



December 10, 2008

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

RE: P050034 – Amendment 18
VisionCare Ophthalmic Technologies Implantable Miniature Telescope
IMT (by Dr. Isaac Lipshitz)TM

Dear Sir or Madam,

Please find enclosed three (3) copies of Amendment 18 to P050034, for the Implantable Miniature Telescope (IMT).

This amendment provides responses to information requested by the Division of Ophthalmic and ENT Devices (DOENTD). These responses were submitted via email to Gene Hilmantel, O.D., M.S. on November 19, 2008, November 21, 2008, and December 2, 2008

Each original email request is followed by VisionCare's response, with the requested information.

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

Sincerely,

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



P050034

**AMENDMENT 018
VISIONCARE OPHTHALMIC TECHNOLOGIES
IMPLANTABLE MINIATURE TELESCOPE™
(IMT BY DR. ISAAC LIPSHITZ)**

VOLUME I OF I

DECEMBER 10, 2008

APPLICANT

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CORRESPONDENT

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**P050034 AMENDMENT 018
VISIONCARE OPHTHALMIC TECHNOLOGIES
IMPLANTABLE MINIATURE TELESCOPE**

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ITEM 1
RESPONSE TO EMAIL DATED
NOVEMBER 19, 2008

From: Hilmantel, Gene N [mailto:gene.hilmantel@fda.hhs.gov]
Sent: Wednesday, November 19, 2008 2:55 PM
To: Judy Gordon
Cc: Calogero, Don; Lepri, Bernard; Hilmantel, Gene N
Subject: P050034 -- Accountability of implanted eyes

Judy & Alan,

Thanks for this clarification.

Can you provide me with the number of IMT-Implanted eyes in the continuation study and the accountability for these eyes? Since implanted eyes are our primary concern in the continuation study, this will help me assess the strength of follow-up on implanted eyes.

Gene

Gene Hilmantel, OD, MS

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Food and Drug Administration
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Rockville, MD 20850
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Fax: (240) 276-4234

From: Judy Gordon [mailto:judy@clinregconsulting.com]
Sent: Friday, November 21, 2008 3:09 AM
To: 'Hilmantel, Gene N'
Cc: 'Calogero, Don'; 'Lepri, Bernard'; 'Allen Hill'
Subject: RE: P050034 -- Accountability of implanted eyes

Dear Gene,

As requested, we have prepared an accountability table for the IMT-implanted eyes in the IMT-002-LTM study. This table is immediately below. Further below in this email is the accountability table provided in Amendment 13, submitted in September 2008 – this original table presented accountability for all operated subjects enrolled in Protocol IMT-002-LTM. Thus, the IMT-implanted subjects enrolled in IMT-002-LTM represented a subset of the operated subjects, however accountability was very similar for both cohorts of patients.

Gene, let me know if you have any questions regarding this email, or if you need any additional information.

**AVAILABILITY AND ACCOUNTABILITY
 IMT-IMPLANTED SUBJECTS
 IMT-002-LTM**

Available for Analysis	n/N (%)	3/3 (100%)	75/75 (100%)	104/114 (91%)	97/117 (83%)
Discontinued - cumulative	n/N (%)			4/114 (4%)	6/117 (5%)
Deaths	n/N (%)			3/114 (3%)	5/117 (4%)
IMT removed postoperatively				1/114 (1%)	1/117 (1%)
Lost to Follow-up	n/N (%)			2/114 (2%)	9/117 (8%)
Missed Visit	n/N (%)			4/114 (4%)	5/117 (4%)
% Accountability = Available for Analysis / (Enrolled - Discontinued)		3/3 (100%)	75/75 (100%)	104/110 (95%)	97/111 (88%)

**TABLE 4 – SEPTEMBER 2008 AMENDMENT 13
 AVAILABILITY AND ACCOUNTABILITY
 OPERATED SUBJECTS
 IMT-002 –LTM**

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%)

Best regards,
 Judy

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**ITEM 2:
RESPONSE TO EMAIL DATED
NOVEMBER 21, 2008**

From: Calogero, Don [mailto:don.calogero@fda.hhs.gov]

Sent: Friday, November 21, 2008 9:33 AM

To: Judy Gordon

Cc: Allen Hill

Subject: IMT Meeting

Importance: High

Judy,

We had a meeting of the review team for the IMT PMA yesterday and it was concluded that some additional tables are necessary before we can schedule a panel meeting. We need a set of tables characterizing safety and effectiveness for the subset of subjects that Vision Care has determined to be best-suited for this device; this is the cohort of subjects that meet all the criteria in the indications for use and in the labeling (subjects of corneal-trained surgeons, without guttata, ACD > 3mm, etc.).

