



November 17, 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 17  
VisionCare Ophthalmic Technologies Implantable Miniature Telescope  
IMT (by Dr. Isaac Lipshitz)™

Dear Sir or Madam,

Please find enclosed three (3) copies of Amendment 17 to P050034, for the Implantable Miniature Telescope (IMT).

This amendment provides responses to information requests by the Division of Ophthalmic and ENT Devices (DOENTD). These requests for information were submitted via email to Gene Hilmantel, O.D., M.S. on October 28, 2008, October 31, 2008, November 6, 2008 and November 7, 2008. Also included is a response to a question presented in a telephone conversation with B. Lepri the week of October 27<sup>th</sup>. Also included is a publication that was published in the November issue of the American Journal of Ophthalmology:

- Item 1: Response to emailed Dated October 28, 2008 (2:37pm)
- Item 2: Response to Telephone Conversation with B. Lepri week of October 27<sup>th</sup>
- Item 3: Response to email Dated October 31, 2008 (1:14pm)
- Item 4: Response to email Dated November 6, 2008 (1:42pm)
- Item 5: Response (From A. Hill) to Email Dated November 7, 2008 (12:44pm)
- Item 6: Response (From J. Gordon) to email Dated November 7, 2008 (1:26pm)
- Item 7: November American Journal Ophthalmology Article

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](mailto:judy@clinregconsulting.com).

Sincerely,

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



**P050034**

**AMENDMENT 017  
VISIONCARE OPHTHALMIC TECHNOLOGIES  
IMPLANTABLE MINIATURE TELESCOPE™  
(IMT BY DR. ISAAC LIPSHITZ)**

**VOLUME I OF I**

**NOVEMBER 17, 2008**

**APPLICANT**

VisionCare Ophthalmic Technologies, Inc.  
14395 Saratoga Ave., Suite 150  
Saratoga, CA 95070

**CORRESPONDENT**

Judy Gordon D.V.M.  
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**P050034 AMENDMENT 017**  
**VISIONCARE OPHTHALMIC TECHNOLOGIES**  
**IMPLANTABLE MINIATURE TELESCOPE**

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**ITEM 1:  
RESPONSE TO EMAILED DATED  
OCTOBER 28, 2008 (2:37PM)**

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

**Sent:** Tuesday, October 28, 2008 2:37 PM

**To:** Judy Gordon

**Subject:** RE: VisionCare response to informal comments from FDA on TOC for Amendment 14

**Importance:** High

Judy,

In response to General Comment #4 in the attached, you referred us to a protocol in Attachment 2.1 in A7.

I am told by our clinician that this protocol refers us to a method for clearance analysis and not ACD measurements. Is this correct?

Is there a protocol for ACD measurements?

Don

**From:** Judy Gordon [mailto:judy@clinregconsulting.com]  
**Sent:** Thursday, October 30, 2008 12:58 PM  
**To:** 'Calogero, Don'  
**Cc:** 'Allen Hill'  
**Subject:** RE: VisionCare response to informal comments from FDA on TOC for Amendment 14

Dear Don,

Thank you for your email. The protocol in Attachment 2.1, Amendment 007 describes the methods for the analysis of clearance, not ACD.

Per the IMT-002 protocol, ACD was measured at baseline using standard ultrasound A-scan as part of the determination of subject eligibility.

Don, please let me know if you need any additional information.

Best regards,  
Judy

**Judy F Gordon, DVM**  
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**ITEM 2:**  
**RESPONSE TO TELEPHONE CONVERSATION**  
**WITH B. LEPRI WEEK OF OCTOBER 27<sup>TH</sup>**

**From:** Judy Gordon [mailto:judy@clinregconsulting.com]  
**Sent:** Thursday, October 30, 2008 1:07 PM  
**To:** 'Lepri, Bernard'; 'Hilmantel, Gene N'  
**Cc:** 'Allen Hill'  
**Subject:** IMT-002-LTM accountability - Amendment 13, Table 4

Dear Bernie and Gene,

In response to your question regarding accountability in the IMT-002-LTM study (Amendment 13, Table 4), the number of subjects increased from 125 at 42 months to 129 at 48 months as a result of enrollment of 4 additional subjects at the 48-month visit.

Please let me know if you need any additional information.

Best regards,  
Judy

**Judy F Gordon, DVM**  
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**ITEM 3:  
RESPONSE TO EMAIL DATED  
OCTOBER 31, 2008 (1:14PM)**

**From:** Hilmantel, Gene N [mailto:gene.hilmantel@fda.hhs.gov]  
**Sent:** Friday, October 31, 2008 1:14 PM  
**To:** judy@clinregconsulting.com  
**Cc:** Calogero, Don  
**Subject:** Clarification needed

Judy,

I am still a bit unclear on the number of late corneal edema cases.

You wrote:

Tables 32.1 and 32.2 present the occurrences of late corneal edema with (early) ECD loss and without ECD loss respectively. Late-occurring corneal edema was observed in 13 eyes, which consisted of 6 reports in IMT-002 and 7 reports in IMT-002-LTM. The 6 subjects with late corneal edema reported in IMT-002 are participating in IMT-002-LTM. Ten of the 13 cases of corneal edema were observed at 24 months or later. The other three cases were observed at 3 months (Patient [REDACTED]), 7 months (Patient [REDACTED]) and 9 months (Patient [REDACTED]) and were reported as resolved. Corneal thickness was within the normal range for 8 of the 10 eyes with unresolved corneal edema; 2 eyes had corneal edema >700 micron at 24 months.

You provided listings for 12 patients in response to a question requesting line listings for patients with edema at >3 months.

Since [REDACTED] was first noted at 72 days postop, am I correct that only 11 patients had edema first noted at >3 months? Is the following table correct?

