

APPENDIX 11

**POST-APPROVAL STUDY
PROTOCOL IMT-002-LTME**



VISIONCARE OPTHALMIC TECHNOLOGIES, INC.

**SEVEN YEAR FOLLOW-UP OF IMT-002 PATIENTS
AN EXTENSION OF THE LONG-TERM MONITORING STUDY, IMT-002-LTM**

PROTOCOL IMT-002-LTME

January 15, 2009

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

I have read and agree to follow the study procedures as outlined in this protocol.

Print Name of Investigator

Investigator's Signature

Date

CONFIDENTIAL - DO NOT COPY

This protocol contains confidential proprietary information with respect to VisionCare products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three years from the date of this agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose has been entered into by the parties.

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PROTOCOL IMT-002-LTME

PERSONNEL AND FACILITIES

L.

STUDY SPONSOR

VisionCare Ophthalmic Technologies, Inc.
14395 Saratoga, Ave., Suite 150
Saratoga, CA 95070
(408) 872-9393 Phone
(408) 872-9395 Fax

MEDICAL MONITOR

Stephen S. Lane, M.D.
Associated Eye Care
232 North Main Street
Stillwater, MN 55082

INVESTIGATORS

Sites that participated in Protocol IMT-002

CLINICAL MONITOR

DataMed Devices, Inc.
Kathryn L. Tsang and Associates
22022 Apache Drive
Lake Forest, CA 92630
(949) 458-6330 Phone
(949) 581-8106 Fax

**SEVEN YEAR FOLLOW-UP OF IMT-002 PATIENTS
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PROTOCOL IMT-002-LTME

STUDY OUTLINE

BACKGROUND	Protocol IMT-002-LTME is intended to provide an additional 24 months of safety data for patients enrolled in protocol IMT-002-LTM, a study that provides a total of 5 years of follow-up on patients participating in the IMT-002 trial. Protocol IMT-002-LTME will provide a total of 84 months (7 years) follow-up on patients participating in the IMT-002 trial, a 24-month pivotal trial conducted to support a marketing application for the IMT (Premarket Application P050034).
OBJECTIVE	The primary objective of IMT-002 LTME is to monitor the long-term safety of the IMT in patients who participated in the IMT-002 trial, a 24-month clinical trial of patients with bilateral moderate to severe central vision impairment due to age-related macular degeneration, irrespective of whether the IMT was successfully implanted or not.
PATIENT POPULATION	Patients who participated in Protocol IMT-002, approved under G000115.
STUDY DESIGN	<p>This is a 7-year study of patients participating in Protocol IMT-002. Patients who participated in the IMT-002 trial will be contacted and asked to participate in this study to monitor the long-term safety of the Implantable Miniature Telescope.</p> <p>Patients will undergo examination at twelve-month intervals to monitor endothelial cell density, posterior capsular opacification, intraocular pressure, visual acuity, device failures, complications and adverse events.</p>
STUDY PARAMETERS	Endothelial cell density, posterior capsular opacification, intraocular pressure, distance visual acuity, device failures, complications and adverse events.
EXAMINATION SCHEDULE	<p>The examination schedule is as following:</p> <ul style="list-style-type: none">• Twelve-month anniversaries of IMT implantation through 7 years of post-implant follow-up: Month 72 (Initial Visit) Month 84 (7 years)

**CLINICAL
PARAMETERS**

The following clinical parameters will be measured at each visit:

1. Intraocular pressure
2. Slit lamp examination
3. Endothelial cell count (implanted and fellow eyes)
4. Best corrected distance visual acuity (implanted and fellow eyes)
5. Pachymetry
6. Complications and adverse events
7. Device failures

NOTE: Personnel at the study site who participate in the conduct of this study must be trained by the study sponsor, the clinical monitor or their designee on the requirements of the protocol and the testing methods referenced therein. The Study Investigator or their designee familiar with the conduct of the study is expected to train personnel who join the study while it is in progress.

1.0 INTRODUCTION & RATIONALE

MACULAR DYSTROPHIES

Acquired and hereditary macular dystrophies are the leading cause of central vision impairment and blindness. Age related macular degeneration (AMD) is the most common form of macular dystrophy. Macular degeneration refers to the breakdown of cells in the macula (the center of the retina). Some degeneration is an inevitable consequence of the aging process. However, when it is coupled with the loss of sight in the central part of the field of vision, an underlying pathology is considered present. It is estimated that in the US, AMD affects 1% of 55-year-olds, and the incidence increases with age, reaching approximately 15% among those aged 80 and over (1). With increasing longevity, it is anticipated that the incidence will increase significantly (1).