We believe that it will be important for the final labeling and also for the panel members to have this information for their deliberations. We will schedule a panel meeting as soon as we are able to complete a review of these new tables.

As the post approval study (PAS) protocol is necessary at the time of the panel meeting, please provide an updated PAS protocol based on previous FDA recommendations.

We will continue to work interactively with you as quickly as possible to provide the best possible panel package.

Regards,

Don

From: Judy Gordon [mailto:judy@clinregconsulting.com]
Sent: Wednesday, December 03, 2008 1:58 PM
To: 'Calogero, Don'
Cc: 'Allen Hill'
Subject: RE: IMT Meeting

Dear Don,

As follow-up to your email of November 21, I am attaching a set of tables as well as Section 6 of Amendment 13 (originally submitted to FDA as Amendment 14 to P050034), which is pertinent to the risk reduced population.

It seems to us that the tables you have requested are a little unusual, in the sense that efficacy is usually presented for the entire efficacy population and then any smaller group pre-specified in the efficacy analysis plan. Then, once efficacy is established, but only then, everyone (the sponsor, CDRH, the panel) looks to see whether the benefit-risk calculation can be improved by the kinds of labeling suggestions (contraindications, warnings, precautions, etc.) we have provided in our draft labeling for the IMT. So as shown in the draft labeling we submitted with our September amendment, A014, and in the various tables and information we have submitted since then, efficacy is shown in the study population, and then risk reduction is further analyzed in various ways (e.g, non-guttata, ACD greater than 3.0, implantation performed by corneal specialist, ECD at baseline per the grid). We had not thought to link efficacy to risk reduction in those specific populations, and don't believe it is really appropriate to do that as a conceptual matter.

Nevertheless, to speed things along, we have prepared tables as requested, in which efficacy is shown for the various risk-reduced populations. The tables are attached. As you can see, efficacy is essentially the same in these populations as it is in the overall study population, which is useful confirmation that reducing risk doesn't reduce efficacy.

