April 19, 2023

NTK Enterprises, Inc.

% Mr. George Aubrey

VIS, LLC

2640 Lake Shore Dr., Suite 1908

Riviera Beach, Florida 33404

Re: G170310/S005/A002

Trade/Device Name: VIS Optimal Keratoplasty (Opti-K) System

Dated: March 16, 2023

Received: March 20, 2023

CMS Category: B

Annual Report Due: May 16, 2023

Dear Mr. Aubrey:

The Food and Drug Administration (FDA) has reviewed the supplement to your Investigational Device Exemption (IDE) application to expand your pivotal study for a significant risk device proposing the addition of 4 institutions and 75 patients. FDA has determined you have provided sufficient data to support expansion of your human clinical study; this means that there are no subject protection concerns that preclude expansion of the investigation. Your supplement is therefore approved, and you may expand your study. Your investigation is limited to 4 US institutions and 75 US subjects.

Your IDE application has been approved as a staged study. You may request approval to expand enrollment in your study when you have submitted at least 6 months follow-up data after re-treatment on at least 50 re- treated subjects. You should modify the IDE protocol to include this specification, so that it is consistent with the Agency's approval.

You must also obtain institutional review board (IRB) approval before implementing this change in your investigation as required by 21 CFR 812.35(a) because FDA believes this change affects the rights, safety, or welfare of subjects.

FDA will waive those requirements regarding prior approval of a supplemental IDE application for investigational sites (21 CFR 812.35(b)) provided that the total number of investigational sites does not exceed the limit identified in this letter. Under this waiver, the study may be initiated at new sites, up to the approved limit, and updated information required by 21 CFR 812.20(b) on participating investigators and associated Institutional Review Boards (IRBs) and the IRB approval documentation may be submitted all at once in your IDE annual progress report. You must, however, submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the site limit specified in this letter. In addition, you must maintain current records as required by 21 CFR 812.140 and submit reports as required by 21 CFR 812.150. If a reviewing IRB requires any significant changes in the investigational plan or in the informed consent that may increase the risks to subjects or affect the scientific soundness of the study, then

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this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site (21 CFR 812.35). Minor changes requested by the IRB may be made without prior FDA approval. FDA also will waive the requirement for 6-month current investigator lists (21 CFR 812.150(b)(4)) provided that current investigator information is submitted every 12 months as part of the IDE annual progress report.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website

(http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

In order for your study to serve as the primary clinical support for a future marketing approval or clearance, FDA has provided additional study design considerations as an attachment to this letter. These recommendations do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study. You are reminded that prior to implementing any significant modifications to the approved investigational protocol you must obtain FDA approval, and, if appropriate, IRB approval for the changes.

We note that you have designed this protocol to collect safety and effectiveness data to support submission of a future PMA application. Regarding the statistics to be presented in the PMA, we expect analysis of the primary dataset to contain one line per unit (e.g., person, sample, observation) with clinical outcomes and baseline covariates. You should also provide the statistical program code which produces the above analyses and which clearly documents variable definitions and coding schemes, as well as the data, in an electronic format (e.g., SAS, S-Plus or R, Excel, ASCII).

If approved, it is likely that a post-approval study (PAS) may be requested as a Condition of Approval (CoA). As the original IDE cohort can sometimes be used to gather long-term safety and effectiveness data after market approval, we suggest you consider obtaining patient informed consent and IRB approval at the initiation of the study so that enrolled subjects will be followed for a period of at least 5 years . FDA believes this may reduce patient loss to follow-up during the marketing application review process and keep many subjects available to participate in such a PAS if ordered. In addition, please note that other clinical studies apart from continued follow-up of IDE subjects, including prospective studies which enroll new patients, may also be required as CoA should a future marketing application be approved.

We strongly encourage you to request a Pre-Submission (Pre-Sub) meeting with FDA prior to your future marketing submission or application, as we believe this may lead to a more complete submission and, thus, facilitate FDA's review of your submission. Please submit your Pre-Sub as a valid eCopy with a single paper copy of your signed cover letter to the address listed below. You should submit a Pre-Sub no less than ninety

(90) days prior to submission of the marketing submission or application so that you will have the opportunity to incorporate any comments you may receive during the meeting into your marketing submission or application. For additional information regarding Pre-Subs, please refer to the guidance "Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions" at https://www.fda.gov/media/114034/download. FDA's guidance represents FDA's current approach to this issue.

Future correspondence concerning this application should be identified as an IDE supplement referencing the IDE number above, and must be submitted following eCopy guidelines to:

U.S. Food and Drug Administration

Center for Devices and Radiological Health

IDE Document Control Center - WO66-G609

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The Federal Food, Drug, and Cosmetic Act (the Act), as amended by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes FDA to require an electronic copy (eCopy) for certain types of submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or other electronic media, accompanied by a single paper copy of your signed cover letter. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

For more information about FDA's eCopy program, including the technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at https://www.fda.gov/media/83522/download. In addition, we strongly encourage you to visit FDA's eSubmitter website at https://www.fda.gov/industry/fda-esubmitter/cdrh-esubmitter-program in order to develop an eCopy in accordance with the technical standards prior to sending it to FDA.

If you have any minor clarification questions concerning the contents of the letter, please contact Jennifer Brown at 301-796-5626 or Jennifer.Brown@fda.hhs.gov.

Sincerely,

Sieuvi H. Nguyen -S

Tieuvi Nguyen, Ph.D.

Director

DHT1A: Division of Ophthalmic Devices

OHT1: Office of Ophthalmic, Anesthesia,

Respiratory, ENT and Dental Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

Additional Recommendations and Considerations

ADDITIONAL RECOMMENDATIONS AND CONSIDERATIONS

The recommendations and/or considerations below do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study.

Study Design Considerations

FDA believes that additional modifications are needed in order for your study design to support marketing approval or clearance. We recommend, but do not require, that you modify your study to address the following issues:

1. You propose (Section 9.1) significant changes to your clinical study design and state that, "The Phase IIIa Pivotal Study patient population will involve the treatment of 75 subjects. Based on the outcomes from the Phase IIIa Pivotal Study the sample size for the remainder of the Pivotal Study (Phase IIIb) will be defined." You do not provide us with sufficient details regarding Phase IIIb of this study to allow us to determine whether your study is adequately designed to support a future premarket submission. In addition, we note that based on how you have described Phase IIIa, including your plan to use the outcomes of this phase of the study to design Phase IIIb , it appears that Phase IIIa is actually intended to be used as a feasibility study, rather than part of the pivotal trial. These types of studies usually focus on providing initial clinical safety and effectiveness information or capturing data to guide the development of a pivotal study. Therefore, please be aware that no labeling claims can be made based on this study. Please also be advised that beyond this feasibility phase, a full pivotal study (assessing both safety and effectiveness) will be needed to support your proposed indication for use. From a statistical perspective, we do not believe it is appropriate for you to pool the Phase IIIa data with future pivotal trial data. We recommend that you include the following statistical elements to your protocol and/or Statistical Analysis Plan (SAP) in your future pivotal protocol (i.e., Phase IIIb):

   a. Clear statements of the primary hypothesis and/or other hypotheses for endpoints that will be pursued in labeling claims, preferably in statistical formula, and justify each hypothesis clinically.

   b. Justification of the representativeness of the participating investigational site and the generalizability of the study.

   c. The overall study success criterion.

   d. Sample size justification.

   e. Analysis population and method for each endpoint.

   f. If you want to pursue labeling claims of any secondary endpoints, an appropriate multiplicity adjustment strategy should be specified to control the overall type I error rate.

   g. Details of the sensitivity analysis for assessing impact of missing data.

h. Blinding assessment if applicable.

i. Subgroup analyses if applicable.

j. Statistical Analysis Plan.

To avoid a negative impact on the validity of the study design and conclusions, all the above elements should be prospectively specified in the protocol. In addition, please be advised that the statistical plan that is not statistically appropriate makes it difficult to determine with adequate certainty that the device is safe and effective for its intended use.

2. You state (p. V1-55) that, "The following Study Design and Future Considerations will be addressed by the Company in the future request to proceed to the larger Phase IIIb Pivotal Study, as described in the response to Deficiency 1a: Study Design Considerations 1, 10a, 15, 28, 29, 30, 32 and Future Considerations 1-4." Please be advised that these outstanding SDCs and FCs contain recommendations for major changes to your proposed clinical study design. Therefore, our recommendations in the current letter are meant to optimize your currently proposed study, with the caveat that we continue to believe that your currently proposed study design requires major study design modifications to support a future marketing application. Since some study design elements are influenced by other study design elements, please be advised that the SDCs and FCs in this letter may no longer be relevant or appropriate if you decide to change major elements of the study design in response to outstanding SDCs and FCs or in response to the SDCs and FCs in this letter. We strongly recommend that you submit a pre-submission to obtain additional FDA feedback on a proposed path forward. If the Agency cannot come to an agreement with you on an appropriate study design, it makes it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use.