**EYES WITH LATE CORNEAL EDEMA**

[Reviewer-Generated Table]

Approximate Time Postop that Edema was First Noted      Eyes with new corneal edema

("U" indicates "unresolved at any time"

"V" indicates "resolved"      Cumulative Number of Eyes with Unresolved Corneal Edema  
 Cumulative

% of Implanted Eyes with Unresolved Corneal Edema

N=206 Implanted Eyes

6 Months			
9 Months	[REDACTED] U	1	0.4%
12 Months			0.4%
18 Months			0.4%
24 Months	[REDACTED] U		

[REDACTED] (R)

	2	1.0%
30 Months		1.0%
36 Months	012-212R*	
	5 - 6	2.4% - 2.9%
42 Months		
	7 - 8	3.4% - 3.9%
48 Months		3.4% - 3.9%
54 Months		8 - 9 3.9% - 4.4%
60 Months		
		3.9% - 4.4%

The following 3 IMT-implanted eyes were reported with corneal edema at unscheduled visits without being reported at the scheduled visits: [redacted] at 211 days; [redacted] at 1445 days, 1470 days and 1563 days; [redacted] at 1662 days.

[redacted] R (211 days potop, resolved at 9 month visit.  
 [redacted] R (reported resolved at 2.5 yrs, but CCT remains increased.)  
 [redacted] was at 72 days

Late-occurring corneal edema was observed in 13 eyes, which consisted of 6 reports in IMT-002 and 7 reports in IMT-002-LTM. The 6 subjects with late corneal edema reported in IMT-002 are participating in IMT-002-LTM. Ten of the 13 cases of corneal edema were observed at 24 months

or later. The other three cases were observed at 3 months (Patient [redacted]), 7 months (Patient [redacted]) and 9 months (Patient [redacted])

[redacted]

Thanks for addressing this minor issue.

Gene

Gene Hilmantel, OD, MS

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender immediately by e-mail or phone.

Food and Drug Administration  
 HFZ-460  
 9200 Corporate Boulevard  
 Rockville, MD 20850  
 Ph: (240) 276-4232 (Note New Number)  
 Fax: (240) 276-4234

**From:** Judy Gordon [mailto:judy@clinregconsulting.com]  
**Sent:** Friday, November 07, 2008 6:03 AM  
**To:** 'Hilmantel, Gene N'  
**Cc:** 'Calogero, Don'; allen@visioncareinc.net  
**Subject:** RE: Clarification needed

Dear Gene,

In response to the question in your October 31, 2008 email, regarding the number of eyes with corneal edema, there are 12 IMT-implanted eyes with "late" corneal edema. We included the eye with corneal edema starting at Day 72 (Patient [REDACTED]), since the edema continued after that time, thus would have been present at >3 months.

Here is a list of the IMT-implanted eyes with "late" corneal edema grouped by eyes where corneal edema resolved (N=3), eyes where corneal edema did not resolve (N=5), and eyes that underwent corneal transplantation (N=4). Gene, please note that Patient [REDACTED] had "late" corneal edema (>3 months), however, this eye underwent intraoperative removal of the IMT, so the available follow-up is for a non-implanted eye. Patient [REDACTED] was identified in Table 32.1, Amendment 13, dated September 2, 2008. The 12 other patients in your message are also identified in Tables 32.1 (11 plus [REDACTED]) and 32.2 ([REDACTED] the patient with late edema but no late ECD loss).

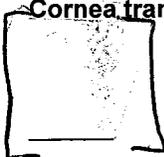
Corneal edema resolved  
(high ECD)



Unresolved corneal edema



Cornea transplant



I have also attached a table summarizing this information for you, as well as the patient line listings for eyes with corneal edema, submitted to you last week in response to your email of October 16, 2008. All but two of these eyes [REDACTED] and [REDACTED] had at least 1 risk factor for corneal edema, i.e., ACD <3.0 mm, operated by a non-cornea specialist or surgical order  $\leq 5$  cases. Of the 12 eyes, 9 eyes had 2 or 3 risk factors for corneal edema, and 4 of these 9 eyes had all 3 risk factors.

Gene, let me know if you have any other questions.

Best regards,  
Judy

## RESPONSE TO EMAIL DATED OCTOBER 16, 2008

*With regard to the late cases of corneal edema and the line listings provided in amendment 13, we have been unable to locate any information on how they were treated (hyperosmotics? And whether or not the late corneal edema has resolved in any way, the decompensation and transplant cases excepted. Could you please provide us with this information? For each eye, please include duration of the adverse event, treatment, sequelae, and investigator's evaluation of the relationship of the event to the device.*

### Response:

The previously submitted line listings on cases of corneal edema have been expanded to include the requested information. We have also included comments on each subject with late corneal edema previously included in various submissions, to facilitate review of the available information on these study subjects.

**DATA LISTING FOR IMT-IMPLANTED EYES WITH CORNEAL EDEMA AT > 3 MONTHS**

**N = 12**

02/21/03	PREOP	-40	2642	59.7	35.3	546	Corneal edema reported on 08/08/06 (1224 days postop, 42 month visit)	None	Corneal edema unresolved	Not Related	None
06/20/03	3M	79				574					
08/26/03	6M	146	2274	52.0	36.3	561					
01/16/04	9M	289	2326	63.3	37.0	578					
03/19/04	12M	352	1855	49.3	36.0	569					
09/14/04	18M	531	1929	56.0	35.0	586					
03/08/05	24M	706	1011	58.7	32.3	597					
08/08/06	42M	1224	508	33.0	28.7						
03/06/07	48M	1434	660	61.0	25.3	656					
08/28/07	54M	1609	556	50.0	46.0	642					
02/26/08	ECD only (60 Months)	1791	505	33.0	17.5						
<b>COMMENTS</b>											
Transient corneal edema reported on Day 1.											



08/06/03	PREOP	-42	2908	59.0	31.0	607	Corneal edema reported on 05/15/06 (971 days postop, at 36-month visit)	Loteprednol	Corneal Decompensation 02/02/07 (1,234 days postop)  Subject died of unknown case on 10/01/07	Possibly Related	None
12/12/03	3M	86	432	52.7	35.3	621					
03/16/04	6M	181	452	49.7	27.0	677					
05/18/04	9M	244	397	38.3	42.3	601					
08/24/04	12M	342	361	67.0	33.5	694					
01/11/05	18M	482	351	54.3	33.7	700					
05/10/05	24M	601				771					
05/15/06	36M	971									
02/02/07	42M	1234				771					
09/04/07	48M	1448				920					

**COMMENTS:**

For Subject [REDACTED], the study investigator documented operative trauma consisting of endothelial touch during implantation, with resulting early change in ECD, and early corneal edema (Day 1) as well as late corneal edema leading to corneal decompensation.