Best regards,
Judy

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SECTION 1

VISUAL ACUITY

ENDOTHELIAL CELL DENSITY LOSS

PRESERVATION OF BEST CORRECTED VISUAL ACUITY

FIGURE 1

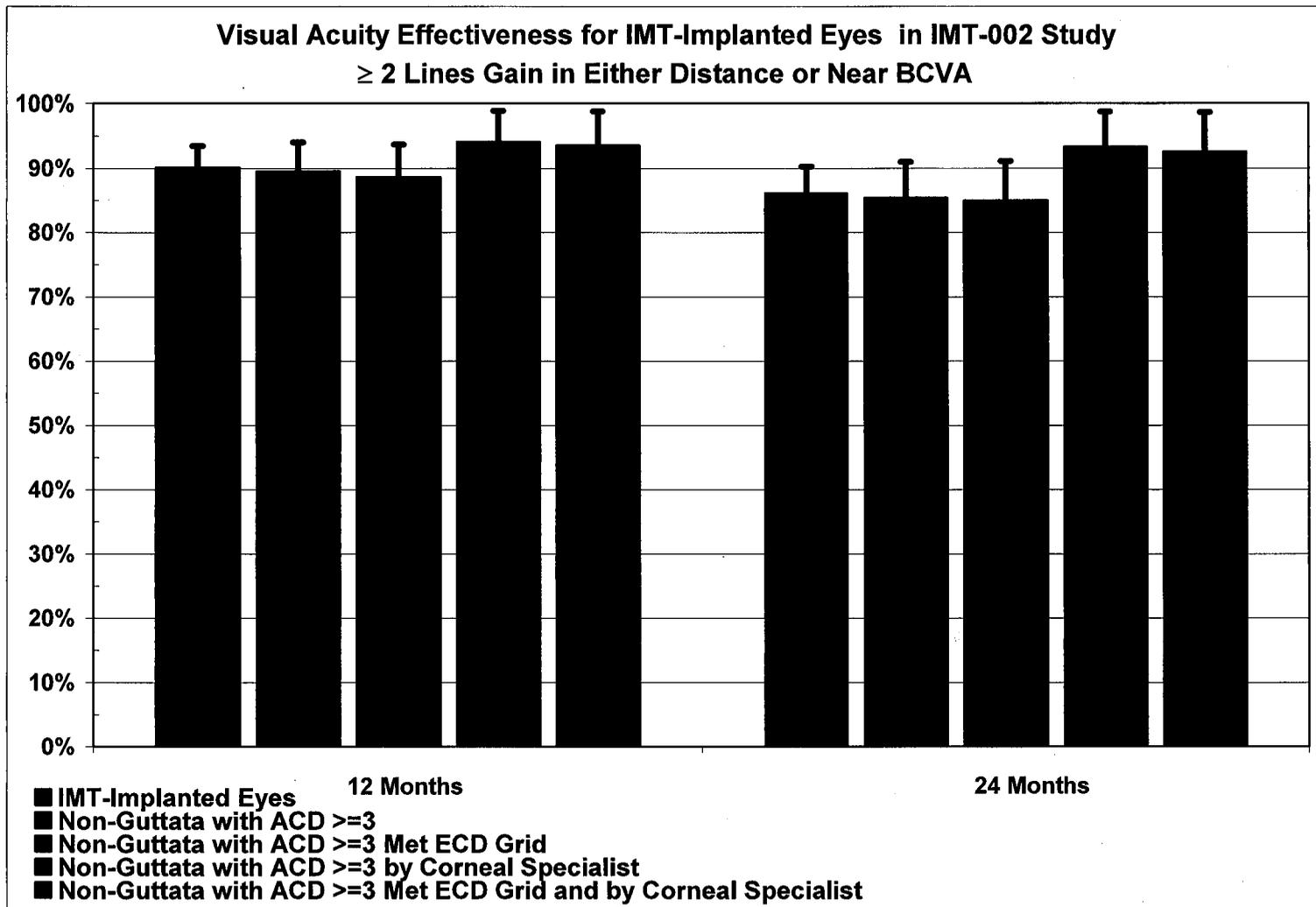


TABLE 1
VISUAL ACUITY EFFECTIVENESS
IMT-IMPLANTED EYES IN IMT-002 STUDY AND RISK REDUCED POPULATIONS
≥ 2 LINES GAIN IN EITHER DISTANCE OR NEAR BCVA AND
≥ 2 LINES GAIN OF BCDVA AND BCNVA

Number of eyes	192	105	88	34	31	173	96	80	30	27
	<i>173 (90.1%)</i>	<i>94 (89.5%)</i>	<i>78 (88.6%)</i>	<i>32 (94.1%)</i>	<i>29 (93.5%)</i>	<i>149 (86.1%)</i>	<i>82 (85.4%)</i>	<i>68 (85.0%)</i>	<i>28 (93.3%)</i>	<i>25 (92.6%)</i>
≥2 lines gain of BCDVA and BCNVA	141 (73.4%)	77 (73.3%)	62 (70.5%)	27 (79.4%)	24 (77.4%)	114 (65.9%)	64 (66.7%)	50 (62.5%)	22 (73.3%)	19 (70.4%)

TABLE 2
MEAN ENDOTHELIAL CELL DENSITY AND MEAN PERCENT CHANGE IN ENDOTHELIAL CELL DENSITY
IMT-IMPLANTED EYES IN IMT-002 STUDY