3. We previously conveyed concerns regarding the proposed enrollment criteria.

   a. In SDC 2a (FDA letter dated July 6, 2022), we re-iterated our concerns that:

      - the effectiveness outcomes from your proposed intended population are unlikely to be poolable,
      - the potential benefit for the first subpopulation [patients with a baseline MRSE (Manifest Refractive Spherical Equivalent) of +0.50 with a required reading add of +2.50 D (referred to below as subpopulation #1)] is small, if any (i.e., these patients are likely to still need reading glasses after treatment), calling into question the benefit-risk profile of your proposed treatment in this subpopulation,
      - the potential benefit for the second subpopulation [patients with baseline MRSE of -0.75 and required reading add of +1.00D (referred to below as subpopulation #2)] is also small (i.e., these patients likely already have decent unaided near vision at baseline), calling into question the benefit-risk profile of your proposed treatment in this subpopulation.

      We have the following concerns with your response.

      i. You propose (Section 9.6) to add "additional effectiveness endpoints" to the statistical plan to address our concerns. However, these new endpoints do not address our concern that the data are not poolable for effectiveness across the proposed study population. Lack of poolability of the data across the entire study population makes it difficult to determine that the device is effective for its intended use.

iii. Your new proposed "additional" endpoints for refractive predictability are based upon a new parameter that you call Intended Refractive Target, and we do not believe that your definition for Intended Refractive Target will demonstrate a clinically meaningful improvement in near vision for "subpopulation #1". Therefore, your proposed addition of these endpoints does not address our concern that "subpopulation #1" is unlikely to achieve clinically meaningful benefit from the device treatment.

We continue to recommend that you make significant modifications to your IFU statement, study design, and/or marketing plan in order to address our concern that subpopulation #1 has a small potential benefit, calling into question the benefit-risk profile of the device in this subpopulation.

b. In SDC #2b (FDA letter dated July 6, 2022), we conveyed our concern that "subpopulation #2" may already meet the key effectiveness endpoints, even without device treatment.

   i. In response, you modified the statistical plan (Section 9.6) to include new "additional" effectiveness endpoints. However, these new endpoints are not key endpoints, and they are not associated with any pre-specified statistical tests. Therefore, they are not adequate to support your claims of device effectiveness for the study population. In addition, you stated (p. V1-21) that you believe "that the benefit to the patient is achieved whether the patient achieves one or both of the primary or secondary endpoints, and that the study meets the criteria for success providing a benefit with no known risks." Since you have not changed the key effectiveness endpoints that will be used to demonstrate individual subject success, you have not adequately addressed our concern that "subpopulation #2" may already meet the key effectiveness endpoints, even without device treatment.

   ii. In your response to SDC #2b, you state (p. V1-15) that, "Finally, with the additional rigorous care taken during the screening procedure to exclude any subject with UNVA better than 20/63 will ensure that no subject will be included in the treatment population with 20/40 or better uncorrected near vision even with an MRSE of -0.75, a reading add of +1.00 D, and an accommodative reserve of 1.0 D (the maximum found in this population in the Feasibility Study)." However, the current study will enroll subjects as young as 40 years old, and 40-year-old patients often have more than 1D of accommodative reserve. One cannot assume that the baseline characteristics of one study will be mimicked in a new separate study at different investigational sites.

In summary, our concern remains that "subpopulation #2" may already meet the key effectiveness endpoints, even without device treatment. This raises uncertainty regarding whether the device is effective for its intended use. We recommend that you address this outstanding concern. One way to do this would be to modify the enrollment criteria to exclude "subpopulation #2" from the study population. Alternatively, you could modify the effectiveness endpoints to become clinically meaningful for this subpopulation (i.e., so that the effectiveness endpoints are clinically meaningful for the entire proposed study population).

c. In SDC #5 (FDA letter dated July 6, 2022), we noted that your proposed Inclusion Criterion #6 allowed enrollment of subjects with visual acuity as good as 0.32 logMAR uncorrected near visual acuity (UNVA). We noted that it is possible that many enrolled subjects could meet the study endpoint target even prior to device treatment by improving their visual acuity by a few ETDRS letters (which could be achieved with extra effort to use their accommodative reserve). In response, you did not modify the inclusion criterion. Therefore, our concern remains that the proposed secondary effectiveness endpoint is not clinically meaningful for the proposed study population,

which raises uncertainty regarding the effective of the device for its intended use. We recommend that you address this concern. You may consider modifying the enrollment criteria and/or modifying the effectiveness endpoint.

d. You propose (enrollment criteria, Section 6.1 and 6.2) to enroll subjects with a minimum required reading add power of +1.00D, a minimum age of 40 years old, and subjects with baseline myopia up to -0.75D MRSE with baseline UNVA worse than 20/40. A subject with these baseline characteristics is likely to meet the secondary effectiveness endpoint, even without being treated with the device. This raises great uncertainty regarding whether your device is effective for its intended use. We recommend that you modify the enrollment criteria to increase the minimum reading add power, increase the minimum age to 50 years old, and exclude subjects with baseline myopic refractive errors.

4. In SDC #3 and #4b (FDA letter dated July 6, 2022), we previously requested that you modify the study design to use an active control group.

a. It appears that your discussion points in response to SDC #4b (p. V1-21) are the same discussion points that you previously provided (G170310/S005/A001) to support your proposal to not use a separate, active control arm. Therefore, our prior comments and responses to your proposal still remain(see our recommendations in in SDC #3 of FDA letter dated July 6, 2022).

b. In SDC#3 (FDA letter dated July 6, 2022), we recommended that:

i. You use an active control arm (sham)

ii. You mask the vision assessors

iii. Modify the study endpoints to prespecify a comparison to the control arm

iv. Modify the study design to use randomization and masking

In response to SDC #3 (FDA letter dated July 6, 2022), you state (p. V1-17) that, "Active control arms including a sham control nor masked study subjects are not routine in IDE ophthalmic refractive investigations performed to date, and therefore VIS does not plan any protocol revisions to create study requirements not previously required for other refractive IDE study sponsors." However, please note that all class 3 devices requiring a premarket application must stand on its own merit, and the data requirements for each individual device may differ based on the device design, intended patient population, safety profile, etc. In addition, we would like to point out the most recent public discussion regarding an ophthalmic refractive device with an indication for the improvement of unaided near vision-- Ophthalmic Devices Panel discussion of the Visibility Micro Insert System, P170040 (November 9, 2020, Panel Transcript available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-9-2020-ophthalmic-devices-panel-medical-devices-advisory-committee-meeting-announcement). The Ophthalmic Devices Panel experts made several relevant comments regarding the need for a masked, randomized, controlled study:

- One panelist stated it would have been good if the study design used a "different control sham study". (p. 101 of Panel Transcript)

- The Panel Chair summarized the Panel's discussion as, "…there is great concern from the Panel regarding the bias introduced by perhaps the lack of controls, for example, the sham procedure was done or at least the study participant was masked that we were looking for improvement and you can see that, perhaps, even if somebody had a sham procedure, so it was difficult to judge what the magnitude of the improvement, due to the procedure, really was as a cause and effect relationship." (p. 196)

- The Panel Chair summarized the Panel's discussion as, "maybe even additional studies that have some controls if you're trying to use objective outcomes like the near visual acuity with distance correction that are being done, that these need, perhaps, some controls as well to understand the outcomes." (p. 212)
- One panelist stated that other panelists "expressed concern about the trial quality and I agree, the largest part of the study is nonrandomized without blinding and also sort of lacks the most relevant control." (p. 221)

In summary, consistent with the Ophthalmic Panel discussions, the Agency's current recommendation on the appropriate clinical study design for ophthalmic devices with an intended use of improving near vision in phakic, presbyopic patients is for an actively control, randomized, and double-blinded study (e.g., subjects are blinded to whether they received investigational treatment or sham; vision-assessors are blinded to which subject received sham or investigational treatment). This is needed to reduce the potential for study bias and to better understand the study outcomes. The current study design (no sham control, no randomization, no masking of subjects or vision assessors with respect to which subjects received investigational treatment or sham treatment) greatly increases the uncertainty regarding the effective of your device for its intended use. We recommend that you modify the study design accordingly.

