

FDA PRIMARY CLINICAL REVIEW: PMA P050034 – VisionCare Technologies, Inc. Implantable Miniature Telescope (IMT™) July 10, 2006

Introduction:

The sponsor evaluates a novel device for the rehabilitation of selected patients with central vision loss. The device addresses a major public health problem at this time.

This review identifies several methodology concerns. These concerns lead one to question the validity of the results. Most, if not all, of these concerns could be addressed by additional analyses of the sponsor. It is recommended that these additional analyses are completed before a final conclusion is made regarding the safety and effectiveness of the device.

Study Design Limitations

Major study design limitations are enumerated below, with suggestions in italics at the end of each section to indicate how the deficiencies could be resolved.

1. There are no controls.

Without controls, it is impossible to determine if the visual acuity outcomes are **worse** than might occur with no IMT. While visual acuity improvements are noted in a proportion of subjects (e.g., 141 [73%] of 192 eyes improved by 2 or more lines from baseline at 12 months), all of these eyes underwent cataract surgery, and all of these subjects underwent rehabilitation. It is possible, for example, that 95% of such eyes would have improved by 2 or more lines from baseline at 12 months following cataract surgery with a standard IOL and rehabilitation but without the IMT, such that 22% of eyes were “harmed” by the procedure).

A similar limitation exists with respect to the NEI-VFQ results. The improvement noted could have been associated with the cataract surgery or the rehabilitation or both in the absence of an IMT.

A control also would allow one to determine if use of an external low vision aids, such as a telescope, in controls undergoing cataract surgery and rehabilitation led to better outcomes than seen with subjects undergoing implantation.

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The results are not overwhelming enough to conclude any true effectiveness in the absence of controls.

2. The analysis omits outcomes of 11 eyes that underwent surgery in which complications prevented implantation of the IMT (5 eyes) or in which the device was implanted but removed (6 eyes) so that only 206 eyes of the 218 enrolled are evaluated.

1 eye of 218 enrolled was removed from analysis because surgery was cancelled. While it might be appropriate to exclude this case from analysis (although an intent to treat analysis even would include this case), it is inappropriate to remove the other 11 cases from analysis.

If one is evaluating the safety and effectiveness of the device, one must evaluate

individuals who underwent surgery to implant the device, since in the practice of using the device, one does not know if one will be successful at implanting the device. As an extreme example, if all 11 patients decreased to light perception, then 11 (5%) of 217 subjects undergoing IMT go to light perception. This hardly represents a safe outcome in someone with a stable central scotoma, and the upper limit of the 95% confidence interval around this point estimate of 5% is much higher. Furthermore, the effectiveness on visual acuity needs to include these 11 eyes.

The sponsor indicates their results apply to all “eyes successfully implanted” but the objective in the protocol states that the objective “is to evaluate the safety and effectiveness of the Implantable Miniature Telescope (IMT)”. ***It does not say to evaluate the safety and effectiveness of successfully implanted IMTs.***

The outcome parameter in the protocol states “The procedure will be considered successful if there is an improvement of 2 lines or greater in either near or distance acuity in 50% of the implanted eyes at 12 months post-implantation.” ***It does not state that the procedures will be considered successful if there is an improvement of 2 lines or greater in either near or distance acuity in 50% of the successfully implanted eyes at 12 months post-implantation.***

The safety and effectiveness must be evaluated by the inclusion of the outcomes at 12 months in these 11 eyes. If such information is not available, the last observation could be used, but the frequency of imputing missing data, and the length of time from imputation to 12 months would need to be considered when considering the strength of imputed evidence.

3. The analysis appears to omit outcomes of 8 eyes that underwent surgery in which complications led to removal of the IMT after successful implantation.

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It was a little difficult for this reviewer to determine with certainty, but it seems that 8 eyes had the IMT removed after initial successful implantation because of some complication. It seems that the outcomes of these eyes also were removed from safety and effectiveness outcomes. Again, for the same reasons as outlined in number 2 above, these eyes should be included in the analyses.

As in number 2 above, the safety and effectiveness must be evaluated by the inclusion of the outcomes at 12 months in these 8 eyes. If such information is not available, the last observation could be used, but the frequency of imputing missing data, and the length of time from imputation to 12 months would need to be considered when considering the strength of imputed evidence.

4. It is unclear what data was used at 12 months for missing data besides the 11 cases discussed in number 1 above and the 8 cases discussed in number 2 above.

If such information is not available, the last observation could be used, but the frequency of imputing missing data, and the length of time from imputation to 12 months would need to be considered when considering the strength of imputed evidence.

5. The Professional Use Information states that the Activities of Daily Living (ADL) questionnaire is a modified version of the Activities of Daily Vision Scale to more appropriately address challenges facing individuals with end-stage macular degeneration. There is no reference to indicate if this modified version has been validated in a population with eye disease, or with age-related macular degeneration. There is no information regarding what a clinically relevant change would be for this instrument.