N	206	193	198	190	186	180	171
Mean (SD) ECD	2496 (354)	1995 (585)	1937 (580)	1891 (572)	1871 (592)	1878 (618)	1808 (596)
Mean (SD) ECD % Change		-20% (21%)	-22% (21%)	-24% (21%)	-25% (21%)	-25% (22%)	-28% (22%)
RISK REDUCTION POPULATIONS							
N	112	102	107	103	103	100	95
Mean (SD) ECD	2534 (329)	2080 (556)	2046 (525)	1968 (534)	1935 (530)	1935 (567)	1907 (548)
Mean (SD) ECD % Change		-18% (21%)	-19% (19%)	-22% (20%)	-24% (20%)	-24% (21%)	-25% (20%)
N	94	85	89	86	86	83	79
Mean (SD) ECD	2610 (285)	2115 (557)	2081 (524)	2010 (531)	1975 (533)	1973 (563)	1948 (551)
Mean (SD) ECD % Change		-19% (21%)	-20% (19%)	-23% (20%)	-24% (20%)	-25% (21%)	-26% (20%)
N	36	31	36	32	33	31	30
Mean (SD) ECD	2488 (288)	2128 (550)	2099 (493)	2047 (514)	2007 (511)	2024 (518)	2024 (483)
Mean (SD) ECD % Change		-14% (21%)	-15% (18%)	-17% (20%)	-19% (20%)	-19% (19%)	-19% (18%)
N	32	28	32	29	30	28	27
Mean (SD) ECD	2532 (262)	2147 (568)	2131 (504)	2068 (524)	2023 (525)	2052 (533)	2062 (485)
Mean (SD) ECD % Change		-14% (22%)	-15% (19%)	-18% (20%)	-20% (21%)	-19% (20%)	-18% (19%)

TABLE 3
PRESERVATION OF BEST CORRECTED VISUAL ACUITY
IMT-IMPLANTED EYES IN IMT-002 STUDY AND RISK REDUCED POPULATIONS
PERCENT OF EYES WITH > 2 LINES LOSS OF BCDVA AND NO CHANGE/LOSS OF BCNVA
OR > 2 LINES LOSS OF BCNVA AND NO CHANGE/LOSS OF BCDVA

N	200	201	195	193	179	173
n (%)	6 (3.0%)	9 (4.5%)	9 (4.6%)	10 (5.2%)	8 (4.5%)	11 (6.4%)
RISK REDUCTION POPULATIONS						
N	107	108	105	105	100	96
n (%)	4 (3.7%)	6 (5.6%)	5 (4.8%)	6 (5.7%)	5 (5.0%)	7 (7.3%)
N	90	90	88	88	84	80
n (%)	4 (4.4%)	6 (6.7%)	5 (5.7%)	6 (6.8%)	5 (6.0%)	7 (8.8%)
N	34	36	33	34	32	30
n (%)	2 (5.9%)	1 (2.8%)	2 (6.1%)	1 (2.9%)	1 (3.1%)	1 (3.3%)
N	31	32	30	31	29	27
n (%)	2 (6.5%)	1 (3.1%)	2 (6.7%)	1 (3.2%)	1 (3.4%)	1 (3.7%)

SECTION 2

QUALITY OF LIFE – VFQ-25

ENDOTHELIAL CELL % HEXAGONALITY AND COEFFICIENT OF VARIATION

CENTRAL CORNEA THICKNESS

ENROLLMENT BY SITE

TABLE 4
VFQ CHANGE FROM BASELINE AT 12 MONTHS
IMT-IMPLANTED EYES ENROLLED IN IMT-002 STUDY

General Vision	N	193	105	88	34	31
	Mean (SD)	14.09 (21.99)	12.76 (21.51)	11.82 (20.26)	13.53 (21.86)	12.26 (19.78)
Near Activities	N	193	105	88	34	31
	Mean (SD)	11.16 (19.28)	9.80 (19.09)	9.56 (18.33)	11.76 (18.48)	11.29 (17.82)
Distance Activities	N	193	105	88	34	31
	Mean (SD)	7.90 (24.68)	5.87 (22.90)	3.22 (21.25)	5.39 (24.91)	3.23 (21.75)
Social Functioning	N	193	105	88	34	31
	Mean (SD)	8.61 (26.63)	6.79 (24.21)	5.26 (22.80)	6.25 (25.79)	4.44 (24.91)
Dependency	N	193	105	88	34	31
	Mean (SD)	10.02 (27.53)	9.60 (25.21)	9.66 (24.76)	7.35 (27.51)	6.45 (26.33)
Mental Health	N	193	105	88	34	31
	Mean (SD)	9.29 (22.54)	8.93 (21.44)	8.45 (20.52)	9.74 (24.91)	7.26 (21.96)
Role Difficulties	N	193	105	88	34	31
	Mean (SD)	7.25 (26.13)	3.93 (25.44)	2.98 (24.42)	5.51 (25.96)	5.65 (25.99)
Color Vision	N	185	102	85	33	30
	Mean (SD)	3.38 (24.56)	3.19 (24.29)	3.24 (22.09)	3.03 (23.18)	1.67 (23.61)
Peripheral Vision	N	190	103	86	34	31
	Mean (SD)	-5.92 (30.99)	-7.28 (32.96)	-6.98 (33.79)	-5.88 (35.92)	-6.45 (37.06)
Driving	N	179	99	85	30	28
	Mean (SD)	-0.52 (7.00)	-0.66 (7.45)	-0.76 (8.04)	-1.83 (8.25)	-1.96 (8.54)
Ocular Pain	N	193	105	88	34	31
	Mean (SD)	0.58 (18.85)	-1.31 (18.58)	-1.70 (19.71)	-1.10 (21.40)	-1.21 (21.49)
Overall	N	193	105	88	34	31
	Mean (SD)	6.03 (14.41)	4.68 (13.34)	4.09 (12.50)	5.06 (14.15)	3.93 (13.17)
General Health	N	193	105	88	34	31
	Mean (SD)	-5.05 (21.73)	-5.95 (21.24)	-5.68 (22.34)	-6.62 (20.70)	-6.45 (21.38)