The main effect of AMD is to reduce the ability of the individual to engage in everyday activities that require clear central vision. It is associated with elevated risk of depression, increased levels of dependency, and an overall decrease in the quality of life (2-4). Currently there is no effective treatment for the majority of patients. For a minority of patients, (i.e., those with wet AMD resulting from choroidal neovascularization (CNV), advances in new therapies have led to improvements in the management of the rate of vision loss. New treatments include photodynamic therapy, trans-pupillary thermal therapy, submacular surgery and photoablation. However, no viable treatments are available for the several hundred thousand individuals with moderate to severe central vision loss due to late stage dry, atrophic AMD, end stage CNV with disciform scar.

The only corrective interventions currently available are low vision aids such as special spectacles and head-mounted or hand-held telescopes, which magnify images onto the retina. These aids are widely available but have only limited acceptance by patients. Patients find these aids bulky, uncomfortable and unattractive. In addition, use of external telescopes requires suppression of natural eye movements. Instead, the patient has to learn to scan the visual field by moving his/her entire head. If not properly adapted to this behavioral change requirement, a conflict between the visual and vestibular systems will arise, resulting in nausea.

**THE
IMPLANTABLE
MINIATURE
TELESCOPE
(IMT)**

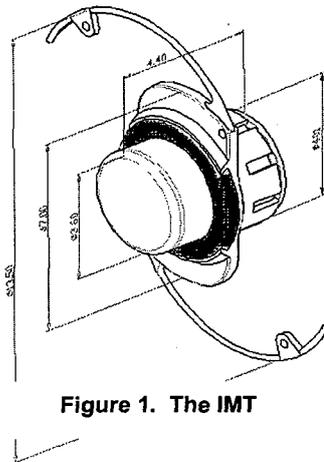


Figure 1. The IMT

VisionCare's Implantable Miniature Telescope (IMT™) is an intraocular implant which, when combined with the optics of the cornea, constitutes a telephoto lens (Figure 1). The IMT contains two micro lenses, which magnify objects in the central visual field, allowing the patient to see without the need of external low-vision aids. A magnified image is projected by the IMT onto the retina, enabling the patient to recognize and identify objects that could not otherwise be seen. The IMT provides improved near or distance vision

correction in the same fashion as an external telescope. The optical component is embedded in a carrier, which is intended to be implanted in the capsular bag in the posterior chamber of the eye, in place of the eye's crystalline lens. It is held in position by haptic loops using a surgical procedure similar to that used in refractive cataract surgery.

The IMT is indicated for use in patients with bilateral, stable macular degeneration. Vision loss must be sufficiently advanced to have caused significant or complete loss of normal central vision, but adequate peripheral vision must be retained. The IMT is only implanted in one of the patient's eyes. In this way, the implanted eye provides central vision and the non-implanted eye can continue to provide peripheral vision.

**ADVANTAGE OF
THE IMT OVER
ALTERNATIVE
LOW VISION
TREATMENTS**

The primary advantage of the IMT over alternative treatments for low vision is that the IMT allows scanning of reading materials and other images using natural eye movements, rather than head movements. Since there is no relative movement between the eye and the telescope, there are no optical aberrations and a wider visual field (central field of 20° or more on the retina) is achieved. The placement of the magnifying device entirely inside the eye eliminates increased speed of motion and vestibular conflict.

If there is further deterioration of the macula after the implantation, the amount of magnification can be significantly increased by bringing the object closer to the eye and adding low-plus eyeglasses (+1.00 to +3.2 D). With glasses, up to 8X magnification can be achieved at 18 cm with the Wide Angle (WA) 3.0X IMT.

2.0 STUDY OBJECTIVE

The primary objective of this study is to further monitor the long-term safety of the Implantable Miniature Telescope (IMT) in patients with bilateral moderate to severe central vision impairment due to age-related macular degeneration. Data from this study is intended to provide long-term safety information on the IMT.

3.0 STUDY DESIGN

IMT-002-LTME is a 7-year study of patients enrolled under Protocol IMT-002. Patients who participated in the IMT-002 trial, irrespective of whether the IMT was successfully implanted or not, will be contacted and asked to participate in this study to monitor the long-term safety of the Implantable Miniature Telescope.

Participation will require new informed consent form to be signed by IMT-002 patients, since these patients completed and exited the IMT-002 trial as well as the IMT-002-LTME trial.

