanted eyes:
    - N=206
    - Observed rate is 25%
    - 95% CI: (22%, 28%)
  - The subgroup proposed by the sponsor for indication:

    Age $\geq$ 65, ACD $\geq$ 3.0, non-Guttata
    - N=99
    - Observed rate is 23%
    - 95% CI: (19%, 28%)

Biexponential Model

$$ECD(t) = pe^{-at} + qe^{-bt}$$

where

ECD(t) = Endothelial Cell Density at time t

$p \times e^{-at}$ --- "rapid" rate of loss associated with surgery

$q \times e^{-bt}$ --- "slow" rate of loss after stabilization

t = time from implantation

Estimated Annual ECD loss Based on Biexponential Model

Annual ECD Loss	Estimate	90% C.I.
All Implanted Eyes (n=206)	4.8%	(3.4%, 6.2%)
"Guttata-Free, ACD ≥ 3.0" Sub-Cohort (n=112)	3.8%	(2.0%, 5.5%)

Estimates of the long-term rate of loss do not appear to differ statistically.

Sponsor's estimates using 48-month data.

Proposed Grid of Preoperative ECD Required for IMT Implantation
Based on IMT-Implanted Eyes without Guttata and With ACD ≥ 3.0 mm

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

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

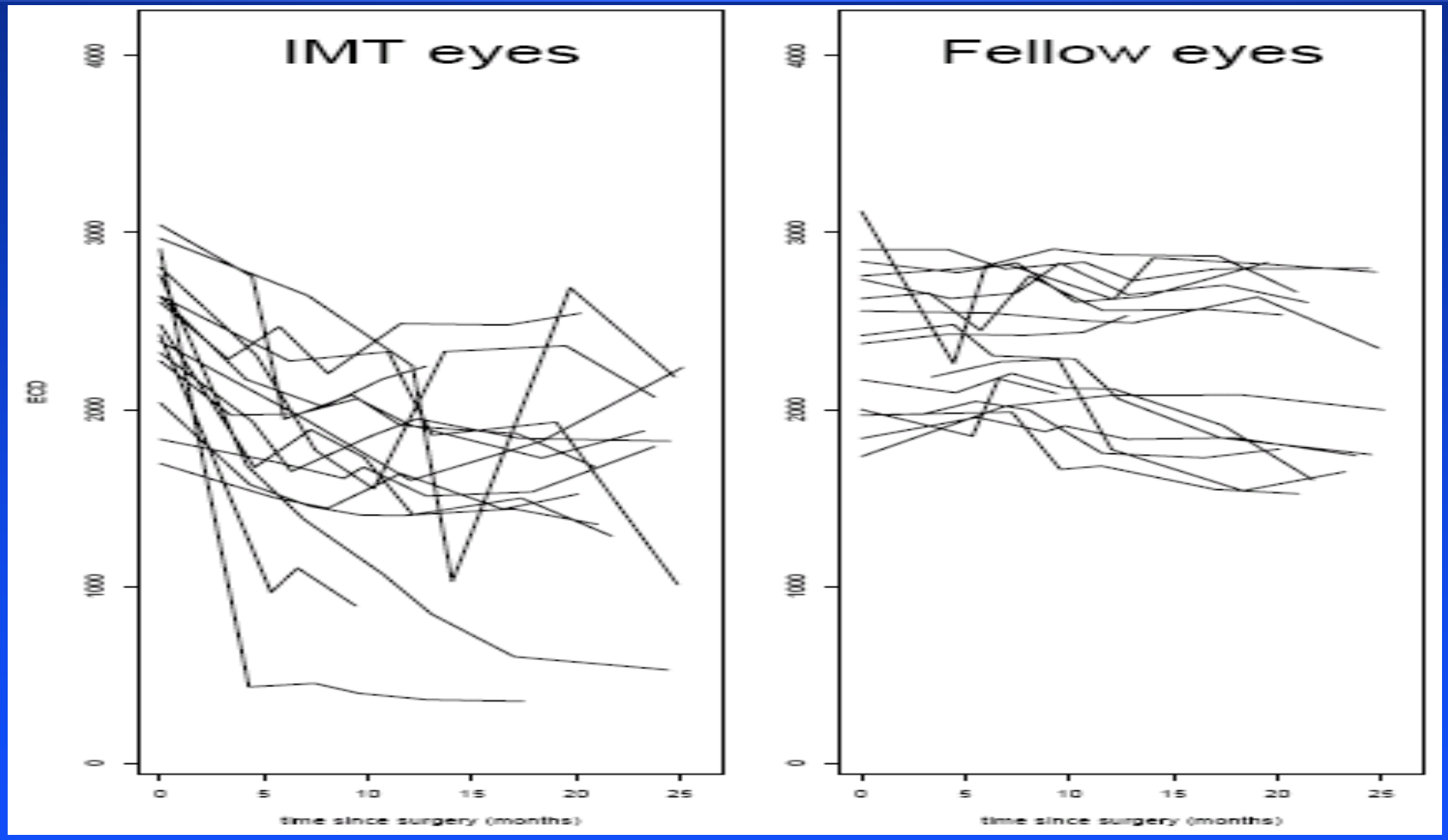
Cell density at end of life

Years post implant when cell density reaches 500 cell per mm2

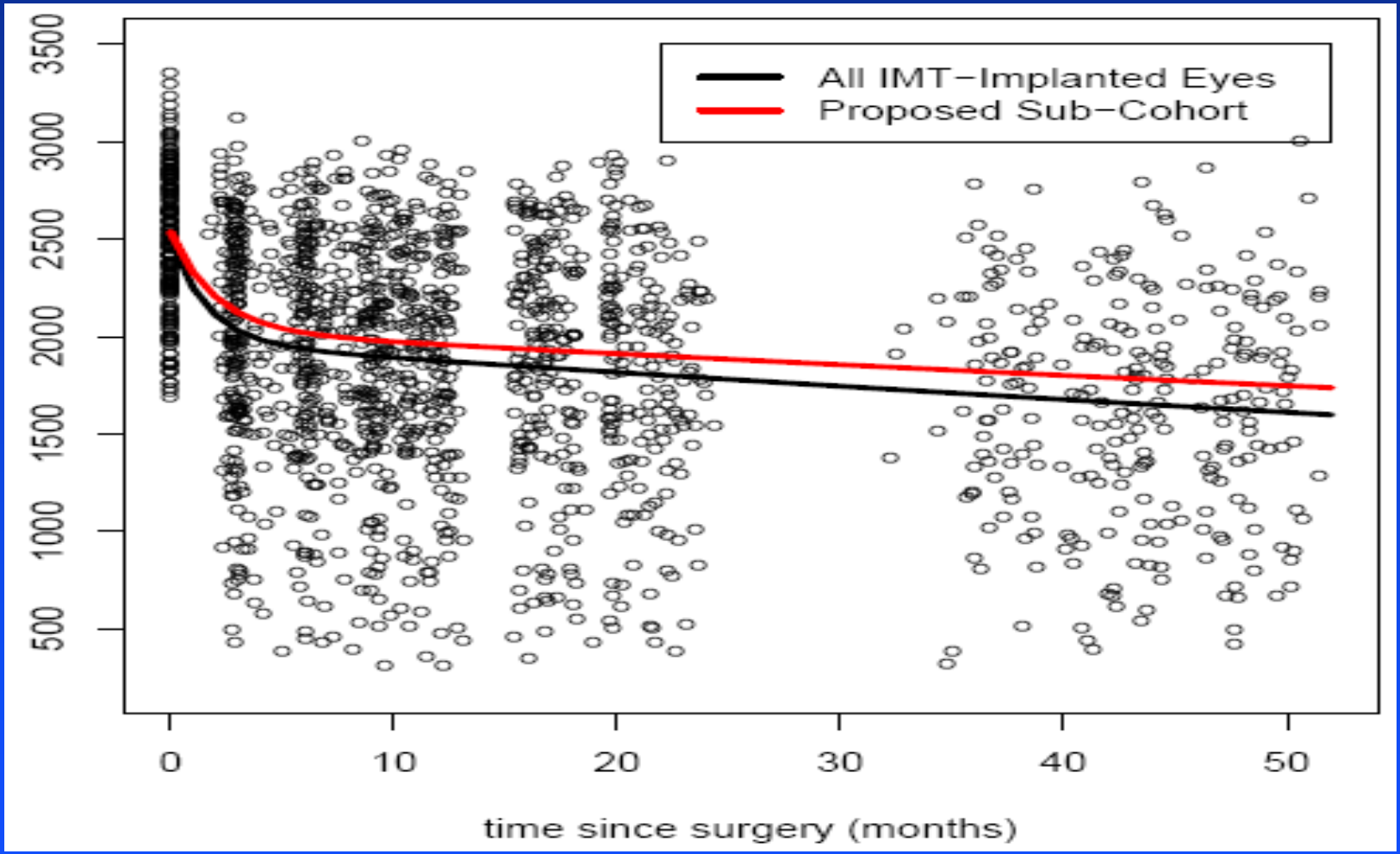
Caveats Regarding Extrapolation

- Extrapolation to 20-25 years based on 48-month data
- Extrapolation beyond the range of the data should always be only done with extreme caution:
  - Current model may not fit outside the data range
  - Sensitive to variability in estimates
  - Sensitivity increases the further we extrapolate