TABLE 5
ENDOTHELIAL CELL % HEXAGONALITY AND COEFFICIENT OF VARIATION
IMT-IMPLANTED EYES IN IMT-002 STUDY

N	206 ¹	193	198	190	186	180	171
Mean (SD) % Hexagonality	59.3 (5.8)	56.2 (5.5)	56.7 (5.9)	57.2 (6.0)	58.0 (5.9)	57.5 (6.8)	57.4 (6.9)
Mean (SD) CV	34.4 (4.7)	33.5 (4.6)	33.8 (4.1)	33.5 (4.8)	33.4 (5.1)	33.4 (4.8)	33.6 (5.5)
RISK REDUCTION POPULATIONS							
N	112	102	107	103	103	100	95
Mean (SD) % Hexagonality	58.3 (6.0)	56.0 (5.6)	56.6 (5.8)	56.8 (6.0)	58.2 (5.3)	57.7 (5.8)	57.5 (6.3)
Mean (SD) CV	35.3 (5.1)	34.0 (4.6)	34.3 (4.3)	34.5 (4.6)	34.2 (4.7)	34.5 (4.8)	34.8 (5.3)
N	94	85	89	86	86	83	79
Mean (SD) % Hexagonality	58.1 (6.0)	55.5 (5.6)	57.0 (5.6)	56.5 (6.4)	58.1 (5.4)	57.8 (6.0)	57.0 (6.6)
Mean (SD) CV	35.5 (5.1)	34.3 (4.8)	34.6 (4.4)	34.6 (4.6)	34.4 (4.8)	34.7 (4.8)	35.1 (5.5)
N	36	31	36	32	33	31	30
Mean (SD) % Hexagonality	58.8 (6.3)	56.2 (4.9)	58.0 (5.7)	57.2 (6.4)	57.7 (5.9)	58.6 (4.8)	58.1 (7.4)
Mean (SD) CV	34.9 (5.6)	33.9 (4.7)	33.9 (4.1)	35.1 (4.2)	34.7 (4.9)	34.9 (4.7)	34.8 (4.9)
N	32	28	32	29	30	28	27
Mean (SD) % Hexagonality	58.7 (6.5)	55.7 (4.9)	58.3 (5.9)	56.8 (6.6)	57.4 (5.9)	58.5 (4.9)	57.5 (7.6)
Mean (SD) CV	35.2 (5.8)	34.2 (4.8)	34.0 (4.4)	35.4 (4.3)	35.1 (5.1)	35.3 (4.6)	35.2 (5.0)

¹ One eye did not have the CV value.