4.0 STUDY PARAMETERS

- Endothelial cell density (implanted and fellow eyes)
- Slit lamp examination (corneal health and posterior capsular opacification)
- Intraocular pressure
- Pachymetry
- Best corrected distance visual acuity (implanted and fellow eyes)
- Adverse events and complications

5.0 PATIENT POPULATION

Patients who participated in the IMT-002 trial will be contacted and asked to participate in this study to monitor the long-term safety of the Implantable Miniature Telescope, provided they conform to the following criteria.

5.1 INCLUSION CRITERIA

- Patients must have participated in the IMT-002 trial.
- Patients must be able to understand and comply with the requirements of the clinical study, and be able to abide by the requirements and restrictions of the study.
- Patients must be able to provide voluntary informed consent, and must sign and be given a copy of the written Informed Consent form.

5.2 EXCLUSION CRITERIA

NONE

6.0 INVESTIGATIONAL PROCEDURES

6.1 SUBJECT ENTRY

6.1.1 PATIENT CONTACT

Patients participating in the IMT-002 trial will be contacted and asked to participate in the IMT-002-LTME study. Three attempts will be made to contact each study patient, two by phone and one in writing. The Investigator or a designee will explain the study purpose, procedures, and patient responsibilities to the potential participant. The patient's willingness and ability to meet the follow-up requirements will be determined by the investigator or a designee.

6.1.2 INFORMED CONSENT

When it has been established that the patient may be eligible, written informed consent will be obtained (**Appendix 1**). The patient will sign and date the consent form in the presence of a witness. The Investigator will also sign and date the consent form. One copy of the informed consent form will be retained with the patient records and a copy will be provided to the patient. The patient is now considered enrolled.

6.1.3 PATIENT REFUSAL, PATIENT INABILITY TO PARTICIPATE, OR INABILITY TO CONTACT

If the patient refuses or is unable to participate in the IMT-002-LTME study, the reason for refusal or inability to participate will be documented. Documentation will also be provided for patients who could not be contacted.

6.2 EXAMINATION SCHEDULE

Subjects will be examined and evaluated according to the following schedule of visits:

- Study entry (If outside the windows noted below)
- 72 Months (+/- 3 months)
- 84 Months (+/- 3 months)

A full description of the examination schedule and clinical parameters can be found in **APPENDIX 2**.

NOTE: Follow-up visits from 72 month through 84 months should not occur less than twelve weeks after the previous visit.

6.3 CLINICAL PARAMETERS

The clinical parameters to be evaluated at study visits are:

1. Best spectacle-corrected distance acuity, using ETDRS VA charts (implanted and fellow eyes)
2. Intraocular pressure
3. Slit lamp examination
4. Specular microscopy of the central cornea: (implanted and fellow eyes)
5. Pachymetry
6. Device failures
7. Complications
8. Adverse events.

Postoperative visual examinations may be performed by the Investigator, or by ophthalmic technicians, optometrists and/or ophthalmologists under the supervision of the Investigators using methods described in **APPENDIX 2**. Patients are allowed to utilize low vision counseling and rehabilitation services as needed.

6.4 DATA COLLECTION AND VALIDATION

A Case Report Form (CRF) booklet will be provided by the Sponsor or its designee for each patient enrolled in the study. A sample Case Report Form may be found in **APPENDIX 3**. The appropriate Case Report Form will be completed and signed by the Investigator at each examination. Case Report Forms will be completed in a legible manner in black ink. Any corrections will be made by drawing a single line through the incorrect entry, entering the correct information, and initialing and dating the change. Data entries boxes or spaces should not be left blank, but instead should indicate: NA = not applicable, ND=not done, NE=not evaluable or NAV for missing or not available data. The original signed forms, not copies, will be returned to the Sponsor.

Clinical data generated in the study will be submitted to the Sponsor or its designee for quality assurance review, data entry, and statistical analysis. Forms will be reviewed for completeness and evident recording errors will be rectified by contact with the appropriate clinical site. Double-entry routines will be utilized to reduce data entry errors, and computerized editing routines will be used to identify unusual data entries for verification prior to statistical analysis. The database will be equivalent to that used for the IMT-002 trial, a validated database, which contained data for the Sponsor's PMA, M050004. Study data will be maintained on a secure computer with appropriate data security provisions.

6.5 STUDY COMPLETION PROCEDURES

6.5.1 PATIENT COMPLETION

Patients are considered to have completed the study if they have completed all follow-up examinations through 7 years post IMT implantation.

6.5.2 PATIENT TERMINATION

Patients may be terminated from the study at the discretion of the Investigator only if continuation would jeopardize the patients' health and/or welfare. Terminated patients will be considered to have completed the study. Every effort will be made to follow terminated patients for safety reasons using the appropriate case report forms until the planned end of the study period. NOTIFICATION OF A PATIENT TERMINATION WILL BE MADE IMMEDIATELY TO THE SPONSOR OR ITS DESIGNEE.