5. In SDC #4b (letter dated July 6, 2022), we explained that we did not believe that the proposed key effectiveness endpoints were clinically meaningful. In response to this SDCs and other SDCs, you modified (Section 5.4, Instruction Manual) the Indications for Use to include a single re-treatment. You also modified (Section 9.6, IDE protocol) the primary and secondary effectiveness endpoints to the following:

   Primary Effectiveness Endpoint

   The proportion of treated eyes (target: at least **50%)** that achieve an uncorrected near visual acuity **(UNVA)** that is 2 or more lines better than Screening following treatment at **3** months after the primary treatment and **3** months after retreatment for subjects who undergo retreatment.

   Secondary Effectiveness Endpoint

   The proportion of eyes (target: at least **50%)** that achieve a binocular uncorrected near visual acuity **(UNVA)** of 20/40 or better at **3** months after the primary treatment and **3** months after retreatment for subject who undergo retreatment."

However, we continue to believe that the proposed key effectiveness endpoints may not be adequate to support the proposed indication, as described below. Please be advised that the evaluation of effectiveness should be achieved in your clinical trial to support approval of any future premarket application. However, without meaningful clinical endpoints and hypothesis testing, the device

effectiveness cannot be claimed. Therefore, we recommend that you define or provide the statistical hypotheses for clinically meaningful primary effectiveness endpoints. In doing so, we recommend that you propose your hypotheses in words, and in mathematical forms, and state the success criteria.

a. We do not agree with your proposed effectiveness endpoints, proposed performance targets, nor your proposed criteria for individual success. As we previously discussed, if a subject has UNVA of 0.72 logMAR, then a 2-line improvement would result in UNVA of 0.52 (Snellen equivalent around

20/63). While you propose to consider this outcome an individual success because this subject would pass the primary effectiveness endpoint, we do not believe that would be clinically meaningful to most adult patients because they will still not be able to read small print, paperback books, and newspapers, per the Near Vision Snellen Test Chart that you provided (Table 1, p. V1-20).

b. We do not agree with your proposed secondary endpoint because it is a binocular assessment whose target is too permissive. Subjects can be enrolled in the study if each eye sees 0.32 logMAR monocularly. These subjects are likely to succeed on the secondary endpoint even without receiving the investigational treatment because there is an additive effect when both eyes are used together to view something. Therefore, we do not believe that the proposed binocular endpoint is clinically meaningful. We recommend that key endpoint related to a minimum level of UNVA be a monocular endpoint (as we previously conveyed in SDC #31 of FDA letter dated July 6, 2022).

c. In SDC 4b, we stated that, "we continue to recommend that you use a control arm and that you include a statistical comparison to the control arm into your key effectiveness endpoints, as previously recommended in SDC #8.b.ii." However, you did not modify the statistical plan to include a statistical comparison to the control arm in your proposed analyses of the key effectiveness endpoints. Without an adequate comparison to an adequate control arm, it is difficult to interpret the study outcomes, and raises great uncertainty regarding the effective of your device for its intended use. We continue to recommend that you use a control arm and that you include a statistical comparison to the control arm into your key effectiveness endpoints.

Please note that it is difficult for us to provide definitive recommendations on a specific statistical plan to demonstrate device effectiveness because you choose not to address other related important study design considerations that we previously conveyed in FDA letter dated July 6, 2022. We strongly recommend that you submit a pre-submission with your proposed approach to addressing the concerns outlined in this comment. As a starting point, you could consider standardizing the treatment protocol to require that the retreatment be performed on all eligible subjects at a pre-specified, standardized time point (relative to the initial treatment), and prespecify a single time point for the primary analysis of the key effectiveness endpoints. In addition, we would be interested in the outcomes at multiple times points because the device's effectiveness is temporary and fluctuates over time. Therefore, we recommend that you propose statistical methods to account for multiple treatments.

6. You modified (Section 8.8) the re-treatment eligibility criteria in response to SDC #19 (FDA letter dated July 2, 2022) to specify that "subjects who meet the following retreatment criteria may elect to undergo a single retreatment…" and the first proposed criterion is: "UNVA returning to within 1 line of improvement over baseline within 3-6 months following Primary Treatment". However, your proposal lacks important details, and this will make it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use.

a. It is not clear what you mean by "within 3-6 months following Primary Treatment". We note that you

have established visit windows around the Month 3 and Month 6 visits (Month 3 = 10 to 14 weeks (70 to 98 days) and Month 6 = 20-26 weeks (140 to 182 days)). Therefore, it is not clear whether you mean to include the entire visit windows when you state "within 3-6 months following Primary Treatment". In addition, it is not clear at what time point the Investigator will apply these retreatment criteria. For example, will the investigator apply the criteria only at the Month 3 Visit and Month 6

visit? Will the investigator apply the criterion at unscheduled visits that fall "within 3-6 months following Primary Treatment"? We recommend that you modify the re-treatment criterion to clarify the range of time at which UNVA will be assessed for this criterion and to clarify the range of time that a subject becomes eligible for retreatment.

b. The protocol does not provide instructions as to when the single re-treatment is to be performed. As currently written, it appears that you leave it up to the Investigator to choose a time for re-treatment. Therefore, the retreatment could occur as early as 3 months after the initial treatment, or maybe it could be performed at the 12 month study visit. It will be difficult to determine that the device is safe and effective if you do not standardize (with respect to the initial treatment date, "Visit Tx") the time point at which the single re-treatment is performed. We recommend that you modify the protocol to standardize the time point at which the single re-treatment is performed. This will enable you to fix the time point at which the primary analysis of the key effectiveness endpoints is performed. If you do not standardize the time point at which the single re-treatment is performed, then a fixed single time point for the primary analysis of the key effectiveness endpoints is unlikely to be adequate to characterize device effectiveness.

c. In SDC #4c, we explained that we did not believe that a 3-month time point is a clinically meaningful time point for the primary analysis of the effectiveness endpoint in light of your expectation that patients will undergo multiple repeated treatments post-market. In response, you modified (Section 9.6) the key effectiveness endpoints to state that both the primary and secondary endpoints will be analyzed "at 3 months after the primary treatment and 3 months after retreatment for subjects who undergo retreatment." However, you have not specified which of these time points should be considered the primary analysis of these endpoints. If your intent was to analyze effectiveness outcomes over multiple time points, you have not provided statistical methods that detail how you intend to do this. An unclear statistical plan makes it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use.

We recommend that you modify the statistical plan to address these concerns.

7. In SDC #18a (FDA letter dated July 6, 2022), we conveyed our concern that your proposal to allow subjects to choose whether they want a single re-treatment could add uncertainty to the study outcomes. For example, there could be selection bias because subjects may not opt for re-treatment if they were dissatisfied with the initial treatment. In response, you propose to keep re-treatments optional and administer a "re-treatment questionnaire" (Appendix C, CRF), stating that, "The purpose of this Retreatment Questionnaire will be to better understand the reasons why a subject chose not to undergo retreatment." However, using the questionnaire to better understand the reasons for declining retreatment does not address our underlying concern that there could be selection bias associated with your current proposal to allow re-treatments to be optional. Study bias makes it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use. We believe that the more effective way to reduce potential study bias would be to modify the study design to require that a single re-treatment be performed on all subjects who meet the pre-specified re-treatment criteria. This approach will minimize potential selection bias, and it has the added benefit of being less burdensome than your

proposed approach because requiring eligible subjects to undergo re-treatments will likely result in a larger number of re-treated subjects. Since your proposed Indications for Use includes a single re-treatment indication, it is important that you have adequate numbers of re-treated subjects to characterize

device safety and effectiveness for the re-treatment indication. We recommend that you modify the study protocol and informed consent document to require all eligible subjects to undergo the single re-treatment.

8. In response to SDC#7a and b (FDA letter dated July 6, 2022), you modified the effectiveness endpoints to include new "Additional Effectiveness" endpoints:

   i. Percentage of eyes that achieve predictability (attempted versus achieved) at Month 3* of the MRSE of:

      o ±0.50 D

      o +1.00 D

      o ±2.00 D

      (Target = to achieve change from baseline in MRSE that is within ± *0.5* D of 0.63 D at Month 3* for at least 50% of subjects)

   ii. Percentage of eyes at Month 3* that are overcorrected by

      o >1.00 D

      o >2.00 D

      (calculated using the Month 3* average change from baseline in MRSE of -0.63 D for the attempted correction)

   iii. Percentage of eyes at Month 3* that are undercorrected by

      o >1.00 D

      o >2.00 D

      (calculated using the Month 3* average change from baseline in MRSE of -0.63 D for the attempted correction)

      *Endpoint analyses will be conducted 3 months after the Primary Treatment and 3 months after Retreatment for those subjects that undergo retreatment.