01/17/03	PREOP	-40				516	Corneal edema reported on 01/18/05 (687 days postop, 24 month visit)	Muro 128; Prednisolone acetate	Corneal Transplant 12/06/06 (1379 days postop)	Definitely related	<ul style="list-style-type: none"> <li>▪ ACD &lt;3.0 mm</li> <li>▪ Surgical order ≤ 5</li> <li>▪ Non-cornea specialist</li> </ul>
01/23/03	ECD only (Preop)	-34	2763	67.3	28.0						
05/22/03	3M	85	1684	60.3	34.0	528					
08/12/03	6M	167	1380	51.7	32.3	508					
12/04/03	9M	281	1070	64.0	31.0	516					
02/12/04	12M	351	845	52.0	27.0	499					
06/10/04	18M	470	604	20.0	21.0	569					
01/08/05	ECD only (24 Months)	682	529	56.3	23.7						
01/18/05	24M	692				580					
03/20/07	48M	1483				550					
07/24/07	54M	1609				558					
02/26/08	60M	1826				602					

**COMMENTS:**

Subject [REDACTED] presented with ACD <3.0 mm, surgical order ≤5, and was operated by a non-cornea specialist, all risk factors for greater endothelial cell loss.

Iris damage and corneal touch were reported intraoperatively, with transient corneal edema at Day 1 and Day 7. BCVA improved following surgery through 12 months, but decreased over time as a result of corneal edema. ECD had decreased to 529 cells/mm<sup>2</sup> at 24 months. At approximately 48 months postoperatively, penetrating keratoplasty was performed, and the IMT was left in place. Post-keratoplasty, recovery was uneventful and visual acuity improved very significantly, from 20/800 to 20/160.



08/01/03	PREOP	-41	2860	57.3	33.7	610	Corneal edema reported on 04/09/04 (211 days postop)	Prednisolone acetate 1% q2h while awake for 1 week, QID for 1 week, TID for 1 week, BID for 3 days	None, corneal edema resolved	Probably Related	Corneal guttata
12/01/03	3M	81	2694	55.0	35.7	602					
02/02/04	6M	144	2737	60.3	32.0	607					
04/09/04	Interim	211				721					
05/03/04	9M	235				592					
05/04/04	ECD only (9 Months)	236	2816	54.3	35.7						
07/19/04	12M	312	2434	37.0	30.3	595					
11/06/06	36M	1152	2336	59.0	32.0	593	Resolution 05/03/04, at 9 month visit				
							Duration 24 days				

**COMMENTS:**

In Subject: [REDACTED], corneal edema was observed between the 6-month and 9-month visits, and resolved completely, with no corneal edema was observed in this subject at 12 and 36 months. ECD remained high at 2336 cells/mm<sup>2</sup> at 36 months.

*NB: Review of this case by a medical monitor suggests that corneal edema may be inflammatory in nature, or have an inflammatory component and can be managed by steroids, as evidenced by the good resolution of corneal edema in this eye.*



06/30/03	PREOP	-11	2455	55.0	36.3	546	Corneal edema reported on 04/15/05 (644 days postop)  Resolution 10/28/05 (interim visit)  Duration 196 days	Muro 128 QID	Corneal edema reported to have resolved; however, CCT remains increased from baseline	Not related	<ul style="list-style-type: none"> <li>▪ ACD &lt;3.0 mm</li> <li>▪ Non-cornea specialist</li> </ul>
10/10/03	3M	91	2211	54.3	35.0	542					
01/14/04	6M	187	1074	48.0	37.7	559					
04/05/04	9M	269	1048	48.3	32.7	567					
07/14/04	12M	369	955	62.0	29.7	633					
01/07/05	18M	546	553	45.0	26.3	662					
04/15/05	24M	644				716					
06/20/05	Interim	710	519	46.0	21.7	548					
08/21/06	36M	1137				658					
01/03/07	42M	1272	618	56.3	30.7	724					
06/11/07	48M	1431	719	40.0	30.0	633					

**COMMENTS:**

Subject [REDACTED] presented with ACD <3.0 mm and was operated by a non-cornea specialist, risk factors for greater endothelial cell loss. Early corneal edema was reported on Day 1.

08/29/03	PREOP	-24	1909	61.0	32.7	553	Corneal edema reported on 06/25/04 (277 days postop, at 9 month visit)	Muro 128 drops and ointment	Corneal Decompensation 06/25/05 (277 days) Corneal Transplant 09/01/04 (345 days).	Probably Related	<ul style="list-style-type: none"> <li>▪ ACD &lt;3.0 mm</li> <li>▪ Non-cornea specialist</li> </ul>
01/14/04	3M	114	633	58.3	22.0	565					
04/27/04	6M	218	463	59.0	31.3	635					
06/25/04	9M	277				730					
08/17/04	12M	330				155					
09/09/04	Interim	353	3128	58.0	37.3	629					
10/07/04	Interim	381	3442	55.3	34.3	581					
01/18/05	Imterim	484	3133	50.3	42.0	549					
05/11/05	Interim	597	2984	51.3	35.3	546					

**COMMENTS:**

Subject [REDACTED] presented with ACD <3.0 mm and was operated by a non-cornea specialist, both risk factors for greater endothelial cell loss.

In Subject [REDACTED] during implantation of the IMT, spontaneous prolapse of the superior iris occurred, preventing visualization of the capsular bag. The IMT was placed in the ciliary sulcus, and at the end of the procedure, the IMT was in place with moderate depth of the anterior chamber. The superior iris was atrophic due to the prolapse and did not constrict with a miotic agent. On postoperative day 1, best corrected visual acuity was limited to hand motion; slit lamp examination revealed corneal edema, endothelial folds, and anterior chamber cells and flare, and anterior synechiae. Intraocular pressure was 22 mmHg. The anterior chamber was deep and the IMT was centered. Anterior synechiae persisted through the course of follow-up.