6.5.3 PATIENT EXIT

A patient exit form must be completed for patients who either complete, discontinue, are considered lost to follow-up, or are terminated from the study. Before a patient is considered "lost to follow-up", there should be three documented attempts to reach patients. At least one of these attempts must be in writing by certified / return receipt mail, a copy of which should be included in the patient's medical / clinic chart.

7.0 STATISTICAL METHODS, REPORTING, DATA COLLECTION, DATA VALIDATION

7.1.1 STATISTICAL METHODS

Due to the observational, non-comparative nature of this study, the primary statistical analysis will be based on descriptive statistical techniques using 95% confidence intervals.

7.1.2 REPORTING

Planned analyses will be performed as follows:

Slit lamp findings

Endothelial cell density (ECD)

- Endothelial cell density (ECD)
- Change in endothelial cell density (ECD) from baseline
- Percent change in endothelial cell density (ECD) from baseline
- Change in ECD between consecutive postoperative visits

- Percent change in ECD between consecutive postoperative visits
- Percent change in ECD between consecutive postoperative visits pseudophakic fellow eyes of subject implanted with IMT

Adverse events and complications

- Ocular complications
- Ocular adverse events

Distance visual acuity

- Change in best corrected distance visual acuity stratified by IMT model and visit

8.0 ADVERSE EXPERIENCES REPORTING / DEVICE MALFUNCTIONS

8.1 ADVERSE EXPERIENCES

Throughout the course of the proposed study, efforts will be made to remain alert to possible adverse experiences or untoward findings. If adverse experiences occur, the first concern will be the safety and welfare of the patient. Appropriate medical intervention will be made. Any adverse experiences or complications observed by the Investigator or reported by the patients, whether or not ascribed to the IMT, will be recorded in the appropriate section of the patient's Case Report Form.

ANY SERIOUS ADVERSE EXPERIENCES AND UNANTICIPATED, SEVERE, SIGHT-THREATENING ADVERSE REACTIONS, WHETHER OR NOT ASCRIBED TO THE IMT, WILL BE COMMUNICATED PROMPTLY, BY TELEPHONE, TO THE SPONSOR AND TO THE IRB. THESE REPORTS MUST BE CONFIRMED IN WRITING WITHIN FIVE DAYS OF THE OCCURRENCE. Any patients who are terminated from the study due to adverse experiences will be followed until their medical outcome is determined, and written reports will be provided to VisionCare Ophthalmic Technologies by the investigator.

Below is a list of potential or anticipated Adverse Events based on prior IMT clinical trials or known to be occasionally associated with similar types of anterior segment surgery. This list should not be considered comprehensive, but rather identifies events which can be reasonably anticipated.

Table 1 – Adverse Events

➤ Anterior chamber inflammation
➤ Choroidal detachment
➤ Choroidal neovascularization
➤ Choroidal hemorrhage
➤ Corneal decompensation
➤ Corneal edema
➤ Corneal transplant
➤ Cyclitic membrane
➤ Diplopia
➤ Distorted pupil
➤ Endophthalmitis
➤ Flat anterior chamber
➤ Hyphema
➤ Hypotony
➤ Hypopyon
➤ IMT dislocation
➤ IMT repositioning
➤ IMT removal
➤ Increased IOP requiring treatment
➤ Iridotomy
➤ Iris atrophy
➤ Iris damage
➤ Iris prolapse
➤ Iris transillumination
➤ Iritis
➤ Optic atrophy
➤ Precipitates or deposits on IMT
➤ Pupillary block
➤ Retinal detachment
➤ Retinal vascular occlusion
➤ Subretinal hemorrhage
➤ Synechiae
➤ Uveitis/Vitritis
➤ Vitrectomy/vitreous aspiration
➤ Vitreous hemorrhage
➤ Vitreous in anterior chamber
➤ Zonular dehiscence

8.2 DEVICE MALFUNCTIONS

A device malfunction is defined as a failure of the IMT to meet its performance specifications or otherwise perform as intended. Performance specifications include claims made in this protocol or the product associated labeling. Device malfunctions will be recorded in the appropriate field on the patient Case Report Forms.