Distribution of ECD Data



Biexponential Model Fit to 48-mth Data



Statistical Limitations on Subgroup Analysis

- Unplanned post hoc subgroup analyses should be conducted with caution.
- Repeatability is an issue:
  - Will we see the same differences if we do the experiment again?
- Are there clinically meaningful differences?
- If so, still need to address repeatability of the difference between subsets.

Summary

- The study did not meet the safety endpoint of ECD loss at 12 months. Nor did the selected subgroup.
- Caution is needed for data extrapolation.
- Results from the subgroup may not be repeatable.

Panel Question

- In an attempt to identify the characteristics of a sub-group with an improved safety profile, the sponsor performed multiple sub-group analyses. Considering the statistical issues associated with these analyses, please discuss whether the data constitute valid scientific evidence for evaluation of safety of this device.

Thank You !

P050034
Implantable Miniature Telescope IMT®

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Center for Devices and Radiological Health

Ophthalmic Devices Panel Meeting
March 27, 2009

Outline

- Postmarket Concerns
- Overview of Sponsor's Post-Approval Study (PAS) Proposal
- Assessment of Proposed PAS Protocol
- PAS Issues for Panel Discussion

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean that FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Principles for PAS

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Need for Post-Approval Studies

Gather postmarket information

- Longer-term performance
- Real world experience
  (Safety and Effectiveness)
- Effectiveness of training programs
- Sub-group performance

Implantable Miniature Telescope IMT® Postmarket Concerns

The risk of the following outcomes when the IMT is used in the 'real world'* and long-term are unknown:

- Risk of ECD losses that fall below the threshold of where corneal function is irreversibly compromised

  (as a result of the combined effect of surgery-related decline during IMT implantation and the chronic age-related ECD decline)

*'Real World': in the postmarket environment, where implantations are performed by a diverse group of anterior segment surgeons

Implantable Miniature Telescope IMT® Postmarket Concerns (*cont'*.)

- Risk of failed implantations and potential sequelae related
- Risk of removals, replacements, repositioning and device failures of the IMT after successful implantations
- Risk of the improvements in visual acuity after IMT implantation not being sustained long-term

Sponsor's PAS Proposals: 2006 vs. 2009 Panel Meeting

- 2006
  - IMT-002-LTM Protocol ("Guttata-free, Large ACD" Sub-cohort): Follow-up of IMT IDE Study cohort through 5 years post-implantation
  - IMT-PA-01 Protocol: 60 month follow-up study of 5,000 newly enrolled IMT Patients
- 2009
  - **The Sponsor believes that a PAS is not necessary** because most subjects in the "Guttata-free, Large ACD" Sub-cohort have had 48-month exam.
  - If the PMA is approved and a PAS is recommended, Sponsor proposes to conduct IMT-002-LTME study to follow the "All IMT-Implanted" cohort for 2 additional years, (for a total of **7 years)** post implantation.
    (Protocol submitted Feb. 6, 2009)

Overview of IMT-002-LTME
Long-term Monitoring Study Extended

Objective	• Monitor the long-term safety of the IMT in the "All IMT-Implanted" cohort
Study Design	• prospective study; non-comparative descriptive study
Population & Study Size	• Subjects in "All IMT-Implanted" cohort (including but not limited to "Guttata-free, Large ACD" Sub-cohort) • Study size not specified
Duration of Follow-up	• 2 years (for a total of 7 years post-implantation)
Follow-up Examinations	• Post-implant at 72 and 84 months. If study entry falls outside follow-up window, then also at study entry

Overview of IMT-002-LTME Long-term Monitoring Study Extended

Primary Endpoint	• Not specified
Clinical Parameters	• Endothelial cell density (ECD) (implanted and fellow eyes) • Posterior capsular opacification • Intraocular pressure (IOP) • Best corrected distance visual acuity (implanted and fellow eyes) • Device Failures • Ocular complications and ocular adverse events • Pachymetry • Slit lamp examination
Hypotheses	• Not specified
Statistical Analysis	• Descriptive techniques using 95% CI