At the 7 day visit, the corneal incision was secure, and Seidel negative, with IOP of 18 mmHg. The anterior chamber was shallow with the IMT surface close to the corneal endothelium. However, the subject was not using a protective shield at all times and was not limiting activity, as instructed by the study investigator.

At the 6 month visit, visual acuity had improved by 4.6 lines. Slit lamp examination revealed normal cornea, 1+ folds, no cells and no flare in the anterior chamber. Endothelial cell density had further decreased to 463.3 cells/mm.<sup>2</sup> Intraocular pressure was 14 mmHg. The IMT was centered and on close inspection, there was a subtle area of Descemet's fold.

At the 9 month visit, best corrected visual acuity was 20/300, and intraocular pressure was 14 mmHg. The anterior chamber was deep and the IMT was centered. The superior iris was updrawn. Centrally, the cornea had 2+ endothelial folds. A diagnosis of corneal decompensation was made by the study investigator, most likely attributable to endothelial touch during the first postoperative week when the subject as not wearing a shield and not limiting his activity, despite instructions to the contrary. Treatment with Muro 128 was initiated, and the subject underwent corneal transplantaion September 1, 2004; the IMT was removed and a MA60 22.0 diopter lens was implanted in the ciliary sulcus.

The postoperative follow-up for this subject was uneventful. The subject was evaluated for 6 months following the transplant, and there were no sequelae of the corneal transplant procedure.

\*Post transplant ECD excluded from primary ECD analyses

06/05/03	PREOP	-39	2465	66.0	29.7	551	Corneal edema reported on 06/28/07 (1,145 days postop, at interim visit)	None	Corneal Decompensation 10/24/07 (1,563 days)  Subject died of lung cancer on 06/27/08	Probably Related	<ul style="list-style-type: none"> <li>▪ ACD &lt;3.0 mm</li> <li>▪ Surgical order ≤ 5</li> <li>▪ Non-cornea specialist</li> </ul>
10/14/03	3M	92				590					
10/27/03	ECD only (3 Months)	105	782	57.0	25.3						
02/03/04	6M	204	431	42.7	28.0	626					
04/27/04	9M	288	309	50.0	14.7	708					
07/14/04	12M	366	311	39.0	26.0	736					
12/15/04	18M	520	664	26.0	33.3	641					
04/19/05	ECD only (24 Months)	645	503	49.0	28.0						
04/20/05	24M	646				611					
09/19/06	36M	1163	823	61.3	41.3						
02/14/07	42M	1311	594	58.0	20.0	706					
06/12/07	48M	1429	501	25.0	37.0	741					
<b>COMMENTS</b>											
Subject [REDACTED] presented with ACD <3.0 mm, surgical order ≤5, and was operated by a non-cornea specialist, all risk factors for greater endothelial cell loss.											

09/26/03	PREOP	-24				565	Corneal edema reported on 10/25/06 (1,101 days postop, at 36 month visit)	Muro 128 Pilocarpine	Corneal Transplant, IMT left in eye 08/15/07 (1,395 days)	Definitely Related	<ul style="list-style-type: none"> <li>▪ Guttata</li> <li>▪ Surgical order &lt;5 cases</li> </ul>
10/06/03	ECD only (Preop ECD)	-14	2774	58.0	40.0						
01/07/04	3M	79				585					
04/27/04	6M	190	2566	45.0	28.5	590					
06/09/04	9M	233	2814	57.3	42.7	596					
08/25/04	12M	310	2959	51.0	45.3	599					
02/08/05	ECD only (18 Months)	477	2748	51.0	41.3						
02/09/05	18M	478				605					
06/07/05	ECD only (24 Months)	596	2860	58.7	39.7						
06/08/05	24M	597				640					
10/25/06	36M	1101	2444	53.3	39.0						
12/04/06	CCT only (36 Months)	1141				655					
05/07/07	42M	1295	841	53.3	34.7	770					
10/25/07	48M	1466	2153	58.3	32.0	534					
04/22/08	ECD only (54 Months)	1646	1405	53.0	32.0						

#### COMMENTS

In Subject [REDACTED] the IMT was successfully implanted, however the device was tilted, such that the superior haptic pressed against the temporal iris. In this eye, only relatively modest decreases in ECD were observed through 36 months of follow-up, when the subject presented with localized corneal edema, in the inferotemporal cornea corresponding to intermittent touch of the IMT to the endothelium. The position of the IMT was initially managed with the use of 1% pilocarpine, however, proper positioning of the IMT was achieved only intermittently. Although the study medical monitor and the sponsor communicated to the study investigator that IMT repositioning was not advisable, repositioning of the IMT was attempted. This procedure induced further trauma to the endothelium with corneal touch.

Following this attempt at repositioning the IMT, there was further deterioration of the cornea, with corneal edema and loss of visual acuity. Corneal transplantation was performed approximately 48 months following original placement of the IMT, and the device was left in place. Recovery was uneventful, with a clear graft and good visual rehabilitation.

04/30/03	PREOP	-35	2738	62.0	31.7	557	Corneal edema reported on 03/09/05 (644 days postop, at 24 month visit)	Muro 128 QID, Prednisolone Acetate QID	None, corneal edema resolved	Probably Related	<ul style="list-style-type: none"> <li>▪ ACD &lt;3.0 mm</li> <li>▪ Surgical order ≤ 5</li> <li>▪ Non-cornea specialist</li> </ul>
08/12/03	3M	69	1315	57.7	34.7	519					
12/18/03	6M	197	846	68.7	30.0	619					
03/10/04	9M	280	656	46.0	23.3	646					
06/30/04	12M	392	446	64.3	30.7	604					
12/08/04	Interim	553	628	60.0	25.0	645					
03/09/05	24M	644	676	50.0	14.0	715					
09/20/06	42M	1204	983	56.7	44.0						
07/18/07	48M	1505	851	48.3	32.3	598	Duration 861 days (was resolved at 48 month visit)				

**COMMENTS:**

Subject [REDACTED] had an anterior chamber depth of <3.0 mm, was an early surgical case (surgical order ≤5), and the surgery was performed by a non-cornea specialist, all risk factors for greater endothelial cell loss.

