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Via Federal ExpressFood and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

WARNING LETTER

Jon L. Siems, M.D.
Siems Advanced Lasik Center
1000 South Rampart Boulevard, Suite 10
Las Vegas, NV 89145

Dear Dr. Siems:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also requests that prompt corrective actions be implemented in response to the violations cited and that you provide a written reply informing us of your corrective actions. Mr. Anthony E. Keller, an investigator from the FDA's San Francisco District Office and Mr. Levering Keely, a Consumer Safety Officer from the FDA's Center for Devices and Radiological Health, conducted the inspection from October 27 through November 18, 2003. You participated as a clinical investigator in the study entitled [REDACTED] sponsored by [REDACTED]. Data from the study conducted at your site was submitted to the FDA in connection with a study under an investigational device exemptions (IDE).

The purpose of Mr. Keller's visit was to determine whether your activities and procedures as a clinical investigator in this study complied with applicable regulations. The [REDACTED] is a device as that term is defined under Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

This inspection was conducted under a program designed to ensure that data and information contained in applications for IDEs, Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate, as well as to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

We have completed our review of the inspection report submitted by the San Francisco District Office. The report reveals significant violations of the requirements under Title 21, Code of Federal Regulations (21 CFR), Part 50 - Protection of Human Subjects; and 21 CFR Part 812 - Investigational Device Exemptions. At the conclusion of the inspection, Mr. Keller discussed the listed deviations that were noted in the Form FDA 483 "Inspectional Observations," and presented the form to you and to Dr. [REDACTED] for review. The violations noted on the Form FDA 483 and in our subsequent review of the inspection report are discussed below:

Failure to conduct the investigation according to the signed agreement with the sponsor, the investigational plan, and any conditions imposed by the Investigational Review Board (IRB). (21 CFR 812.100 and 812.110(b))

Under FDA regulations, you are required to conduct your clinical investigation in accordance with any conditions of approval imposed by the reviewing IRB (21 CFR 812.110(b)). On December 11, 2002, your IRB approved your study to treat up to 10 subjects. You treated 18 subjects total, 8 subjects beyond that approved by your IRB.

You are also required by FDA regulations to conduct your investigation in accordance with your signed agreement with the study sponsor and with your investigational plan, which includes the study protocol. Our investigation revealed several deviations from the signed agreement and investigational plan, including the following:

1. The protocol required the depth of ablation of the scleral tissue to be [REDACTED] of the scleral thickness. All six of the subjects' records audited demonstrated that you exceeded [REDACTED] depth of cut. For example, five of the six subjects' records audited (Subjects [REDACTED]; and [REDACTED]) revealed depth of some or all cuts at [REDACTED] percent. One subject ([REDACTED]) had depth of cuts at [REDACTED] percent in one eye.
2. The protocol required that subjects were to have subjective symptoms, including the presence or absence of pain, recorded during each visit on the case report forms (CRFs). For all of the six subjects' records audited, there was no documentation that subjects were asked about pain, and no documentation regarding the presence or absence of pain.
3. According to the protocol, contrast sensitivity was to be tested using goggles supplied by [REDACTED]. After the first eight subjects were enrolled in your study, contrast sensitivity testing was done using goggles supplied by [REDACTED].
4. The protocol required that pupil size was to be determined using a pupilometer manufactured by [REDACTED] that is accurate to 0.1 mm. This measurement was completed using a [REDACTED] pupilometer, and you did not produce documentation regarding the accuracy of this device. Moreover, this pupilometer was recalibrated due to "inaccurate readings."
5. The following inclusion/exclusion criteria in the study protocol were violated:
 - a. According to the protocol, subjects taking antihistamines should have been excluded from the study. At least two subjects were taking antihistamines [REDACTED] (Subjects [REDACTED] & [REDACTED] and [REDACTED] [Subject [REDACTED]]).
 - b. Stable refraction for one year prior to surgery, as required in the protocol, was not documented for any of the subject records reviewed.
 - c. One inclusion criterion in the protocol required subjects' [REDACTED], [REDACTED], and [REDACTED] to be normal. For the records reviewed, there was documentation of these tests, but no documentation that the results obtained were considered to be normal.