   These endpoints are analyzed using a new parameter that you call "Intended Refractive Target". You state (Section 8.2.1, clinical protocol) that:

   - "The Intended Refractive Target should be calculated for each study subject prior to treatment and recorded on the Treatment or Retreatment case report form (CRF)."
   - "The Intended Refractive Target Range for this study is -1.38 to -0.13 D at 3 months after the

primary treatment and at 3 months after retreatment… The Intended Refractive Shift should be calculated utilizing the following Figure 8.2.1.-1 which illustrates refractive change with 0pti-KTE in treated eyes during the Feasibility Study…"

- Intended Refractive Target = MRSE at Screening visit + MRSE Shift between Screening and 3 Month visit (primary treatment or retreatment).

Example: Intended Refractive Target = -1.13 D = (-0.5 D) MRSE at Screening visit + (-0.63D) MRSE Shift between Screening and 3 Month visit (following a primary treatment or a retreatment)"

We have the following concerns regarding your new proposals.

"Intended Refractive Target". You propose to base the Intended Refractive Target on prior feasibility study results ("IDE G170310 Feasibility Study of Presbyopia Correction using the NTK

Optimal Keratoplasty (Opti-K) System, p. V2-18). and not on the subject's desired refractive outcome. In addition, you state that the Intended Refractive Target can be as little as -0.13D. However, the intended use of the device is to temporarily improve near vision. Therefore, the Intended Refractive Target should be based upon the goal of achieving clear unaided near vision, not on the limited capability of the device to provide benefit as characterized by the feasibility study. For example, we do not believe that a myopic shift of -0.13D will provide any clinically meaningful improvement in near vision, even with the potential added change to spherical aberration induced by the investigational device treatment. Since the intended use of the device is to improve near vision, the refractive target should enable the subject to see clearly at near (40cm) unaided by spectacles or contact lenses. We recommend that you modify your proposed definition for Intended Refractive Target (in the study protocol and Case Report Forms). We recommend that you modify the Intended Refractive Target calculation such that it equals the amount of refractive change that is needed for the subject to achieve unaided, unaccommodated (i.e., push plus during clinical assessment) monocular near vision at 40cm of at least 0.20 logMAR. Alternatively, you may propose a different method for calculating the Intended Refractive Target so long as you provide adequate scientific justification for your proposal. If you continue to use your currently proposed method for calculating the intended refractive target, this raises uncertainty regarding the effective of your device for its intended use.

a. You propose the following endpoint as an "additional effectiveness" endpoint:

Percentage of eyes that achieve predictability (attempted versus achieved) at Month 3* of the MRSE of:

o ±0.50 D

o +1.00 D

o ±2.00 D

(Target = to achieve change from baseline in MRSE that is within ± *0.5* D of 0.63 D at Month 3* for at least 50% of subjects)"

Your proposed approach makes it difficult to determine, with adequate certainty, that the device is effective for its intended use, for the reasons described below.

i. You state a performance target: "Target = to achieve change from baseline in MRSE that is within ± *0.5* D of 0.63 D at Month 3* for at least 50% of subjects." Since you propose to include subjects who have some degree of hyperopia or myopia at baseline, it does not appear that the same amount of refractive shift (i.e., +/- 0.50D of 0.63D) will provide a clinically meaningful benefit for some of the treated subjects. In addition, we do not believe that the target of 50% is high enough to support a future marketing application, given that the intended use of the device is to improve near vision, and the baseline requirement for refractive correction for some patients in this study could be as little as 1.0D (e.g., Inclusion Criteria #2 requires subjects to need +1.00D to +2.50D of reading add). We recommend that you modify the performance target for this endpoint and that you provide adequate scientific

justification for the revised performance target, given the alternative treatments available on the US market.

i i . In SDC #7a, we asked you to make this endpoint a “key” effectiveness endpoint because you had stated that a change in refractive error is one of the ways that the device improves near

vision and, therefore, it is important to characterize refractive predictability. We believe that it will be necessary for you to demonstrate adequate refractive predictability in order to support a future marketing application. We continue to recommend that you modify the statistical plan to make this endpoint either a primary or secondary effectiveness endpoint and that you specify that this endpoint must be met in order to achieve study success.

iii. You did not propose performance targets for refractive predictability of eyes that achieve MRSE within 1.00D and within 2.00D. Without pre-specified targets for these parameters, it makes it difficult to determine, with adequate certainty, that the device is effective for its intended use. We recommend that you modify the proposed analyses of this endpoint to pre-specify performance targets for these parameters, along with adequate scientific justification,.

b. In SDC 7a, we requested that you add an "additional" effectiveness endpoint of "Change in BCDVA" because we believe that this endpoint would be important to characterize device effectiveness. For example, demonstration of only small changes in manifest refraction spherical equivalent (MRSE) across study visits is an indicator of MRSE stability. In response, you did not add this endpoint to the statistical plan, and you did not provide any justification for not doing so. We continue to believe that this endpoint is important to demonstrate device effectiveness because refractive stability is an important characteristic for devices that intend to change the refractive state of the eye. We recommend that you add this endpoint to the statistical plan.

To demonstrate that your device has a favorable benefit-risk profile for its intended use, we continue to recommend that you make significant modifications to your IFU statement, study design, and/or marketing plan in order to address these concerns.

9. In SDC #4b (letter dated July 6, 2022), we recommended that you modify the statistical analysis plan to define the criteria for individual success and study success. In response, you stated (p. V1-21) that "A subject entering the study with the lower end of the inclusion criterion of > 20/100 with 2 lines of improvement would achieve UNVA ≥ 20/60 (J7) which from Table 1 provides functional (clinically meaningful) vision. Hence, we believe that the benefit to the patient is achieved whether the patient achieves one or both endpoints and that the study meets the criteria for success providing a benefit with no known risks." However, you did not modify the IDE protocol (Statistical analysis plan) to specify the criteria for individual success, nor did you modify the statistical plan to specify the criteria for study success. Without a clearly written, pre-specified statistical analysis plan, it is difficult to determine, with adequate certainty, that the device is safe and effective for its intended use. We continue to recommend that you modify the statistical analysis plan to define the criteria for individual success and study success.

10. In SDC #6 (FDA letter dated July 6, 2022), we recommended that you modify the statistical plan to include an effectiveness endpoint related to refractive stability. In response, you stated (p. V1-24) that, "The Company has modified the protocol as recommended, to incorporate the evaluation of refractive stability as part of the overall effectiveness endpoint analyses." However, we are unable to locate any pre-specified effectiveness analysis that will characterize the amount of change in refraction across study

visits (i.e., refractive stability). We continue to believe that refractive stability is an important characteristic of device effectiveness. Without characterizing the refractive stability of the device, it makes it difficult to determine that the device is effective for its intended use. We recommend that you modify the statistical plan to make the evaluation of refractive stability an "additional" effectiveness

endpoint. For additional guidance on the types of refractive stability analyses that the Agency would consider, we recommend that you see Section F.3 of ANSI Z80.11 Laser Systems for Corneal Reshaping (R2017).

11. In response to SDC #9.f.ii (FDA letter dated July 6, 2022), you modified (Section 9.7.2) the statistical plan to include a "Co-Primary Safety Endpoint" of "Induced manifest refraction astigmatism > 2.0D" with a target of "< 5%". However, the proposed target does not appear to be adequate to demonstrate a favorable benefit-risk profile, in light of the feasibility study results that show a small amount of temporary benefit. A safety target that is too high makes it difficult to determine, with adequate certainty, that the device is safe for its intended use. We recommend that you modify the target rate to be < 1%, similar to your other proposed co-primary safety endpoint target rates.

12. In response to SDC #9b (FDA letter dated July 6, 2022), you modified the statistical plan to specify that co-primary safety endpoints will be analyzed at the same time point as the key effectiveness endpoints. While we agree with this proposal, we also believe that additional (secondary) analyses of the safety data are necessary to characterize device safety. Since you are collecting safety data throughout the entire study duration, we recommend that you modify the statistical plan to include a secondary analysis of the key safety endpoints at the final study visit. This is because we are interested in the cumulative incidence of adverse events. Without these analyses, it makes it difficult to determine that the device is safe for its intended use and the impact of the safety data when evaluating the totality of the data and benefit/risk.