*NB: Review of this case by a medical monitor suggests that corneal edema may be inflammatory in nature, or have an inflammatory component and can be managed by steroids, as evidenced by the good resolution of corneal edema in this eye.*

07/15/03	PREOP	-76				599	Corneal edema reported on 04/17/08 (1,662 days postop, at 54-month visit)	None	Corneal edema unresolved	Definitely Related	<ul style="list-style-type: none"> <li>▪ ACD &lt;3.0 mm</li> <li>▪ Non-cornea specialist</li> </ul>
08/26/03	ECD only (Preop ECD)	-34	2463	66.3	29.7						
01/21/04	3M	114	1901	59.0	27.3	536					
03/23/04	6M	176	1554	55.3	31.0	559					
05/11/04	9M	225	1170	59.0	32.0	658					
08/19/04	12M	325	901	70.7	22.3	588					
01/28/05	18M	487	638	56.0	22.3	534					
05/10/05	24M	589	544	57.3	25.0	640					
08/14/06	36M	1050	386	55.7	30.3						
02/19/07	42M	1239	393	50.0	9.5	553					
08/27/07	48M	1428				612					
04/17/08	54M	Only an adverse event form has been submitted, reporting corneal edema									

**COMMENTS:**

Intraoperatively, Subject [REDACTED] had extensive complications, including posterior capsule rupture and vitreous loss requiring vitrectomy. This subject had a shallow anterior chamber (<3.0 mm) at baseline, as well as surgery performed by a non-cornea specialist, both risk factors for greater endothelial cell loss.

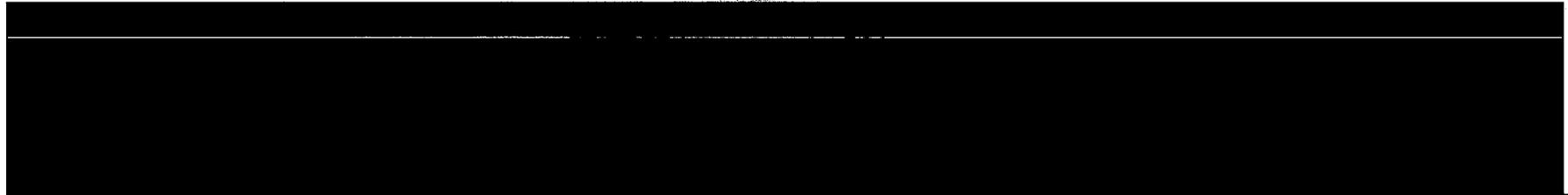
Vitreous was observed in the anterior chamber on Day 7, and was still present at 1 month. At the 1 month visit, iris atrophy and transillumination defects were reported, and both of these findings persisted through the available follow-up for this subject.



09/25/03	PREOP	-34	1769	67.0	27.7	600	Corneal edema reported on 09/06/06 (1,043 days postop, 36 month visit)		Corneal edema not resolved	Definitely Related	▪ ACD <3.0 mm ▪ Non-cornea specialist
01/07/04	3M	70	916	55.7	31.7	576					
04/29/04	6M	183	646	67.0	24.0	705					
07/08/04	9M	253	531	67.0	19.7	433					
09/14/04	12M	321	519	53.3	28.0	570					
02/01/05	18M	461	457	60.7	29.7	589					
06/14/05	24M	594	505	51.3	37.0	631					
09/06/06	36M	1043	324								
04/18/07	42M	1267	709	47.0	32.0	712					

**COMMENTS:**

Subject [REDACTED] had a shallow anterior chamber (<3.0 mm) at baseline and were operated by non-cornea specialists, both risk factors for greater endothelial cell loss.



08/20/03	PREOP	-48	2118	61.3	31.3	607	Corneal edema reported on 12/18/03 (72 days postop, 3 month visit)	None	Corneal decompensation 06/17/04 (254 days)  Corneal transplant 08/10/04 (308 days)	Definitely Related	<ul style="list-style-type: none"> <li>▪ ACD &lt;3.0 mm</li> <li>▪ Surgical order ≤ 5</li> </ul>
12/18/03	3M	72				706					
03/04/04	6M	149	385	46.0	30.5	742					
08/05/04	12M	303				955					
10/16/06	36M	1105				641					
04/03/07	42M*	1274	1857	60.3	35.3	622					
10/25/07	48M	1479				622					

**COMMENTS:**

In Subject [REDACTED], intraoperative positive vitreous pressure resulted in iris prolapse. On the first postoperative day, intraocular pressure was increased and the inferior aspect of the IMT was covered by the inferior iris. Iris atrophy was reported as a complication at Day 1, and corneal edema was observed at Day 1 (3+) and Day 7 (2+), resolving to 1+ at 1, 3 and 6 months. (NB: Since the corneal edema was still present at 3 and 6 months, this has been reported in the category of corneal edema present at >3 months). Corneal edema progressed at 9 months. Over the course of follow-up, the IMT was observed to be decentered inferiorly, with one of the haptics in the sulcus rather than in the capsular bag.

Starting approximately 4 months postoperatively, the subject started to experience poor vision, and visual acuity decreased to count fingers. The IMT was still slightly decentered inferiorly, but stable without any marked decentration or tilting. Over the next several months, the subject's visual acuity gradually deteriorated and corneal edema worsened. Treatment with topical prednisolone acetate 1% was increased, and Muro 128 (drops and ointment) was added to the therapeutic regimen. At 6 months, endothelial cell density had decreased to 385.3 cells/mm<sup>2</sup> and the corneal edema continued to progress. On this basis a decision was made to perform a corneal transplantation.