6. Revised case report forms identifying additional data to be collected (involving slit lamp examinations, eye motility evaluations, and pupillary size evaluations), for which IRB approval was not documented, were used after initiation of the study.
7. The protocol required that adverse effects be recorded on CRFs provided by the sponsor. The CRFs included spaces for recording a variety of adverse effects, including increased intraocular pressure (IOP) and regression. Nonetheless, the following events were not recorded in the relevant CRFs:
 - a. Subject [REDACTED]'s IOP increased from [REDACTED] mm pre-op to [REDACTED] mm one-hour post op (OD [right eye]) and [REDACTED] mm pre-op to [REDACTED] one-hour post-op (OS [left eye]).
 - b. Subject [REDACTED]'s uncorrected near vision regressed from 20/20 after surgery to [REDACTED] (OU [both eyes]), [REDACTED] to [REDACTED] (OD), and [REDACTED] to [REDACTED] (OS) at 6 months postoperatively.

Failure to adequately document informed consent. (21 CFR 50.27)

When you are obtaining informed consent, study subjects are to be provided with the information listed under 21 CFR 50.25(a) and the appropriate information listed under 21 CFR 50.25(b). Except in limited circumstances, informed consent must be documented on an IRB-approved form as described in 21 CFR 50.27.

Our inspection revealed that your consent materials were reviewed by an IRB, but based on available documentation we could not determine whether the form you used with study subjects was the version reviewed by the IRB. Moreover, some of the consent forms reviewed were not complete:

1. The consent form for subject [REDACTED] was incomplete because it lacked identification of whom to contact on the IRB with questions about research subjects' rights and that contact's phone number.
2. The consent forms for four subjects ([REDACTED] and [REDACTED]) were not fully completed because they lacked the referral phone number for the IRB contact.
3. Subject [REDACTED] signed the consent form on [REDACTED]; however, the witness signed the consent on [REDACTED].

Failure to maintain accurate, complete, and current records relating to the investigator's participation in an investigation, including records of each subject's case history and exposure to the device. (21 CFR 812.140(a)(3))

FDA regulations require investigators to maintain accurate, complete, and current records as described in 21 CFR 812.140(a). Included in these required records are documentation of each subject's case history and exposure to the investigational device. Our inspection revealed numerous deficiencies in these records for your study subjects, including the following:

1. All medical records/case reports audited had numerous write-over corrections which lacked dates and initials.

2. During the inspection, subject [REDACTED] was reported to have two blebs (one in each eye) which “probably occurred during the first week post-operatively” but were identified later. These blebs were not identified in any of the CRFs. Moreover, information you provided after the inspection indicated that the blebs actually occurred in subject [REDACTED] and not subject [REDACTED].
3. Total energy use reported in several subjects was not accurately represented, based on the sums of energy used for individual cuts. For example, while the reported total energy for subject [REDACTED]’s left eye ablations was [REDACTED]mJ, adding together the individual cuts reported identified the energy total as [REDACTED]mJ. Similar discrepancies were noted with subjects [REDACTED] and [REDACTED].
4. Topographic ‘[REDACTED]’ values reported on the pre-operative CRF did not agree with [REDACTED]-generated values. For instance, for subject [REDACTED] the CRF reports the OS pupil size is [REDACTED] mm, and topography steepest at [REDACTED]D at [REDACTED] degrees and flattest at [REDACTED]D at [REDACTED] degrees. According to the [REDACTED] data these values are 3.1 mm, [REDACTED]D at [REDACTED] degrees, and [REDACTED]D at [REDACTED] degrees respectively.
5. The 2-month axial length (OD) for subject [REDACTED] is reported on the CRF as [REDACTED], but as [REDACTED] on [REDACTED] printout.
6. According to the 6-month CRF for subject [REDACTED], the pupil sizes are both [REDACTED]mm (OD and OS). According to the data generated by [REDACTED], the right pupil is [REDACTED]mm and the left pupil is [REDACTED] mm.
7. There are three operative reporting forms (OD, OS, and OU) for subject [REDACTED]. They differ in reported speed, smoothness, shape of cut, charring, and pupillary size.
8. There are three post-operative CRFs/medical records for subject [REDACTED] dated [REDACTED] (the 3-month follow-up time period). Two forms indicate they are for the 6-month visit, and one form indicates the data are from the 3-month visit.
9. There are two pre-operative CRFs/medical records for subject [REDACTED] that appear to refer to the same visit and data but have two different visit dates ([REDACTED] and [REDACTED]). In addition, the data for the axial length were changed and the corrected value is not entirely legible.
10. There are two 6-month post-operative CRFs/medical records for subject [REDACTED] dated [REDACTED]. Values for visual acuity and amplitude of accommodation do not match between the two versions:
 - a. Far Best Corrected (OU), [REDACTED] on one CRF, is [REDACTED] on the other.
 - b. Near Uncorrected (OS and OU), reported as [REDACTED]+ and [REDACTED] respectively on one CRF, are both reported as 20 on the other.
 - c. Near corrected without "add" (OS) is reported as [REDACTED] on one CRF and [REDACTED]- on the other.
 - d. Amplitude of accommodation – push up (OD) on one CRF reports [REDACTED] while the other CRF reports [REDACTED].
11. Both plus (+) and minus (-) were circled on the CRFs/medical records for subject [REDACTED] identifying OD sphere on [REDACTED] and OS cylinder on [REDACTED].
12. Intraocular pressure (OS) for subject [REDACTED] at the 3-month visit is not entirely legible.
13. [REDACTED] topographic exam data were not available for subject [REDACTED] for either the right eye on the pre-operative examination or for both eyes on the 6-month follow-up.
14. Inclusion/exclusion CRFs for subject [REDACTED] were not found during the audit.