13. In SDC #16 (FDA letter dated July 6, 2022), we conveyed our safety concern for corneal endothelial cell loss associated with the investigational device treatment. While you provided (p. 30, original G170310 submission) histology results of pig eyes that underwent a single treatment, and these data were sufficient to support IDE initiation, these data are not adequate to support a future marketing application for the device for the proposed intended use (i.e., single re-treatment). Damage to the endothelial cells from the Opti-K device treatment is a safety concern. We recommend that you modify the study protocol to include assessments of corneal endothelial cell density and that you modify the statistical plan to include a safety endpoint for the analysis of the corneal endothelia cell density. Without this information, it makes it difficult to determine, with adequate certainty, that the device is safe for its intended use.

14. In response to SDC #18b (Volume 1 page 33), you present the retreatment questionnaire. Please address the following concerns regarding the retreatment questionnaire:

    a. The retreatment questionnaire includes the instructions, "We would like to ask a few questions as to why you have chosen not to go ahead with a second treatment". This part of the instructions implies that the retreatment questionnaire may be administered verbally. Verbal administration may introduce bias into the responses by deviating from the written questionnaire, inserting additional information, or inducing method effects such as satisficing. The 2022 guidance, *Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome (PRO) Instruments for Use in Medical Device Evaluation,* states one of the factors to consider whether a PRO instrument is fit-for- purpose is: "Does the evidence support the PRO instrument's use in measuring the COI as

specified in the clinical study protocol and statistical analysis plan?" Absent of standard procedures for verbal administration, you have not provided evidence that verbal administration would be equivalent to written administration. As such, verbal administration may impact the confidence placed in the results of the retreatment questionnaire, which is needed to evaluate safety of the device. A

reasonable assurance of safety may not be possible without quality results from the questionnaire, which could affect the approvability of a future marketing submission. For these reasons, we recommend you modify the questionnaire instructions to limit the administration to electronic or paper versions. If you chose to administer verbally, we recommend you develop a script for verbal administration to ensure consistency and lower the chance of bias. In either case, the retreatment questionnaire should be administered, verbally or by handing or emailing it to the patient, by a member of study staff who is not responsible for patient care.

b. The retreatment questionnaire includes the statement, "I have a feeling of imbalance between my eyes." The 2022 guidance, *Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome (PRO) Instruments for Use in Medical Device Evaluation* recommends you ensure PRO instruments are understandable to patients. It is unclear if patients will interpret an imbalance between their eyes, as failure to adapt to monovision resulting in experiencing noticeable differences in vision between the eyes. This would introduce variance due to patients misunderstanding the question, detracting from the intended information regarding reasons for declining retreatment. As the reasons for declining retreatment are an important component of the safety evaluation, which could affect the approvability of a future marketing submission, we recommend you test the wording of this item with patients who have experienced the treatment or have other experiences with monovision and have not been able to tolerate monovision.

c. Your "Retreatment Questionnaire" (p. V2-281) contains several items, including:

"We would like to ask a few questions as to why you have chosen not to go ahead with a second treatment. Please check as many responses that apply.

1. I will not have the time or ability for additional follow-up visits.

2. I am moving out of the area and will not be able to attend the additional follow-up visits…"

We note that Exclusion Criterion #14 of this study (Section 6.2) requires exclusion of: "Persons who may not be able to complete the requirements of returning to the investigator's clinic over the period of the study, or who may be difficult to locate or contact on short notice. This does not preclude vacations or travel." Therefore, we do not believe it is appropriate to include items #1 and #2 in the Retreatment Questionnaire, because those subjects should not have been enrolled in the study in the first place. We recommend that you remove items #1 and #2 from the Retreatment Questionnaire. A patient-reported outcome measure that contains inappropriate items makes it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use.

15. In Volume 2, page 28, you state that subjective improvement as measured by the patient satisfaction questionnaire will be included in the primary effectiveness evaluation. The 2022 guidance, *Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome (PRO) Instruments for Use in Medical Device Evaluation,* notes that the strength of evidence needed to support the measurement properties of a PRO Instrument depend on the role of the instrument in the clinical study protocol. You

have not provided evidence sufficient to justify the use of the satisfaction questionnaire as a primary effectiveness endpoint. Strong evidence of the relevance of the content, and reliably and validity of the score, is needed to justify the interpretation as a primary endpoint. Without sufficient validity evidence, listing a PRO measure, such as the satisfaction questionnaire, as a primary endpoint may not be appropriate and may impact the approvability of a future marketing submission. We recommend you

provide validity evidence sufficient to justify the interpretation of the satisfaction questionnaire as a primary endpoint, or reclassify it to a more appropriate endpoint. More information on appropriate validity evidence can be found in the guidance cited above, or the 2009 guidance, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.*

16. In Volume 2, page 283, you provide the pre-operative questionnaire, which is based on the PROWL study survey. The surveys used in the PROWL studies were composed of several PRO measures, which contained sub-scales. In some cases, you included the full sub-scale of a measures. For instance, both items from the worry sub-scale of the National Eye Institute Refractive Error Quality of Life Instrument (NEI-RQL) are present (items 3 and 4). However, other subscales, such as the clarity of vision sub-scale, are either missing items, have additional items, or have been split up. It is not clear if the sub-scales are being used appropriately. The 2022 Guidance, *Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation* recommends you clearly define what is being measured and how it is being measured and interpreted. When PRO measures are administered and scored counter to the developers instructions, such as adding or removing items from subscales, the interpretation of the scores may not be possible due to no prior information on how to interpret the modified scores within the context of use. Consequently, conclusions cannot be drawn from the data, which may affect the approvability of a future marketing submission. We recommend you administer and score the different PRO measures and sub-scales from the PROWL studies in accordance with the PRO measure's developer's recommendations.

17. In SDC #20 (FDA letter dated July 6, 2022) we requested sample size information regarding a defocus curve substudy. In response, you provided the following description of the substudy:

> *Binocular defocus curves data will be collected on study subjects in the Phase IIIa Pivotal Study as described in the response to Deficiency 1. Based on the data collected, a decision will be made as to the need for the collection of additional binocular defocus curve data in the remainder of the overall Phase III Pivotal Study population (Phase IIIb).*
>
> *The following Section in Appendix B TEST METHODS AND RECOMMENDED EQUIPMENT LIST has been updated to reflect the subject number (**Appendix A Protocol**):*
>
> *"**Binocular Defocus Curves** will be measured using the Clinical Trial Suite (CTS) from M&S Technologies (Niles, IL) for a subset of 50 subjects representing the full range of MRSEs, accommodation magnitudes, and pupil diameters encountered in the Pivotal Study cohort. The software will be programmed (by M&S) to achieve a stepwise range from distance ((4 m) to near 40 cm)."*

This response is generally acceptable, but the test methods for the defocus curves should specify the test procedure in more detail. Specifically, the description of the test procedure should specify that the test will be conducted with the subjects wearing -0.25 D add lenses at the 4 m test distance to simulate

uncorrected VA at infinite distance, and additional test distances (without add lenses) will simulate 0.5D steps of defocus, i.e., 2 m, 1 m, 67 cm, 50 cm, and 40 cm. Subjects' heads should be restrained by a chin and forehead rest to ensure accurate test distances. It is important for these procedural details to be explicit and implemented consistently for the substudy to yield interpretable effectiveness data. Therefore, we recommend that you modify your clinical protocol to specify these details.

18. In response to SDC #21, (FDA letter dated July 6, 2022) you modified the study design to state (Appendix B, Test Methods and Recommended Equipment List) that, "Stereopsis disparity thresholds will be evaluated according to the manufacturer's instructions using the Clinical Trial Suite (CTS) from M&S Technologies (Niles, IL) at baseline (Screening), 1 month, and 6 months for all subjects in the Pivotal Study. For comparison both the treated (study) and untreated (fellow) eyes will be measured." We have the following concerns regarding your proposal:

    a. You identify the manufacturer of the stereopsis test that you propose to use in your study, but you provide no description of the test, the testing conditions, instructions for administering the test, or whether it is quick screening test or a more sensitive test capable of determining stereopsis thresholds. We recommend that you provide this information to allow us to determine whether the test is adequate to assess the safety and effectiveness of your device with respect to its effect on stereoscopic vision.

    b. Since a stereopsis test is a test of how two eyes of a single subject work together (i.e., binocular assessment), it does not make sense to compare the treated (study) eye to the untreated (fellow) eye. A non-sensical analysis makes it difficult to determine that the device is safe for its intended use. We recommend that you remove this statement.

    c. You propose to assess stereopsis at 1 month and 6 months, but you propose to analyze the key effectiveness endpoints at Month 3 and at 3 months after re-treatment. Your proposal makes it difficult to determine that the device is safe and effective because you are not assessing stereopsis at the same time points at which you are assessing the effectiveness. We recommend that you modify the study design to include assessments of stereopsis at Month 3, Month 12, and any other time point at which the key effectiveness endpoints will be analyzed.

    d. We previously recommended that you modify the statistical plan to include an "additional" safety endpoint that evaluates the loss of stereopsis. However, you did not heed this recommendation, nor did you provide a justification for not doing so. Loss of stereopsis is a safety concern and lack of assessment of this safety concern makes it difficult to determine that the device is safe for its intended use. We continue to recommend that you modify the statistical plan to include an "additional" safety endpoint that evaluates the loss of stereopsis.