The subject underwent corneal transplantation on August 10, 2004. During corneal transplantation, the surgeon attempted to reposition the IMT, however, when the

surgeon tried to move the haptic from the sulcus, the posterior capsule ruptured. Subsequently an anterior chamber IOL was inserted.

The postoperative period was uneventful. At three subsequent examinations on November 22, 2004, December 16, 2004 and February 23, 2005, slit lamp examinations revealed normal cornea, no endothelial folds, with no cells and no flare in the anterior chamber. Intraocular pressure was varied from 12 to 22 mmHg. No complications or adverse events were reported.

\*Post transplant ECD excluded from primary ECD analyses

**IMT-Implanted Eyes  
Patients with Corneal Edema Reported at 3 Month Visit or Later**

(Refer to Patient Line Listing provided in Response to October 16, 2006 email from FDA)

E- Edema Reported, PK – Penetrating Keratoplasty, R – Resolved Edema, U – Unresolved Edema

Patient	Postop Visit/Months Edema Reported	Edema Status													
[Redacted]	42M	U								E	U	U			None
	55M	U											E		ACD < 3.0 MM, Non-Cornea Specialist
	36M	U								E	U	U			ACD < 3.0 MM, Non-Cornea Specialist
	36M	U								E	U	U			None
	48M	U										E			ACD < 3.0 MM, Surgical Order ≤ 5, Non-Cornea Specialist
						0	0	0	0	0	0	2	3	4	5
%					0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%	1.5%	1.9%	2.4%	2.4%

Patient	Postop Visit/Months Edema Reported	Edema Status	PK Procedure Months Postop												
[Redacted]	24M	PK/R	46M						E	E	E	PK/R	PK/R	PK/R	ACD < 3.0 MM, Surgical Order ≤ 5, Non-Cornea Specialist
	9M	PK/R	12M			E	E	PK/R	PK/R	PK/R	PK/R	PK/R			ACD < 3.0 MM, Non-Cornea Specialist
	36M	PK/R	47M							E	E	PK/R			ACD < 3.0 MM, Surgical Order ≤ 5, Non-Cornea Specialist
	3M	PK/R	10M	E	E	E	PK/R	PK/R	PK/R	PK/R	PK/R	PK/R			ACD < 3.0 MM, Surgical Order ≤ 5
					1	1	2	2	2	3	4	4	4	4	4
				0.5%	0.5%	1.0%	1.0%	1.0%	1.5%	1.9%	1.9%	1.9%	1.9%	1.9%	

\* 54 and 60 month visits have not been completed at date of data lock

\*\* Patient [Redacted] 3 month visit occurred at 72 days postop within the protocol specified visit window

Patient [Redacted] - aborted IMT implant procedure, reported with 1+ corneal edema 36, 42 and 48 month visits



**IMT-Implanted Eyes**  
**Patients with Corneal Edema Reported at 3 Month Visit or Later (n = 12)**  
 (Refer to Tables XX, Amendment XX for Patient Line Listing)

E- Edema Reported, PK – Penetrating Keratoplasty, R – Resolved Edema, U – Unresolved Edema

Patient	Postop Visit/Months Edema Reported	Edema Status	Edema Resolved Months from 1st Report	
I	7M	R	1M	Guttata ACD < 3.0 MM, Non-Cornea Specialist ACD < 3.0 MM, Surgical Order ≤ 5, Non-Cornea Specialist
	22M	R	7M	
	24M	R	29M	

**ITEM 4:  
RESPONSE TO EMAIL DATED  
NOVEMBER 6, 2008 (1:42PM)**

**From:** Hilmantel, Gene N [mailto:gene.hilmantel@fda.hhs.gov]  
**Sent:** Thursday, November 06, 2008 1:42 PM  
**To:** Judy Gordon  
**Cc:** Calogero, Don  
**Subject:** P050034

Judy,

In your response to the Oct. 20th e-mail, you provided the following table:

**Table 2**

**ECD < 1000 cells/mm<sup>2</sup> Before or At 24 Months**

**IMT-Implanted Eyes**

**IMT-002 Risk**

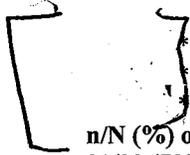
**Preop 3M 6M 9M 12M 18M 24M Factor**  
**n and % of Eyes with ECD < 1000 cells/mm<sup>2</sup> At ≤ 24 Months**  
**n/N (%)** 0/206 (0%) 16/193 (8%) 17/198 (9%) 16/190 (8%) 21/186 (11%) 21/180 (12%)  
 19/171 (11%)

**Mean ECD for Patients with ECD < 1000 cells/mm<sup>2</sup> At ≤ 24 Months**

**Mean** 2335 1057 952 871 795 765 771

**Patients with ECD < 1000 cells/mm<sup>2</sup> At ≤ 24 Months (N = 29)**

	2908	432	452	397	361	351			
	2763	1684	1380	1070	845	604	529	2, 3, 4	
424	966	1105	890					2, 3, 4	
	2477	1072	1320	1309	957	1328	1117	3, 4	
709	583							2, 4	
	2160	1625	983	1582	997	1546	1234	1, 4	
	2532	803	793	782	789	785	831	1, 2, 3, 4	
	2487	909		1278	952	982		3, 4	
009	754	890	698	791	813	825		1, 4	
065	1307	1554	971		804	1294	3		
	1739		925	1051	858	901	730	2, 3	
853	911	888	792	877	782	772		3, 4	
821	1606	1673	1297	1214	736			4	
*	2455	2211	1074	1048	955	553	519	2, 4	
*	1768	949	876	699	747	754	672	3, 4	
*	1909	633	463					2, 4	
*	2812	1280	1533	1241	1091	1077	956	1, 2, 3, 4	
2225	679	753	608	504	434	436		3, 4	
*	3012	755	884	865	1000	698	1000	3, 4	
*	2465	782	431	309	311	664	503	2, 3, 4	
*	2598	1187	615	568	592	639	615	3, 4	
*	1862	492	488	515	478	489	386	1, 2, 3, 4	
2234	1235	1385	905	960	813	796		3, 4	
*	2738	1315	846	656	446	628	676	2, 3, 4	
*	2463	1901	1554	1170	901	638	544	2, 4	
*	1769	916	646	531	519	457	505	2, 4	



2889	808	1083	821	742	659	735	1, 3, 4
2457	733	713	1011	874	1009	1088	2, 3, 4
2118	385						2, 3

**n/N (%) of Subjects Above Continuing into IMT-002-LTM Study**  
 21/29 (72%)

ECD after IMT explant was excluded.  
 Risk Factors: 1: guttata, 2: ACD < 3.0 mm, 3: Surgical Order 1 to 5, 4: Non-Cornea Specialist  
 IMT-002 minimum ECD exclusion criteria – ECD < 1600 cells/mm<sup>2</sup>  
 \* Continuing to IMT-002-LTM Study.