FDA Assessment of PAS Protocol

Study Design

a prospective study; non-comparative descriptive study

- ECD and best corrected distance visual acuity will be assessed in fellow eyes; % change in ECD is one the clinical parameters
- Study is comparative since fellow eyes will be used as controls for IMT implanted eyes

FDA Assessment of PAS Protocol

Population and Study Size

Subjects in the "All IMT-Implanted" Cohort (including but not limited to the "Guttata-Free, Large ACD" Sub-Cohort)

- Loss to follow-up/Refusals on enrollment bias
- Loss to follow-up during PAS and potential bias
- If subject was in the "All IMT-Implanted" Cohort but not in the "Guttata-Free, Large ACD" Sub-Cohort: 36 and 48 months data will be missing

Issue: Potential bias and generalizability of results to eligible patient population under conditions of use.

FDA Assessment of PAS Protocol

Population and Study Size (Continued)

Subjects in the "All IMT-Implanted" Cohort: (including but not limited to the "Guttata-Free, Large ACD" Sub-Cohort)

- Population for 2009 proposed indication: Non-guttata, age 65 or older, Anterior Chamber Depth ≥3.00 mm

  Issue: Generalizability of results to eligible patient population in the postmarket environment

FDA Assessment of PAS Protocol

Population and Study Size (continued)

Study size not specified

- Must be able to detect clinically significant ECD changes after 7 years
- Primary safety endpoints should drive study size/statistical power calculations

FDA Assessment of PAS Protocol

Primary Endpoints
not specified

- ECD variables
  - Change in ECD (from baseline and between consecutive post-op visits)
  - % change in ECD (from baseline and between consecutive post-op visits)
  - Change in ECD between consecutive post-operative visits
- Relative risks (RR) of corneal edema (any and late-occurring), and corneal decomposition based on comparison of IMT and fellow eyes

FDA Assessment of PAS Protocol

Follow-up Examinations

Study entry, 72 months, 84 months

12 month Interval between follow-up visits

- IMT-002-LTM protocol interval between follow-up was 6 months.
- Consider potential clinical consequences of not detecting a clinically significant ECD change that occurs during the 12 month interval.

FDA Assessment of PAS Protocol

Hypotheses

no hypotheses specified

- Comparison of ECD changes over time and between IMT eyes and fellow eyes
- A statistical hypothesis increases the scientific rigor and public health utility of the post-approval study

FDA Assessment of PAS Protocol

Statistical Analysis

Descriptive techniques using 95% CI

- Calculation of Relative Risks (for ECD below threshold, corneal edema, etc.)
- Device survival analyses
- Plan for evaluating and handling missing values, and sensitivity analysis to evaluate impact of missing values on study results

Panel Question

At the time of the July 2006 panel meeting, the sponsor submitted protocols for two post-approval studies (PASs):

(1) Five Year Follow-up of IMT-002-LTM Patients – A Long-Term Monitoring Study of IMT-002 Patients and

(2) A Prospective Multicenter Post-approval Study of the Implantable Miniature Telescope (IMT Patients with Central Vision Impairment Associated with Age Related Macular Degeneration (a follow-up study of newly enrolled patients who receive the IMT after approval out to 5 years)).

Panel Question (*cont'.*)

On February 6, 2009 the sponsor indicated that they do not believe a PAS is warranted at this point because most subjects followed in IMT-002 LTM (5 year study) have reached the 4 year follow-up examination.

However, to address the possibility that a PAS may be recommended, the sponsor submitted a protocol to follow some of the subjects implanted under IMT-002 for two additional years.

Panel Question (*cont'*.)

a. Given the currently available safety and effectiveness data, and if this device is approved, is a PAS recommended?

b. If a PAS is recommended, does the panel agree with the sponsor's proposal to follow currently implanted patients to 7 years? If not, what do you recommend?

c. Is a PAS of newly enrolled patients needed to evaluate the performance of the device when used in the post market environment?

Panel Question (*cont'*.)

d. If a PAS is recommended, what do you recommend for the following PAS elements?

- the objectives
- clinical endpoints (i.e., what to measure, and the method and frequency of these evaluations), including the need to assess the rate of endothelial cell density loss over time.
- the clinically tolerable rate of severe adverse events, such as corneal decompensation-induced device extraction and corneal transplant
- duration of follow-up of study subjects
- other specific issues you would like to be addressed in the PAS

Questions?