9.0 MONITORING

Sponsor personnel or their designee will monitor clinical studies in a manner consistent with applicable health authority regulations and the clinical research standards adopted by the Sponsor. Study monitoring will involve the following elements:

- A. Sponsor personnel or designee may meet with Investigators prior to the initiation of the study in order to review the available patient population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator with the study protocol.
- B. Sponsor personnel or designee may meet with the Investigator(s) at the time study patients begin to be enrolled in order to ensure that patients are being properly recruited and that study data are being correctly recorded.
- C. Sponsor personnel or designee may visit the clinical site at any time during the study to review and/or collect the Case Report Forms.
- D. Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

APPENDIX 1

SUBJECT CONSENT FORM

VISIONCARE OPHTHALMIC TECHNOLOGIES, INC.

**SEVEN YEAR FOLLOW-UP OF IMT-002 PATIENTS
AN EXTENSION OF THE LONG-TERM MONITORING STUDY IMT-002-LTM**

PROTOCOL IMT-002-LTME

1. PARTICIPANT'S NAME: _____

2. PURPOSE OF PROJECT:

You have been invited to participate in a research study sponsored by VisionCare Ophthalmic Technologies, Inc. (the study Sponsor) and

Dr. _____, the study Investigator.

The purpose of this study is to monitor the long-term safety of the Sponsor's Implantable Miniature Telescope (IMT™) in patients with age-related macular degeneration (AMD) who participated in the sponsor's IMT-002 clinical trial. You are a candidate for this study because you participated in the IMT-002 trial. You are being asked to participate in this study in order to obtain long-term data on the IMT device implanted, or not, in one of your eyes in the IMT002 clinical trial. You will be asked to visit your physician for eye examinations every 12 months for the next 2 years.

3. DESCRIPTION OF RESEARCH:

The study you are being asked to participate in is an additional long-term monitoring study for patients who participated in the IMT-002 clinical trial. This study will last approximately 2 years and will involve visits to your eye doctor's office every 12 months until you reach the 7 year anniversary of the date you had surgery for the IMT device irrespective or not of whether you were implanted or still have the implant.

The first step in this study is to determine whether you are able to participate in this trial. This will be accomplished by answering several questions to make sure that you understand the study requirements and can communicate clearly to the study personnel.

You will need to return for examinations on or around month 72 (6 years) and month 84 (7 years) from the original date of your IMT implantation surgery. At the follow-up examinations, some of the same testing that was performed in the IMT-002 trial will be repeated in order to evaluate changes in your vision and the condition of your eyes. This testing includes an eye examination using a slit lamp, intraocular pressure, distance visual acuity testing with an eye chart, pachymetry, and measuring the number of cells on the inside of your cornea using a non-contact specular microscope. Testing that will be performed on your eyes is the same as the testing that was done while you were participating in the original study of the IMT, but fewer tests will be performed.

4. RISKS

There are no new risks to you related to participating in the long-term follow-up study of the IMT. The risks associated with the IMT and the surgery to implant the IMT were discussed with you when you decided to enroll in the IMT clinical study. Those risks and any problems you may be having with the IMT will be evaluated during this longer-term follow-up study that you have been asked to participate in.

5. POTENTIAL BENEFITS

The potential benefit to you of participating in this research study is that you will have continued examination of your eyes to determine if you are having any problems with your IMT eye. This study will also provide needed information on the long-term safety of the IMT.

6. ALTERNATIVE TREATMENTS

Since you already have or did have the IMT implanted in your eye, alternative treatments are not applicable to your situation.

7. CONFIDENTIALITY AND PATIENT AUTHORIZATION

You should understand that your medical records pertaining to participation in this study will be made available for review by your doctor to the Sponsor of the study and to governmental agencies such as the U.S. Food and Drug Administration (FDA). You should also understand that the information in these records will be kept confidential, but, that on rare occasions, disclosure to third parties may be required by law. By signing this form, you authorize access to your study related medical records by the US FDA and other governmental agencies.

You agree that results of your surgery and photographs of your eyes made as part of the study may be published for scientific purposes provided your identity is not revealed. Results of this study may be presented at scientific meetings and published in journals, however, no names will be used in any data summaries or publications and medical data will be protected.

8. COMPENSATION FOR INJURY

You will not be compensated for participation in this study.

You will not receive a bill or be asked to pay for the cost of the study examinations. The study sponsor will cover the costs of testing performed specifically for the study. If a research-related illness or injury occurs at any time during the study, you will receive medical care at _____ Hospital under the supervision of the study Investigator. Any costs for the treatment of research related adverse events not covered by insurance will be paid for or reimbursed by the Sponsor. You will not be compensated monetarily by the study Sponsor, the hospital or other institution, or the study Investigator for lost wages, disability, or discomfort resulting from this type of illness or injury. You should understand that treatment, payment, or enrollment in a health plan or eligibility for benefits is not contingent upon signing this form.