There seem to be a number of apparent inconsistencies between this table and the database that you sent. For example, you indicate with an asterisk that eyes [redacted]\*, [redacted]\*, and [redacted]\* continued on into the LTM study. But the ECD database does not contain any data past 18 months for [redacted], and nothing past 24 months for the other two eyes. Please clarify this situation or point out my error in this matter. If these are in fact errors in this table, please ensure that you check all such entries in information that you have submitted to us. If some eyes had visits without collecting ECD data, please clarify this situation.

Thanks for your help.

*Gene*

Gene Hilmantel, OD, MS

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---

**From:** Judy Gordon [mailto:judy@clinregconsulting.com]  
**Sent:** Monday, November 10, 2008 4:50 PM  
**To:** 'Hilmantel, Gene N'  
**Cc:** 'Calogero, Don'; 'Allen Hill'  
**Subject:** RE: P050034

Dear Gene,

In response to your question in the November 6, 2008 e-mail regarding Table 2, ECD < 1000 Cells/mm<sup>2</sup> Before or at 24 Month IMT-Implanted Eyes, which was provided in response to an e-mail dated October 20, 2008:

1. The only difference between the database and Table 2, is that Subjects [REDACTED] and [REDACTED], who underwent IMT removal and corneal transplantation. Post IMT removal ECDs were not included in the Table 2 for visits after IMT explant (a footnote at the bottom of Table 2 indicates "excluding records after IMT explant")
2. The table below identifies subject, visits ECD data was not reported and the reason the data was not reported in Table 2.

Subject	Visit	ECD reading
	24M	Specular images not readable by core lab
	12M, 18M, 24M	Subject died prior to 12 month visit
	6M, 9M, 12M, 18M 24M	Specular images not readable by core lab
	6M, 9M	Subject refused to complete ECD test
	12M	Investigation site lost visit images
	3M	Specular images not readable by core lab
	24M	Subject missed visit
	9M, 12M	Specular images not readable by core lab
	18M, 24M	Post IMT-removal and cornea transplant
	3M	ECD reading not done by investigation site
	9M, 12M, 18M, 24M	Post IMT-removal and cornea transplant

With respect to Subject [REDACTED] and the IMT-002-LTM trial, specular images were submitted to the core lab but the images could not be read. Regarding Subjects [REDACTED] and [REDACTED], the clinical site (Site 003) made a change in the specular microscopy equipment during the study, such that the image format cannot be read by the specular microscopy reading center. VisionCare has made repeated requests to Site 003 to correct the specular image format, and the site has refused to provide images in the required format for reading by reading center.

Best regards,  
Judy

**Judy F Gordon, DVM**  
**ClinReg Consulting Services, Inc**  
733 Bolsana Drive  
Laguna Beach, CA 92651  
Phone: 949-715-0609  
Fax: 949-715-0610  
[judy@clinregconsulting.com](mailto:judy@clinregconsulting.com)  
[www.clinregconsulting.com](http://www.clinregconsulting.com)

**ITEM 5:**  
**RESPONSE (FROM A. HILL) TO**  
**EMAIL DATED NOVEMBER 7, 2008 (12:44PM)**

**From:** Hilmantel, Gene N [mailto:gene.hilmantel@fda.hhs.gov]  
**Sent:** Friday, November 07, 2008 12:44 PM  
**To:** Judy Gordon  
**Cc:** Hilmantel, Gene N; Calogero, Don  
**Subject:** RE: Clarification needed P050034 A013 & A015

Judy,

I am still a bit confused. Is this statement in your submission incorrect?

"Late-occurring corneal edema was observed in 13 eyes, which consisted of 6 reports in IMT-002 and 7 reports in IMT-002-LTM. "

Is the number "13" a typo? Should it be "12"?

Additionally, it appears to us that since subject [REDACTED] continued to have an increased CCT (633 - 724 microns after "resolution"), that the corneal edema was unresolved. Please provide your rationale for considering this case of edema to be resolved.

If necessary, feel free to call me. I may be misunderstanding some detail.

*Gene*

Gene Hilmantel, OD, MS

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**From:** Judy Gordon [mailto:judy@clinregconsulting.com]  
**Sent:** Friday, November 07, 2008 9:03 AM  
**To:** Hilmantel, Gene N  
**Cc:** Calogero, Don; allen@visioncareinc.net  
**Subject:** RE: Clarification needed

Dear Gene,

In response to the question in your October 31, 2008 email, regarding the number of eyes with corneal edema, there are 12 IMT-implanted eyes with "late" corneal edema. We included the eye with corneal edema starting at Day 72 (Patient [REDACTED]), since the edema continued after that time, thus would have been present at >3 months.

Here is a list of the IMT-implanted eyes with "late" corneal edema grouped by eyes where corneal edema resolved (N=3), eyes where corneal edema did not resolve (N=5), and eyes that underwent corneal transplantation (N=4). Gene, please note that Patient [REDACTED] had "late" corneal edema (>3 months), however, this eye underwent intraoperative removal of the IMT, so the available follow-up is for a non-implanted eye. Patient [REDACTED] was identified in Table 32.1, Amendment 13, dated September 2, 2008. The 12 other patients in your message are also identified in Tables 32.1 (11 plus [REDACTED]) and 32.2 ([REDACTED], the patient with late edema but no late ECD loss).