TABLE 6
CENTRAL CORNEA THICKNESS (PACHYMETRY)
IMT-IMPLANTED EYES IN IMT-002 STUDY

N	206	198	200	191	192	177	172
Mean (SD) CCT	553 (40)	552 (43)	556 (47)	554 (48)	558 (63)	554 (49)	561 (50)
Mean (SD) CCT % Change		-0% (6%)	1% (7%)	0% (7%)	1% (9%)	0% (7%)	1% (6%)
RISK REDUCTION POPULATIONS							
N	112	105	107	104	105	98	95
Mean (SD) CCT	551 (40)	551 (43)	555 (42)	553 (44)	555 (43)	554 (48)	557 (48)
Mean (SD) CCT % Change		-0% (6%)	1% (6%)	0% (6%)	1% (5%)	0% (6%)	1% (5%)
N	94	88	89	87	88	82	79
Mean (SD) CCT	552 (41)	552 (45)	555 (44)	551 (46)	555 (45)	552 (48)	556 (50)
Mean (SD) CCT % Change		0% (6%)	1% (6%)	0% (6%)	1% (5%)	0% (6%)	1% (6%)
N	36	33	36	33	34	32	30
Mean (SD) CCT	555 (52)	558 (50)	560 (48)	558 (44)	556 (46)	564 (51)	558 (56)
Mean (SD) CCT % Change		0% (8%)	1% (7%)	1% (8%)	0% (6%)	2% (7%)	0% (7%)
N	32	30	32	30	31	29	27
Mean (SD) CCT	557 (53)	559 (52)	563 (48)	558 (46)	557 (48)	564 (53)	558 (59)
Mean (SD) CCT % Change		1% (8%)	1% (7%)	1% (8%)	0% (6%)	2% (7%)	0% (7%)

Table 7
Enrollment
IMT-002 AND IMT-002-LTM

Associated Eye Care	13	6.0%	11	8.5%
Baylor College of Medicine	1	0.5%		
University of California at Irvine	4	1.8%	3	2.3%
Fine, Hoffman & Packer	7	3.2%	3	2.3%
University of Michigan/Kellogg Eye Ctr.	12	5.5%	8	6.2%
Discover Vision Centers	9	4.1%	4	3.1%
Retina Group of Washington	13	6.0%	5	3.9%
Manhattan Eye & Ear	2	0.9%	1	0.8%
OCB Boston	9	4.1%	2	1.6%
Massachusetts Eye & Ear	4	1.8%	2	1.6%
Retina Centers PC	25	11.5%	14	10.9%
Dean A. McGee Eye Inst.	10	4.6%	7	5.4%
Emory Eye Center	15	6.9%	11	8.5%
Medical Center Ophthalmology	6	2.8%	5	3.9%
Kraff Eye Inst.	1	0.5%		
Vitreoretinal Foundation	3	1.4%	2	1.6%
Paducah Retinal Center	4	1.8%	1	0.8%
Altos Eye Physician	10	4.6%	8	6.2%
Medical College of Wisconsin Eye Inst.	2	0.9%		
Sarasota Retinal Inst.	5	2.3%	5	3.9%
Southeast Clinical Research	18	8.3%	10	7.8%
Doheny Retina Inst.	5	2.3%	2	1.6%
Retina Associates of Cleveland	12	5.5%	9	7.0%
Vanderbilt Un. Dept. of Oph. & Visual Sciences	5	2.3%	4	3.1%
Wills Eye Hospital, Retina Research	8	3.7%	3	2.3%
Associated Retinal Consultants	6	2.8%	4	3.1%
Duke University Eye Center	6	2.8%	3	2.3%
Johns Hopkins University, Wilmer Ophthalmological Institute	2	0.9%	2	1.6%
Total	217	100.0%	129	100.0%

One IMT-002 subject canceled surgery and was excluded.

6.0 LABELING FOR RISK MITIGATION

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

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

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

The proposed indication for the IMT is:

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

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

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

The instructions for use will provide detailed instructions for performing the surgery. In addition, if FDA agrees, the device will be restricted for use by physicians who have completed the training offered by VisionCare. Both measures will improve the

likelihood that the device will be implanted in a manner that allows it to function effectively.

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

1. The presence of corneal guttata is associated with greater loss of ECD as a result of the implantation surgery. Accordingly, the proposed labeling states that corneal guttata will be a contraindication.
2. Anterior chamber depth less than 3.0 mm will also be a contraindication.
3. In order to minimize the risk that patients will, over time, lose so many corneal endothelial cells that their corneas will decompensate and require a corneal transplant, a grid utilizing age, pre-operative life expectancy, and pre-operative ECD together with expected rates of ECD loss as predicted by the biexponential model will be presented as a contraindication. If patients lack sufficient ECD at baseline to predict ECD of at least 750 cells/mm² at the end of their life span, implantation of an IMT will be contraindicated. The grid, shown in Figure 22 and again on the following page, has been constructed in accordance with the discussion in Section 5.3.