9. VOLUNTARY PARTICIPATION

You should understand that your participation in this study is completely voluntary and that you may withdraw from the study at any time without prejudice to your future medical care. Should you decide to withdraw from the study for any reason, you should contact the Investigator immediately. You may be discontinued from the study at any time if the Investigator considers it to be in your best medical interest. Should your participation in the study be terminated, regardless of the reason, you will not suffer any penalties or loss of benefits to which you are otherwise entitled.

You will be informed of any significant information regarding new findings that may develop during the course of the research study that may relate to your willingness to continue participating as a subject in the study.

10. CONTACT PERSON

If, at any time, you have questions regarding your participation in this study, you can call Dr. _____, your study Investigator, at:
(_____) _____.

11. CONSENT

I have been given an opportunity to ask any questions concerning the research, and my participation, and the study Investigator has answered my questions. By signing this consent form I understand that I have not waived any of my legal rights.

I understand that I will receive a copy of this consent and authorization form, which will show all signatures and dates.

I hereby willingly give my consent to participate in the above-described clinical study.

Patient Signature _____ Date: _____

Printed Name of Patient _____

Witness Signature _____ Date: _____

I have discussed this research study with the patient using language that is understandable and appropriate. I believe that I have fully informed this patient of the nature of this study, and its possible benefits and risks, and I believe the patient understood this explanation.

Investigator Signature _____ Date: _____

APPENDIX 2 STUDY EXAMINATIONS : SCHEDULE & METHODS

**APPENDIX 2
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APPENDIX 2.1
 EXAMINATION SCHEDULE AND CLINICAL PARAMETERS

TABLE 1. SCHEDULE OF EXAMS AND CLINICAL PARAMETERS

EXAM / TEST	VISIT		
	STUDY ENTRY VISIT IF PATIENT IS OUT OF CYCLE		
		72 months	84 months
BEST CORRECTED DISTANCE VISUAL ACUITY (BOTH EYES)	✓	✓	✓
IOP	✓	✓	✓
SLIT LAMP EXAM	✓	✓	✓
SPECULAR MICROSCOPY (BOTH EYES)	✓	✓	✓
PACHYMETRY	✓	✓	✓
DEVICE FAILURES	✓	✓	✓
COMPLICATIONS	✓	✓	✓
ADVERSE EVENTS	✓	✓	✓

APPENDIX 2.2

BCVA TESTING PROTOCOL

∞ INTRODUCTION & SCOPE ∞

Visual acuity will be measured using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. A set of two of these charts (Lighthouse Chart C-110 and C-105 respectively, which have different letter sequences or Precision Vision Chart R (Catalog #2110), Chart 1 (Catalog #2111) and Chart 2 (Catalog #2112) and a retro-illuminated box providing standardized chart illumination¹ will be used to determine visual acuity.

Distance visual acuity testing will be performed at a distance of 2 meters (or at 1 meter for patients who are unable to read 20 letters of the first four lines of the chart at 2 meters).

FACILITIES & MATERIALS

VISUAL ACUITY CHARTS

Charts 1 and 2 are used for testing visual acuity. Chart R is used for refraction. The ETDRS charts consist of 14 lines of 5 high-contrast Sloan letters of equal difficulty and geometric progression of letter size with results in an arithmetic progression of the logarithm of minimum angle of resolution from line to line. Charts 1, 2 and R have different letter sequences. Patients should be prevented from seeing Charts 1 and 2 until refraction has been completed and the visual acuity test begins.

VISUAL ACUITY BOX

The dimensions of the light box are 24-3/4 inches (62.9 cm) by 25-3/4 inches (65.4 cm) by 7 inches (17.8 cm). The light box should be mounted on the wall or on a cylindrical stand manufactured by the Lighthouse Low Vision Services (L-225). The stand is mounted on a five-pronged wheelbase, with each prong about 14 inches (35.6 cm) long. Two of the five wheels are lockable. When the box is mounted on the stand, its height can be varied. The light box should be mounted at a height such that the top of the third row of letters (0.8 log MAR) is 49 ± 2 inches (124.5 cm \pm 5 cm) from the floor.

RETRO ILLUMINATED BOX

The room lights should be turned off during the visual acuity test. The box itself provides sufficient illumination for the examiner to record the results. Additional light can have an adverse effect.

The visual acuity light box is equipped with two 20-watt fluorescent tubes and ballast. The Sponsor recommends these lights be changed out for new bulbs at the start of the IMT-002 Study and at least yearly thereafter or in the event of a bulb failure. At the

¹ manufactured by Lighthouse Low Vision Products (L-220)

beginning of each examination, proper functioning of the two fluorescent tubes should be verified.