In the absence of documentation regarding the validity of this instrument or what a clinically relevant change would be (or the power of this study to detect such a change), it is impossible to assess the results provided.

6. The incidence of posterior capsular opacification cannot be determined reliably from the design of the study as the Case Report Forms *do not ask specifically whether there is posterior capsular opacification at follow-up.*

If one does not ask about this complication, there is no way to determine if and when opacification occurred. For example, there is no indication that the 2 cases that underwent needling of the posterior capsule for posterior capsular opacification ever had posterior capsular opacification documented on a Case Report Form prior to the needling, but it seems unlikely that opacification did not develop before the needling.

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The sponsor needs to determine the incidence of posterior capsular opacification in each subject at this time from a specific “yes” “no” inquiring about its presence, and assume it was present for any subject for whom this information is not available.

7. In the sponsor’s response to deficiency 15c from the December 8, 2005 letter, the sponsor states that subjects reported no symptoms of nystagmus, disorientation or other vestibular problems in your IDE study. The sponsor was asked to clarify whether the subjects were questioned explicitly about these symptoms. The sponsor indicated the subjects were not questioned explicitly about these symptoms, thus, one cannot determine whether these symptoms existed.

The sponsor needs to determine the incidence of these symptoms in each subject at this time from a specific “yes” “no” inquiring about its presence, and assume it was present for any subject for whom this information is not available.

8. It is unclear how many additional procedures were done from the data provided (e.g., corneal transplants, retinal detachment surgery, cryopexy or laser retinopexy to retinal tears, etc).

Safety Concerns

While the limitations to the methodology outlined above preclude determining whether the device is safe or effective, the following comments are noted with respect to safety.

1. The incidence of endothelial cell density (ECD) loss is higher than what was deemed acceptable at the start of the study.

The failure of this main safety outcome suggests that the device, as evaluated in this study, is not safe according to parameters set at the start of the study.

The study is not powered to determine if limiting the intended population based at entry on anterior chamber depth, minimum preoperative ECD, or other factors would mitigate this concern.

2. There is insufficient data regarding the safety of performing YAG capsulotomy as suggested.

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The sponsor should have an observational safety study for subjects in whom YAG capsulotomy is considered.

3. With respect to both safety and effectiveness, the data should be provided on outcomes using an adjusted preoperative visual acuity from magnified images to assess safety and effectiveness.

4. The potential problem with MRI is substantial as there often is no way of knowing if a patient will need an MRI when undergoing this procedure, and emergency MRIs easily could be needed in this population following, for example, a cerebrovascular accident.

Other Comments

1. No vision rehabilitation program is recommended as there is no strong evidence in the literature or this study attesting to its effectiveness.

2. No program is recommended for training one to voluntarily shift binocular suppression as there is no strong evidence in the literature or this study attesting to its effectiveness.

3. Post-approval studies need to include specular microscopy as this was a main safety outcome which failed to occur at a safe level. The sponsor suggests that training will reduce this problem, but there is no strong evidence to justify this conclusion in the absence of collection of such data.

4. Continued follow-up of the current cohort is recommended.

5. How was “active” CNV defined.

6. How did 3 eyes get into the study with only drusen when all other eyes had a form of the advanced stage of AMD (i.e., “dry” geographic atrophy or “wet” choroidal neovascularization, or both).

7. “Moderate” vision loss is mentioned throughout multiple documents, but specific visual acuities should be used.

8. The device description indicates that it is implanted into the posterior chamber, but it certainly goes into the anterior chamber too.

9. The materials state that a 5 point change is clinically relevant on the NEI-VFQ, but data from AREDS suggests that higher amounts of change are associated with clinically relevant changes like 15 or more letter loss or development of choroidal neovascularization.

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10. It is unclear why 10 letter loss or gain was used as a clinically relevant change when quality of life data suggests that changes in quality of life for the AMD population is associated with a 15 or more letter change, especially at lower levels of visual acuity.

11. The sponsor recommends no treatment for AMD over the past 6 months, but patients who have received photodynamic therapy or anti-VEGF therapy may have recurrences of CNV requiring treatment more than 6 months after the last treatment, and many of these recurrences will be difficult, if not impossible, to identify in the presence of an IMT. Perhaps *potential for additional treatment* should be an exclusion criteria.

12. Much of the document states age-related macular degeneration, but inclusion criteria allowed Stargardt’s dystrophy. How many of the “geographic atrophy” cases were this dystrophy instead of age-related macular degeneration.

13. Is IMT in one eye an exclusion from implanting in the other eye; this does not seem to be mentioned in the product label information?

14. How has the near visual acuity measurement protocol been calibrated?