**PROPOSED GRID OF PREOPERATIVE ECD REQUIRED FOR IMT IMPLANTATION
BASED ON IMT-IMPLANTED EYES WITHOUTH GUTTATA AND WITH ACD ≥ 3.0 MM**

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	889	941	889	889	889	889	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	709	646	646	646	646	581	581	581	581
	17	840	840	610	709	610	610	610	610	549	549	549	549
	18	709	794	576	670	576	576	576	576				
	19	670		545	633	545	545	545	545				
	20	633	709		598								
	21	598			566								
	22	565	633		534								
	23	534	598										
	24		566										
	25		534										
	26												

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

Cell density at end of life

Years post implant when cell density reaches 500 cell per mm²

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

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

5. A "cornea specialist" is defined as ophthalmologists who had fellowship or other specialty training in diseases and surgery of the cornea and who were at the time

of the study regularly performing corneal surgical procedures such as penetrating keratoplasty. In IMT-002, patients whose surgeries were performed by cornea specialists incurred less loss of endothelial cell density. Accordingly, the labeling will include a warning stating that implantation of the IMT should be performed only by cornea specialists.

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

Table 39 on the following page shows the currently-proposed Indication, Contraindications, Warnings, Precautions, Restrictions, and other labeling information compared to those proposed at the time of the Panel meeting in 2006 to highlight modifications since the 2006 Advisory Panel review of this PMA in July 2006.

TABLE 39
KEY CURRENT VERSUS PREVIOUS PROPOSED LABELING ELEMENTS

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

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

TABLE 39 (continued)

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

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

From: Judy Gordon [mailto:judy@clinregconsulting.com]
Sent: Wednesday, December 03, 2008 2:08 PM
To: 'Calogero, Don'
Cc: 'Allen Hill'
Subject: Follow-up to Response to November 21, 2008 email

Dear Don,

Just a quick follow-up e-mail to add to my previous email response.

I am sending you Section 5.3 of Amendment 13 to P050034 which discussed use of the biexponential model and a grid of ECD. This section displays the results of modeling for the risk reduced population, and we thought it might be helpful to send for the review team.

Best regards,
Judy

Judy F Gordon, DVM
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judy@clinregconsulting.com
www.clinregconsulting.com

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

A further risk mitigation strategy would allow physicians and patients to calculate the minimum ECD needed before IMT implantation such that the patient would be able to obtain the benefits of improved visual acuity from implantation of an IMT without an undue risk of loss of ECD to a level potentially leading to corneal decompensation and requiring corneal transplant. CDRH has previously used this risk mitigation strategy in the labeling for commercially available phakic refractive intraocular lenses. The phakic IOL labeling utilizes a grid (copy provided in Attachment 7) based on pre-operative ECD, chronic ECD loss, and a "target" ECD at age 75 on which physicians and patients can base their decisions.

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

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

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

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

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

The biexponential model is defined by the equation

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

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

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

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

Applying the biexponential model to the data available from IMT-002 and IMT-002-LTM through 48 months, the mean ECD at 12 months (to incorporate the full effect of surgical loss) was 1954 cells/mm², and the mean annual loss thereafter was 3.8% (Tables 21.1 and 21.2). To make the grid more conservative (i.e., to increase the likelihood that patients will have sufficient ECD to preserve corneal transparency through their life spans), the lower 90% confidence interval for the 1 year mean ECD and the upper 90% confidence interval for annual ECD percent loss are utilized in constructing the grid.

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

- 12-month ECD loss of 24.6%, the lower 90% confidence interval for 12-month ECD, 1911 cells/mm², estimated by the biexponential model, and

- Annual ECD loss of 5.5%, the upper 90% confidence interval for annual loss estimated by the biexponential model, utilizing 48 month data.

The resulting grid, shown in Figure 22 sets minimum endothelial cell density criteria as a function of age that should result in at least 750 cells/mm² at end of average life span.

Detailed results of the biexponential model are shown in Tables 21.1, 21.2 and 21.3.