ROOM FOR VISION TESTING

The room for visual acuity testing must have space for a 2 meter (78.7 inches) lane, the visual acuity box, the stand, and the participant. The lane represents a distance of exactly 2 meters between the patient's eyes and the visual acuity chart. In addition to the 2 meter lane, 13 inches (33 cm) must be allowed for two of the stand's castors to touch the rear wall (or a line marked on the floor when there is no wall) plus space for the patient to sit.

No specular reflection from the chart surface directed towards the patient's eyes is permitted. This is determined with transillumination of the chart turned off and ambient light on.

MARKING THE 1 METER (39.7 INCHES) AND 2 METER (78.9 INCHES) DISTANCES

Floor marks cannot be used reliably to mark either the 1 or 2 meter distances. The horizontal distance between the patient's eye and the chart must be measured individually for each examination. The distance is best measured with one and two meter sticks or a measured non-elastic string from the eye of the patient, who is comfortably seated in a chair with his or her back firmly placed against the chair's back, to the center of the second letter (for left eye) or fourth letter (for right eye) of the third line of the chart.

PROCEDURES

Measurements should be obtained by a physician, optometrist or trained technician supervised directly by the physician or optometrist, before the patient's pupils have been dilated.

TESTING BEST CORRECTED VISUAL ACUITY

TESTING DISTANCE

Visual acuity testing is performed at a distance of 2 meters for all patients, including those who could not be refracted at the two-meter distance. Visual acuity is tested at 1 meter only if the number of letters read correctly at 2 meters is less than 20.

The distance from the patient's eyes to the visual acuity chart must be exactly 2 meters. The patient must sit for the 2 meter visual acuity test. His or her back should be firmly touching the back of the chair. The examiner should ensure that the participant is sitting comfortably, that the head does not move forward or backward during the test, and that the participant's eyes remain at the 2 meter distance.

USING THE ETDRS CHART

First, non-implanted eye after surgery and then IMT implanted eye is tested. Visual acuities will be evaluated with the subject's eyes in the

straight-ahead, primary position of gaze. This will help to assure that visual acuity in the non-implanted eye is measured without the use of peripheral vision. The IMT implanted eye will have no peripheral vision, but for reasons of consistency should be conducted in the same manner.

**TESTING
PRINCIPLES**

1. As previously mentioned, room lights should be turned off during visual acuity testing. The retro-illuminated box will provide sufficient light for the examiner to record results of the test.
2. The patient should be told that the chart has letters only and no numbers. If the patient forgets this instruction and reads a number, he or she should be reminded that the chart contains no numbers and the examiner should request a letter in lieu of the number. Examiners should point to the chart and to specific letters on the chart. Examiners should never read any of the letters during the test.
3. Because each letter will be scored, the patient should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter. The examiner should not proceed with the next letter or line of letters until the patient has given a definitive answer for each letter. It may be useful for the examiner to demonstrate the letter-a-second pace by reciting "A, B, C.". If, at any point, the participant reads too quickly, he or she should be asked to stop and read slowly.
4. Each participant will be encouraged to read the letters on the chart as they become smaller and more difficult to read. Each time a participant says he/she cannot read a letter, the examiner will encourage him/her to figure letters but not to randomly guess at them. If the participant identifies a letter as one of two or more letters, he/she should be asked to choose one only. The examiner should remind the participant to blink normally during testing. Visual acuities are to be evaluated with the patient's eyes in the straight-ahead, primary position of gaze. The testing and recording of answers will continue until the patient states that he/she can no longer read or figure out the letters. The examiner may stop the test at this point provided that the patient has previously made some errors that indicate that the best possible acuity level has been reached. Patients are encouraged to make a best possible choice for several reasons: 1) statements that they cannot identify a letter are often unreliable, and 2) bias may be reduced when effort is maximized through guessing. Furthermore, inter-center variability of visual acuity measurement is minimized when uniform instructions for testing are employed.
5. Where a wrong answer is given, have the patient proceed with the next letter, but re-evaluate the "wrong" letter again after completing the line. If patient loses their place, he/she should be asked to go

back to the top line, and start again, reading only the first or last letter in the line for those lines which were complete, once the missed line is reached, continue with standard examination. This procedure, called the First Letter Technique is used in examinations with low vision charts, also during rehabilitation.

SCORING The examiner records each letter identified correctly by circling the corresponding letters on the Visual Acuity Form. Letters read incorrectly and letters for which no guesses are made are not marked on the form. Each letter read correctly is scored as one point. The score for each line (which is zero if no letters are read correctly) and the total score for each eye is recorded on the Visual Acuity Form after testing is completed.