19. We acknowledge your acknowledgement of SDC #22 (FDA letter dated July 6, 2022): "22. In Deficiency #18 of the disapproval letter dated March 18, 2022, we requested that you specify the exact version of the iPad to be used in your clinical study. In response, you propose (p. 38) to use only one iPad model in the pivotal study: "Apple Model A1416 3rd generation iPad with 64Gb RAM, 8MP wide camera with Auto HDR and 1080p HD video, and 10.5" Retina display. Current iOS 9.3.5." Your response is acceptable; however, as we discussed in that deficiency:

"*Based on your device description, we believe that adequate device centration is dependent upon the device component that is used to visualize and center the laser. In other words, the safety and effectiveness of the device differ depending on what viewing system or "microscope" you use. It is not clear that newer versions of the iPad will provide the User with the same ability to center the laser treatment, which is a serious safety concern. It is important that your pivotal study protocol specify exact*

versions of the iPad to be used and that this is consistent across all study sites...Please note that if you intend to change the version of the iPad during your IDE study you must submit an IDE supplement that includes data demonstrating equivalency of the new iPad to the one previously used to ensure use would not impact the safety and effective use of your new device."

Therefore, we would like to reiterate if you intend to change the version of the iPad during your clinical study, then we recommend that you submit an IDE supplement to ensure the use would not impact the safety and effective use of your new device.

20. In SDC #23 (FDA letter dated July 6, 2022), we asked you to modify the visual acuity methodologies to adjust for optical infinity, and we provided you with general recommendations on how to do this. While you modified (Section 8.2.1 and 8.5) some of the visual acuity assessments as requested, you did not make all of the necessary modifications to completely adjust for optical infinity in your proposed visual acuity assessments. Visual acuity measurements that are not appropriately adjusted for optical infinity make it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use. Therefore, we recommend that you modify Sections 8.2.1, 9.5, and Appendix B, and all other relevant sections, to adequately adjust for optical infinity by instructing investigators to place a +0.25D trial lens in front of each eye when assessing "binocular uncorrected visual acuity".

21. In SDC #25 (FDA letter dated July 6, 2022), we recommended that you adjust the randomization scheme to ensure that there are sufficient numbers of subjects across the range of pupil sizes to assess the effects of pupil size on the safety and effectiveness of the test device. In response, you state (p. V1-53) that you "will closely monitor the distribution of pupil sizes in the Phase IIIa Pivotal Study and reassess pupil size distribution, if necessary, prior to enrollment of the Phase IIIb Pivotal Study population." It is not clear what you mean by "reassess pupil size distribution". We continue to recommend that you adjust the randomization scheme to ensure that there are sufficient numbers of subjects across the range of pupil sizes. Failure to do so will make it difficult to determine that the device is safe and effective for its intended use.

22. In response to SDC #26 (FDA letter dated July 6, 2022), you deleted from all case report forms (CRF) a location to enter the manifest refraction value (e.g., +1.00 -0.050D @090). Instead, you combined the manifest refraction assessment with the visual acuity assessment and stated in the CRF (e.g., p. V2-214) that, "Manifest Refraction / Visual Acuity: (using CTS from M&S Technologies; data to be transmitted to CRO)." In order for the CTS to transmit the manifest refraction to the CRO, the vision assessor must input the manifest refraction value into the CTS system. However, it is not clear whether the CTS system is capable of receiving, storing, and sending this type of input. We recommend that you specify in your response whether the CTS system indeed has the capability. If yes, we recommend that you modify the study protocol and CRF for each study visit to instruct the vision assessor to input the manifest refraction value into the CTS system. If not, we recommend that you modify the CRF for each study visit to re-insert a location for the vision assessor to record the manifest refraction value. Lack of adequate clinical assessment information in the CRF will make it difficult to determine whether the device is safe and effective for its intended use.

23. In Section 7.2 Examination Schedule, you do not propose to perform post-operative Week 1 and Month 1 visits after a re-treatment is performed. We believe that those visits are needed to adequately characterize device safety after a re-treatment. We recommend that you modify the study design to include those

visits. Failure to do so will make it difficult to determine, with adequate certainty, whether the device is safe for its intended use.

24. You propose (Section 6.2) several exclusion criteria. We note that there is now available on the US market a prescription topical ophthalmic medication that is intended to treat presbyopia in adults. However, the enrollment criteria do not exclude subjects who are using this medication. We believe that this topical ophthalmic medication, and similar topical ophthalmic medications, could confound the study data, since the intended use of your device is to improve near vision. This would make it difficult to determine whether the device is effective for its intended use. We recommend that you modify the exclusion criteria and study design to exclude subjects who use topical ophthalmic medications to treat presbyopia and to prohibit use of these medications during the study.

25. You propose (Exclusion criterion #4, Section 6.2) to exclude subjects in whom either eye has "any active ocular surface disease of any severity". However, you state (p. V2-141, Appendix B Test Methods) that, "If the osmolarity score is over 325 mOsm/L and/or the InflammaDry test is positive, the subject is considered to have ocular surface disease (OSD) and is excluded from the study until/unless subsequent treatment corrects the OSD and the subject passes the repeat osmolarity and InflammaDry tests." This second statement is in contradiction to the exclusion criterion. Inconsistencies in the study protocol can lead to erroneous subject enrollment which can lead to patient harm. We had previously conveyed (Deficiency 3d, FDA letter dated March 18, 2022) that, "Our understanding of your proposed study design is that Investigators are permitted to enroll subjects with mild ocular surface disease, and that the ocular surface disease should be treated during the study (after enrollment) prior to device treatment. If this is the case, then the clinical study may not be adequately designed to monitor and treat these ocular surface diseases. Please modify the clinical study design to address this issue. Alternatively, you may modify your clinical study design by revising the enrollment criteria to exclude subjects with any active ocular surface disease of any severity, which is our preferred method for you to address this issue. This is necessary to protect subject safety." In response to this deficiency, you modified the enrollment criteria as requested but we believe you inadvertently failed to remove the wording in Appendix B, Test Methods. We recommend that you modify the wording in Appendix B to something like: "If the osmolarity score is over 325 mOsm/L and/or the InflammaDry test is positive, the subject is considered to have ocular surface disease (OSD) and is excluded from the study."

FDA believes that the following additional modifications are also needed in order for your study design to support marketing approval or clearance. We recommend, but do not require, that you modify your study to address the following issues previously relayed in our July 6, 2022 letter:

26. In SDC #2 of our disapproval letter dated March 18, 2022, we noted that you desired multiple, repeated treatments to be "an intended part of the treatment plan" (Section 1.2, IDE protocol, G170310/S005). You made additional statements regarding multiple re-treatments:

    - "*The treatment is temporary and does regress within 1-2 years for hyperopic treatments and does regress over shorter periods for the treatment of emmetropic presbyopia, but, based primarily on*

OUS data, it is forecast to be repeatable multiple times without adverse effects." (p. 51, G170310/S005)

- "*In the Nassau Study (c.f. 1.1.1), subjects received up to 4 re-treatments without adverse effects.*" (p. 50, G170310/S005)

- "*Opti-K is not ordinarily intended for single-use treatment in the provision of monovision in the phakic presbyope. In our OUS population, patients generally return for a retreatment as they desire and have been retreated so long as their refractive/ocular status still qualifies them (absence of significant presbyopic refractive shift; cf. Figure 1.0-1, p. 34 in IDE G170310/S005).*" (p. 43)