FIGURE 22
PROPOSED GRID OF PREOPERATIVE ECD REQUIRED FOR IMT IMPLANTATION
BASED ON IMT-IMPLANTED EYES WITHOUT GUTTATA AND WITH ACD ≥ 3.0 MM

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
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	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	889	941	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	709	646	646	646	646	581	581	581	581
	17	709	840	610	709	610	610	610	610	549	549	549	549
	18	709	794	576	670	576	576	576	576				
	19	670	794	545	633	545	545	545	545				
	20	633	709	598	598								
	21	598	670	566	566								
	22	565	633	534	534								
	23	534	598										
	24		566										
	25		534										
	26												

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

Cell density at end of life

Years post implant when cell density reaches 500 cell per mm²

TABLE 21.1
BI-EXPONENTIAL MODEL FOR ECD
 $ECD_{month} = p \times e^{-a \times month} + q \times e^{-b \times month} + \epsilon$
NON-GUTTATA IMT-IMPLANTED EYES WITH ACD ≥ 3 MM
BASED ON DATA FROM BASELINE TO 48 MONTHS
IMT-002 AND IMT-002-LTM

p	506.7	65.5	378.1	635.3	7.7	<.001
a	0.5	0.2	0.1	1.0	2.5	0.012
q	2029.7	45.0	1941.4	2118.0	45.1	<.001
b	0.003	0.001	0.001	0.005	3.5	<.001

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

TABLE 21.2
PREDICTED MEAN ECD BASED ON BI-EXPONENTIAL MODEL FOR
NON-GUTTATA IMT-IMPLANTED EYES WITH ACD ≥ 3 MM
BASED ON DATA FROM BASELINE TO 48 MONTHS
IMT-002 AND IMT-002-LTM

3 Months	2109.2	2029.4, 2189.0
12 Months	1954.0	1911.0, 1997.1
24 Months	1879.7	1842.2, 1917.3
36 Months	1808.9	1753.7, 1864.1
48 Months	1740.8	1660.4, 1821.2
60 Months	1675.2	1569.3, 1781.1

TABLE 21.3
PREDICTED PROBABILITY OF ECD LESS THAN THRESHOLD BASED ON
BI-EXPONENTIAL MODEL FOR
NON-GUTTATA IMT-IMPLANTED EYES WITH ACD ≥ 3 MM
BASED ON DATA FROM BASELINE TO 48 MONTHS
IMT-002 AND IMT-002-LTM (EXCLUDING PREOP RESIDUALS)

3 Months	5.0	1.6	0.1
12 Months	7.1	3.2	0.9
24 Months	8.5	4.3	1.3
36 Months	8.9	6.1	1.9
48 Months	9.8	6.9	2.6
60 Months	10.5	7.7	3.5

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

**ITEM 3:
RESPONSE TO EMAIL DATED
DECEMBER 2, 2008**

From: Lepri, Bernard [mailto:bernard.lepri@fda.hhs.gov]
Sent: Tuesday, December 02, 2008 5:54 AM
To: Judy Gordon
Subject: Your labeling

Dear Judy,

Hope you had a pleasant Thanksgiving and that all are well at the Gordon household. I found something that we believe is of importance to your labeling and thought that I would let you know in advance so it's one less thing for us to take care of later.

Regarding ACD measurements: In addition to specifying the minimum ACD for selection for implantation of the IMT, please specify and describe the methodology used to measure the ACD with an emphasis on whether or not it includes the corneal thickness.

Thanks,

Bernie

Bernard P. Lepri, OD, MS, MEd
ODE/DOED/VEDB
Phone: 240-276-4237
FAX: 240-276-4111

From: Judy Gordon [mailto:judy@clinregconsulting.com]
Sent: Wednesday, December 03, 2008 1:37 PM
To: 'Lepri, Bernard'
Cc: 'Allen Hill'
Subject: RE: Your labeling

Dear Bernie,

Thank you for your email – we had a wonderful Thanksgiving and much to be thankful for.

Also, thank you for your feedback on labeling regarding anterior chamber depth. We will describe in labeling that the measurement should be done from the posterior surface of the cornea, i.e., from the endothelium, to the front surface of the crystalline lens, so that this measurement does not include the corneal thickness.

Best regards,
Judy

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