15. Data were not recorded for the following subjects regarding:

- a) IOP (OS) at subject [REDACTED]'s one-hour postoperative exam.
- b) Medical history for subject [REDACTED], except for the date of birth.
- c) Left eye ablation speed, smooth, shape, and charring for subjects [REDACTED], [REDACTED], and [REDACTED].
- d) "ETDRS" (distance best corrected and near best corrected without reading add) at one week visit for subject [REDACTED] ("N/A" was entered on CRF).
- e) "Near vision without correction functional" (OD, OS, and OU), and "Contrast sensitivity" (OD and OS) with glare for the 6-month visit of subject [REDACTED].

In addition to the above, we note the following issues for your consideration:

1. We note that correspondence you received from the sponsor identifying study subjects did not always match the subject identification shown in your records. You did not provide any correspondence from you to the sponsor correcting these misidentifications. The FDA investigator noted that subjects were identified by name (or initials) and by Subject ID; however, in various lists and letters the Subject IDs did not match the subject name (or initials). For the first eight subjects, the subject numbers were not consistently identified between your records and those supplied by the sponsor. For example, subject [REDACTED], identified in your records as [REDACTED], was identified in sponsor records as patient [REDACTED]. As a clinical investigator, it is difficult to clearly identify and follow subjects when subject identification is inconsistent. We recommend in future studies that, should this occur, you contact the sponsor to correct identified problems. Close communication between the clinical investigator, and sponsor is critical in performing accurate clinical investigations and compiling data.
2. You were unable to produce any record of your financial disclosure to the study sponsor. As a clinical investigator, you will need to provide financial disclosure information to the sponsor of the study in accordance with 21 CFR Part 54 and assure it is updated when a marketing application is submitted.
3. During the inspection you were requested to explain and provide any instructions that were given to the subjects regarding exercises to be performed following the investigational procedure. During the inspection, no written instructions were found by your staff and conflicting verbal responses were provided by your staff regarding post-operative exercises. Ultimately, within the site records, directions specifically addressing postoperative exercises were found. These were dated [REDACTED] - over a month after the last subject was enrolled.

In the future, in order to better understand investigational study practices, you might consider attending and having your staff attend training sessions that focus on the operations of investigational studies. Such programs are available from various professional associations. In addition, you will want to ensure that future studies in which you are involved have clearly identified the sponsor and clinical investigator responsibilities, have clearly identified protocols, and are well-monitored. There needs to

be a close cooperation and communication between all participants of the study including the sponsor, the IRB, the investigator, and staff.

We would like to remind you that as a clinical investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations. You should refer to the regulations relevant to device studies, some of which were referenced above, in 21 CFR Part 812. You can refer to the following web site for additional information:

Investigational Device Exemptions -
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

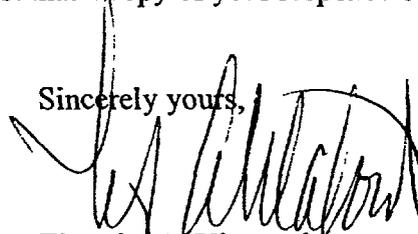
Please advise this office, in writing, **within fifteen (15) working days of receipt of this letter** of the specific steps you have taken to correct the violations noted above and all other violations known to you, and to prevent the recurrence of similar violations in current or future studies. Failure to respond can result in regulatory action without further notice.

You should direct your response to the:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
Program Enforcement Branch II, (HFZ-312)
2094 Gaither Road
Rockville, Maryland 20850
Attention: Mr. G. Levering Keely, BSN, MPA,
Consumer Safety Officer.

A copy of this letter has been sent to our San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, CA 94502. We request that a copy of your response be sent to that office as well.

Sincerely yours,



Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health