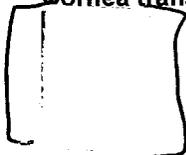
**Corneal edema resolved**  
(high ECD)



**Unresolved corneal edema**



**Cornea transplant**



I have also attached a table summarizing this information for you, as well as the patient line listings for eyes with corneal edema, submitted to you last week in response to your email of October 16, 2008. All but two of these eyes [REDACTED] and [REDACTED] had at least 1 risk factor for corneal edema, i.e., ACD <3.0 mm, operated by a non-cornea specialist or surgical order  $\leq 5$  cases. Of the 12 eyes, 9 eyes had 2 or 3 risk factors for corneal edema, and 4 of these 9 eyes had all 3 risk factors.

Gene, let me know if you have any other questions.

Best regards,  
Judy

**Judy F Gordon, DVM**  
**ClinReg Consulting Services, Inc**  
**733 Bolsana Drive**  
**Laguna Beach, CA 92651**  
**Phone: 949-715-0609**  
**Fax: 949-715-0610**

**From:** Judy Gordon [mailto:judy@clinregconsulting.com]  
**Sent:** Wednesday, November 12, 2008 2:05 AM  
**To:** 'Hilmantel, Gene N'  
**Cc:** 'Calogero, Don'; 'Lepri, Bernard'; 'Allen Hill'  
**Subject:** RE: P050034 -- Accountability of Measurements

Dear Gene,

Here is our response to your email of November 7:

Amendment 13 (9/2/08), Table 32.1 (Occurrences of Late Corneal Edema with Early ECD Loss) identifies 12 subjects with late corneal edema, and Table 32.2 (Occurrence of Late Corneal Edema with No ECD Loss Following IMT-Implantation) identifies 1 subject; a total of 13 subjects. The statement on page 67 "Late-occurring corneal edema was observed in 13 eyes," is correct.

As described in Amendment 13, page 67, subject [REDACTED], while having late corneal edema, had intraoperative IMT removal due to the development of choroidal hemorrhage. This subject was reported with mild (1+) edema at 48 months and an ECD of 1480 cells/mm<sup>2</sup> at the subject's most recent visit. There are 12 IMT-implanted eyes with late occurring corneal edema [REDACTED].

The expanded line listings provided in Amendment 16 (10/29/08) responding to the question in the October 16, 2008 e-mail present information for the 12 IMT-implanted subjects with corneal edema at > 3 months. These are the same IMT-implanted subjects identified in the paragraph above.

Regarding patient [REDACTED], VisionCare's rationale for stating the corneal edema resolved is that the investigator reported no corneal edema as of 10/28/05. Furthermore, the investigator reports no corneal edema at the subject's most recent visit, the 48 month visit. CCT was 633 microns at 48 months.

Best regards,  
Judy

**Judy F Gordon, DVM**  
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**ITEM 6:  
RESPONSE (FROM J. GORDON) TO EMAIL  
DATED NOVEMBER 7, 2008 (1:26PM)**

**From:** Hilmantel, Gene N [mailto:gene.hilmantel@fda.hhs.gov]  
**Sent:** Friday, November 07, 2008 1:26 PM  
**To:** Judy Gordon  
**Cc:** Calogero, Don; Hilmantel, Gene N; Lepri, Bernard  
**Subject:** P050034 -- Accountability of Measurements

Judy,

Please clarify why a significant proportion of patients in the follow-up study did not have ECD and/or CCT measurements.

Reviewer-Generated Table for Accountability of Measurements

	36 Months	42 Months	48 Months	
Available for Analysis	84/85 (99%)	113/125 (90%)	106/129 (82%)	
ECD Measurements Available	70	88		
CCT Measurements Available	43	82	84	

[ECD numbers taken from Table 18.1; CCT numbers taken from Table 7 in your response to the October 6th e-mail.]

Thanks.

*Gene*

Gene Hilmantel, OD, MS

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**From:** Allen Hill [mailto:allen@visioncareinc.net]  
**Sent:** Tuesday, November 11, 2008 10:48 AM  
**To:** Hilmantel, Gene N  
**Cc:** Calogero, Don; Judy Gordon  
**Subject:** VisionCare - November 7, 2008 E-Mail (P050034 -- Accountability of Measurements - another question from Gene)

Hello Gene:

With regard to your November 7, 2008 e-mail to Judy Gordon, the following information is provided to clarify the number of patients with ECD and CCT information in the IMT-002-LTM trial.

1. The accountability reference identified in the message is for operated eyes (Amendment 14, Table 4, Availability and Accountability Operated Eyes IMT-002-LTM). ECD measurements referenced in the message are for IMT-implanted eyes rather than operated eyes (Amendment 14, Table 18.1, ECD, Percent Change in ECD, and Annualized Percent Change in ECD IMT-Implanted Eyes IMT-002 and IMT-002-LTM).

As presented in the table below, at 36, 42, and 48 months, ECD readings were provided for 94%, 97%, and 89%, respectively, of the subjects available for analysis. Please refer to Amendment 14, Table 18.5, ECD and Percent Change in ECD Operated Eyes IMT-002-LTM.

**Operated Eyes IMT-002-LTM Study**

Operated Eyes IMT-002-LTM Study			
Subjects Available for Analysis	84	113	106
N (%) of Subjects Available	79 (94%)	110 (97%)	94 (89%)

2. The IMT-002-LTM protocol was approved in May 2006 and patient enrollment began in June 2006. CCT (pachymetry) was added to the IMT-002-LTM protocol for the 36 month visit in July 2006 and for all visits in August 2006, by which time some patients had the 36-month and 42 month visit windows. CCT measurements were obtained for 46 subjects at the 36 month visit, 55% of the 84 subjects available for analysis; 88 subjects at 42 months, 78% of the 113 subjects available for analysis; and 91 subjects, 86% of the 106 subjects available for analysis at 48 months.

Best regards,  
Allen

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**ITEM 7:**  
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