SCORING FOR 2 METER TESTING If testing at 1 meter is not required, 15 points are automatically scored for the 1-meter test. The total combined score (i.e., the sum of the 2 meter and the 15 points awarded for the 1 meter test) is recorded on the Visual Acuity Form.

SCORING FOR 1 METER TESTING Eyes reading less than 20 letters correctly at 2 meters should be tested at 1 meter. Both the 2 and 1 meter totals should be recorded on the Visual Acuity Form. If the trial frame is to be removed when changing the test distance from 2 meters to 1 meter, the testing chart should first be removed from view to prevent the participant from reading the chart with the fellow eye.

Before testing at 1 meter, a +0.50 sphere should be added to the 2-meter correction already in the trial frame to compensate for the closer testing distance. The participant must sit for the 1-meter test. The avoidance of any head movement forward or backward is particularly important during the 1-meter test.

NOTE: The above Refraction and BCVA Testing Protocol represents a modified version of one published by Lighthouse. The calibration requirements outlined involving a photometer are encouraged if the device is available, but is NOT required as part of the IMT-002-LTME Study. The Sponsor does encourage the site to periodically confirm the luminance quality with the use of a standard light meter.

Appendix 2.3 SPECULAR MICROSCOPY

The main safety concern to be addressed by specular microscopy is the possibility of a chronic loss of endothelial cell density, which, even at a low yearly rate could, over time, lead to corneal edema and decompensation.

To determine endothelial cell density loss, specular microscopy will be performed at scheduled examinations, i.e., month 72 and month 84.

Analyses of specular microscopy data will include the determination of the mean cell density loss over time and a frequency distribution. The mean rate of cell density loss will be calculated via a paired analysis in order to calculate the mean of the differences.

Collection of data

The methods used for the collection and analysis of specular microscopy data are critically important to minimizing the variability associated with these measurements. Common sources of variability in specular microscopy are:

- difficulty in returning to same location on the cornea at each visit;
- poor image quality (less than 100 countable cells);
- technician error; and
- improper reader analysis.

To address differences in location of the image within a given area of the cornea, three acceptable images should be taken at each visit. The mean density from the three images should be used.

Problems due to poor image quality and/or technician error will be ameliorated by using appropriate equipment and trained, experienced clinical sites equipped with non-contact specular microscopes. Images will be stored on 35 mm slides, half-inch video, or in electronic format such as CD's, floppy disks and/or zip drives. Sites may also produce high quality photographic images which can be electronically scanned and digitized.

Specular cameras that can record digitized images on disk are preferable for ease of data transfer.

Prior to the beginning of the study, each site will be required to take an initial set of images for an evaluation of image quality. Training (or retraining) will be performed as necessary and include the following important points:

An acceptable image has:

- distinct cells;
- maximum identifiable (countable) cells, >75 cells preferred; and
- cells that can be grouped in a uniform area.

To capture a good image:

- make sure the patient is comfortable;
- instruct the patient to blink;
- instruct patient not to move and to open eyes wide;
- instruct patient to focus straight ahead or on the green light;
- be patient; and
- if necessary, use the manual setting. (Note that the use of the manual setting may require additional training.)

A central reading center will be retained for both grading the quality of specular micrographs and for analyzing the specular images. The reading center or technician performing the image analysis will be advised of the following:

- The center method for counting cells is recommended.
- The quality of cells in an image is critical. Since the presence of disease can increase variability (e.g., polymegathism/pleomorphism post-contact lens wear, keratoconus), the area with the fewest distortions (not in shadow, washed-out, or blurred) should be used for the image analysis.

SPECULAR MICROSCOPY PROCEDURE A non-contact specular microscope will be used at each site. The mean density from three images of the same location of the cornea will be made.

ENDOTHELIAL IMAGE PHOTOGRAPHY

1. The location to be photographed is selected by clicking on the mark that indicates the location of the fixation target. An image will be taken of the central cornea.
2. Patients will be asked to place their chin on the left chin rest for photography of the right eye and on the right chin rest for photography of the left eye. Adjust the height of the chin rest so that an image of the patient's eye can be seen on the monitor screen with the pupil in the approximate center of the screen. The patient is asked to stare at the fixation target, or straight ahead if unable to see the target, until an image is photographed.
3. An endothelial image is recorded by clicking on the appropriate indicator button on the instrument. The instrument aligns, focuses and takes the endothelial photograph automatically and the endothelial image will appear on the screen immediately.
4. Endothelial images will be recorded and sent to DataMed Devices for archiving before being sent to the specular microscopy reading center for image analysis.