Since it is your expectation that multiple re-treatments in an individual eye will be performed post-market, we recommended in SDC #2 of the disapproval letter dated March 18, 2022, that you: (a) modify the Indications for Use (IFU) statement, (b) provide animal testing data, and (c) modify the study design to evaluate the multiple re-treatments to characterize the effects of multiple re-treatments. In response, you did not modify the study design to evaluate the safety and effectiveness of multiple re-treatments. Instead, you propose (modified protocol, Version 1.08) to keep the same overall study design of: Initial treatment at Day 0, 12M follow-up of initial treatment, then optional single re-treatment performed at 12 months. You have added a new Study Visit occurring 12 months after the single re-treatment is performed. We do not believe that the proposed study design will support a future marketing application because it does not adequately address the safety and effectiveness issues associated with your device when used as a single treatment nor does the current study design adequately address the safety and effectiveness concerns associated with multiple re-treatments. Our safety and effectiveness concerns include, but are not limited to:

- Post-market, it is possible that a patient may decide not to undergo re-treatment if they are not happy with the results. Regarding a single device treatment:
    - What is the safety profile of a single treatment?
    - What is the range of time over which a single treatment maintains clinically meaningful effectiveness?
- Since the treatment only lasts a few months, if a patient is satisfied with the results, then the satisfied patients would desire multiple re-treatment post-market. Regarding multiple re-treatments:
    - Is there diminishing return for effectiveness after each subsequent re-treatment?
    - Is there incremental increased safety concern with each subsequent re-treatment, especially if the laser burns start to overlap with each other (e.g., change to corneal thickness, corneal endothelial cell loss, corneal weakening, scarring, cumulative damage to cornea)?
    - Does the timing of the subsequent re-treatment affect the safety profile of the device? In other words, is it possible that re-treatment on an actively stressed/healing cornea may lead to increased safety problems?
    - Is there an upper limit on number of re-treatments a person can safely undergo?
    - In your response to Deficiency #2b of our disapproval letter dated March 18, 2022, you state that treatment spots are still visible by slit lamp 12 months or more after treatment. This observation indicates that the cornea is still not completely healed from a treatment even after its refractive effects have faded, and suggests that treatment of a previously treated spot may not have the same effect on stromal tissue as the initial treatment. This raises potential new safety concerns related to the likely need for multiple retreatments to maintain the effectiveness of the Opti-K treatments

over longer time periods. These concerns need to be investigated carefully and non-clinically prior to allowing this technology onto the open market, where there will be no effective limit on the number of retreatments that a single eye can receive over time. Your assertion that displacement and overlap of spots from repeated retreatments has not induced significant aberrations that interfere with visual function requires validation, first by longitudinal in vivo animal studies and, if warranted by the results, then by controlled clinical studies. Therefore,

please be advised that you will need to provide evidence from longitudinal animal studies to address these safety concerns prior to initiating a clinical study that evaluates multiple re-treatments.

Your current study design does not include multiple re-treatments, and the timing of the proposed single re-treatment is not consistent with how you expect the device to be used post-market, nor is it consistent with a favorable benefit-risk profile given the limited treatment duration of a single laser treatment. Your current study design also will not gather adequate clinical data to address the safety/effectiveness concerns described in the bullet points above. Therefore, we do not believe that your current study design is adequate to support a future marketing application (for a single retreatment or for multiple retreatments). We recommend that you modify the overall study design, including endpoints, sample size, treatment protocol, and study duration to address our concerns. We note that our recommendations below regarding endpoints and endpoint analyses may change based on what overall study design you choose. We strongly recommend that you submit a pre-submission to discuss these issues to ensure that data collected from this pivotal trial would be supportive of any future premarket application from a benefit/risk perspective.

27. You propose (Section 9.1, A001 Response to March 18, 2022 letter) a sample size of 333 eyes based on the expected observation of zero subjects with a serious adverse event such that the upper one-sided 95% confidence limit is less than 1.0%.

    a. Since you propose an indication for device re-treatment, your sample size should be adequate to characterize the safety and effectiveness of device re-treatments. In order words, it is important for there to be 300 evaluable eyes of re-treated subjects available for the primary analysis of key safety and effectiveness endpoints. We recommend that you modify the protocol to clarify that there should be at least 300 subjects who have undergone re-treatment available for analysis at the time point at which the primary analyses of the key safety and effectiveness endpoints will be performed. If you believe that the total number of subjects enrolled in the study needs to be adjusted to ensure adequate sample size at the time of the primary statistical analyses, we recommend that you modify your request for the total number of subjects to be enrolled in this study and that you include an appropriate scientific justification for your new proposal.

28. In SDC #11 of our disapproval letter dated March 18, 2022, we recommended a 24-month follow-up study visit. In response, you extended (Section 7.2 Examination Schedule) the proposed follow up duration to include a Study Visit occurring 12 months after the single re-treatment procedure. Please be advised that our recommendations regarding total follow-up duration will depend upon how you propose to modify the overall study design in your response (e.g., how many re-treatments are allowed, what time frame are the re-treatments permitted). Our current thinking is that at least 12 months follow-up after the final re-treatment procedure is needed to adequately characterize device safety for an indication for re-treatments. If you decide to modify your overall study design to include multiple re-treatments (which is our current recommendation based on how you expect your device to be used), we recommend that your overall follow-up duration includes at minimum a Study Visit that occurs at least 12 months after the last re-treatment procedure.

29. In your response to statistical study design considerations, SDCs # 21-24 (FDA letter dated March 18, 2022), you have indicated that the full statistical analysis plan (SAP) will be provided prior to the data

analyses. However, the full SAP should be provided at the design stage. Therefore, we recommend that you provide the full SAP in your future amendment to this IDE supplement. This is recommended to imperil the validity of the study design and conclusions.

30. In SDC #22b of our disapproval letter dated March 18, 2022, we recommended that your clinical study protocol and SAP include analysis populations. In your response, you have stated that the analysis populations will be provided in your future SAP. However, your protocol and statistical analysis plan (SAP) should define and include analysis populations prior to the data analysis. Please provide this information. In doing so, please indicate which population will be used for the safety and effectiveness analyses.

31. In SDC #23 of our disapproval letter dated March 18, 2022, we recommended that you revise your clinical study protocol and SAP to include poolability analysis. In your response, you have stated that poolability analyses will be provided at the later stage. However, poolability analysis plan should be included at the design stage. As stated previously, pooling all the subjects' outcome makes a strong assumption that there is no site-to-site variability in the effectiveness of the device, which may not be true. Please note that to evaluate poolability, you need to assess similarity/homogeneity of clinical outcomes among sites, subgroups (e.g., race, gender, age, and other baseline covariates) and regions. Therefore, please revise your protocol and statistical analysis plan to include poolability analysis. As the study is not powered for this analysis, a significance level of 0.15 may be more appropriate.

32. In SDC #24 of our disapproval letter dated March 18, 2022, we recommended that you include a tipping point analysis as part of sensitivity analysis for missing data in the clinical study protocol. In your response, you have stated that the details of missing data analysis plan will be provided prior to analyzing the data. However, the missing data analysis plan should be given along with the plan to analyze the performance of the endpoints. Additionally, it is unclear whether you plan to perform any sensitivity analyses. We recommend that you provide more details regarding how the interpretability of reported study results will be ensured (for example by specifying how missing data and protocol deviations will be handled in the data analysis). Please include tipping point analysis as part of sensitivity analyses for missing data in the protocol.

Although not the basis for our assessment as to whether your study design will support marketing approval or clearance, FDA suggests the following additional modifications for your consideration:

33. You provide (Appendix A) a Study Flow Chart and Examination Schedule. However, your intended meaning is not clear. You state that the clinical assessments should be "OU examinations and/or information". However, the primary effectiveness endpoint is an assessment of treated eyes (i.e., monocular visual acuity), and the secondary endpoint is for binocular acuity. Therefore, it is not clear what you mean by "OU" in the Study Flow Chart. "OU" could mean a binocular assessment, or OU could mean separate, monocular assessments of each eye. We recommend that you modify this table to clarify for each clinical assessment whether the assessment will be performed monocular, binocularly, or both monocularly and binocularly". This confusion also is present in sections 8.5 (Follow-Up Visits:

“Note: All testing is to be performed on both eyes.”) and Section 8.2.1. Screening Eye examination (same “Note” wording as section 8.5). An unclear clinical protocol may lead to major protocol deviations, which can make it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use.

34. You propose (p. V2-60, Appendix B) that there is a "recommended equipment list". However, if these instruments are not required to be standardized in the protocol, then we are concerned that the use of differing device models and manufacturers could lead to non-standardization of the clinical assessment outcomes. This makes it difficult to determine, with adequate certainty, that the device is safe and effective for its intended use. We recommend that you modify this section to instruct Investigators that these devices are "Required Equipment", not merely "recommended" for use.

Although not the basis for our assessment as to whether your study design will support marketing approval or clearance, FDA also suggests the following additional modifications for your consideration that were relayed in the July 6, 2022 letter:

35. In SDC #10 of our disapproval letter dated March 18, 2022, we recommended that you modify the IDE protocol to (a) increase the number of investigation sites to at least 10 sites and (b) require that each investigator contribute a minimum of 20 eyes to the study population but not more than 15% of the eyes in the study. The responses you provided did not address our recommendations; therefore, please consider the following:

    a. In your response, you stated (p. 64) that, "We believe it is unnecessary to expand the overall clinical site number". You explained that 3 of 4 sites will use at least one co-investigator and that 2 sites are free-standing clinics and the other two represent university affiliated centers. We do not agree that these number of investigators and sites are adequate to demonstrate that there is a reasonable assurance of safety and effectiveness across the range of intended users and intended population. As is typical for corneal refractive device pivotal trials, we continue to recommend that you increase the number of investigational sites to at least 10 sites.

    b. It appears that you did not respond to our request to have each investigator contribute a minimum of 20 eyes to the study population, and you did not provide a scientific justification for not doing so. In response to our other request, you modified the protocol (Section 5.0) to state that "No investigator will treat more than 25% of the total population of the pivotal study". However, we believe that 15% cut-off is more statistically appropriate because 25% (83 subjects) is too large. In addition, in the case of 25%, it is very likely that many sites will have very small enrollment, which will cause difficulty in data poolability and hence cause problems in data interpretation. Therefore, we continue to recommend that you modify the protocol to require that each investigator contribute a minimum of 20 eyes to the study population, but not more than 15% of the eyes in the study

If you intend to propose changes to your study to address these Study Design Considerations you should submit an IDE supplement.

Future Considerations

You should also give serious consideration to the following, which FDA considers important for the support of a future submission:

1. In response to SDC 14 (FDA Letter dated July 6, 2022), you agreed to provide Zernike analyses of aberrometry data limited to actual photopic pupil size for eyes having photopic pupils smaller than 4 mm.

This response is acceptable. However, you should be aware that in the event of a future PMA approval, no claims regarding pupil size will be allowed unless you can provide valid evidence that changes in the amount of pupil constriction at near are attributable to the Opti-K treatment. Therefore, we recommend that you make appropriate measurements and conduct appropriate analyses to support any desired claims regarding changes of pupil size. This is important to adequately characterize the effectiveness of your device for your intended patient population.

2. You provide (Appendix 2) the validation protocol and report for your cleaning instructions. Please consider the following recommendations regarding your cleaning validation in your future marketing submission:

   a. You repeat your cleaning and validation steps a total of 6 times to demonstrate your device can be repeatedly reprocessed without adverse effects. However, you do not provide a scientific justification for "6" cycles as it appears the SAWSR accessory may be reprocessed more than 6 times. Therefore, in your future submission, please provide confirmation that the maximum number of re-use cycles is 6 or revise your instructions to provide additional instructions for the end user to inspect the device visually for unacceptable deterioration such as corrosion, discoloration, etc.

   b. You state that worst case cleaning steps were utilized in the cleaning validation. However, the cleaning steps performed during validation appear to be exactly the same parameters that are recommended in your labeling. In your future submission, please describe how the cleaning steps performed during validation represent worst case cleaning or repeat the cleaning validation to employ worst case cleaning parameters. Examples of worst-case processing conditions are using shortest times, lowest temperatures, weakest dilutions, etc., for each of the cleaning instructions.

   c. You state (Appendix 2, Study Conclusion) "Any circumstances during this study that may have affected the quality and integrity of the data are described in the "Test Synopsis" section of this report." However, you do not include a "test synopsis" section in the table of contents or the body of the report. We note that a similarly described "test synopsis" was included in the high-level disinfection table of contents and the body of that report but appears to be missing from the cleaning validation report. In your future submission, please clarify if the "test synopsis" was not applicable and revise your "study conclusion" to reflect this change. Otherwise, please include the "test synopsis" for your cleaning validation report in your future marketing submission.

   We request this additional information regarding your cleaning validation to ensure the cleaning instructions for your semi-critical SAWSR accessory will be consistently rendered clean by the end user to mitigate any risks of transfer of infection between patients.

You should also give serious consideration to the following, which FDA considers important for the support of a future submission that were previously conveyed in our July 6, 2022 letter:

3. In your response to Deficiency #18 and Future Consideration (FC) #2 (FDA letter dated March 18, 2022), you repeat your assertion that the Apple iPad accessory does not affect the surgeon's view of the alignment of the eye or of the telescope image. However, your response does not address our concern that different iPad models may have cameras that are located at different positions on the iPad, and that these differences may require redesign of the mounting brackets that affix the iPad camera in proper alignment with the telescope eyepiece. Therefore, if the current iPad model is to be replaced by a

different model after PMA approval, a PMA supplement will be needed to describe any changes to the iPad mounting and alignment setup and to confirm that the surgeon's view of the telescope output is unchanged. Validation testing on representative models including what you consider the worst case to support generalizability of use of these components for use with your device. If you decide to take this approach, we highly recommend you submit a pre-submission so that we may on your approach. Additionally, we recommend that you state your agreement to provide a PMA supplement for any future change in the iPad model or, alternatively, explain why changes of camera positions on different iPad models will not require any changes in mounting hardware or procedures to align the iPad camera with the telescope output.

4. In SDC #3a of our disapproval letter dated March 18, 2022, we conveyed our concern that there may not be a favorable benefit-risk profile for a single device treatment. In response, you stated (p. 42) that, "Opti-K™ is not ordinarily intended for single-use treatment in the provision of monovision in the phakic presbyope. In our OUS population, patients generally return for a retreatment as they desire and have been retreated so long as their refractive/ocular status still qualifies them (absence of significant presbyopic refractive shift; cf. Figure 1.0-1, p. 34 in IDE G170310/S005)." You also state (p. 42) that, "The overall benefit/risk profile for Opti-KTM is enhanced with retreatment." Please be advised that a successful future marketing application will be contingent upon you demonstrating a favorable benefit-risk profile for your device under the proposed context of use, indications for use, and for the proposed intended population in the United States.

5. You propose (Section 9.7.2) that:

"The following co-primary safety endpoints and target values will be tabulated and reported at all post-treatment examinations for all treated eyes and fellow eyes27 beginning one month postoperatively."
Footnote 27: "As many of the subjects who will all be over 40 may have early cataractous changes not requiring surgery, fellow eyes will be used as surrogate controls to gauge potential advancing aging effects (cataract progression, dry eye disease) that would reduce vision separate from an adverse event (stromal scarring) related to the treatment. Additionally, corneal clarity (light scatter) will be assessed in the unlikely case that a subject's reduced acuity is not obviously due to cataract progression. Forward scatter will be assessed by change in glare sensitivity and back scatter using the corneal densitometry analysis program of a Scheimpflug camera (cornea densito; Pentacam HR; Oculus GmbH)."

It is not clear how you intend to use the assessment of forward light scatter to justify loss of visual acuity as it pertains to categorization of adverse events. While we would consider your discussion of forward light scatter and Pentacam results in our characterization of adverse events, it is important that you provide us with an analysis of the total number of events of loss of 10 or more ETDRS letters (compared to baseline), and that you provide a case narrative for each of these events. In the case narratives, you are welcome to provide the forward light scatter data that you collect. We recommend that in the future PMA submission, you provide an analysis of the total number of events of loss of 10 or more ETDRS letters (compared to baseline), and that you provide a case narrative for each of these events, so that we can determine which of these events should be considered to be an adverse event or serious adverse event.

This is necessary to ensure that you have appropriately analyzed your co-primary safety endpoints.

6. In response to FC #1 of our disapproval letter dated March 18, 2022, you modified (Section 5.1, Instructions for use (IFU)) the proposed Indications for Use statement. Since we continue to recommend

major study design modifications in this letter, please be advised that the final IFU wording will be dependent upon the final study design and results, as well as the totality of scientific evidence that you provide in your future marketing application.

The Future Considerations listed above are intended to assist in your plans for a future marketing application only. No response is necessary under this IDE, unless you wish to modify your device or study to address these concerns, in which case approval of an IDE supplement may be needed.

If you would like FDA's feedback on your plans for addressing any additional recommendations and considerations, please submit a Pre-Submission. Your submission should reference this IDE, identify the specific Study Design Considerations and/or Future Considerations you wish to discuss, and indicate your preferred feedback mechanism (i.e., email, meeting or teleconference). Additional information regarding Pre-Submissions is available in the Guidance for Industry and FDA Staff on Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions at https://www.fda.gov/media/114034/download.