DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

Ref: 08-HFD-45-0502

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Arturo Corces, M.D.
7340 SW 79th Street
Miami Institute for Medical Research
Miami, Florida 33186

Dear Dr. Corces:

Between March 20 and April 26, 2007, Mr. Victor Spanioli, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of two clinical investigations:

- Protocol[ ](IND # 065892): "Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE, Controlled, Double-Blind, Randomized Study of[ ]in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip Replacement," performed for[ ] and

- Protocol[ ](IND[ ]; "A Phase 2B, Randomized, Multicenter, Dose-Ranging Study Assessing the Safety and Efficacy of[ ]in the Prevention of Venous Thromboembolic Events (VTE) in Subjects Undergoing an Elective, Unilateral Total Knee Replacement," performed for [ ]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your May 18, 24 and 31, 2007 letters written in response to the Form FDA 483, including the binders of exhibits prepared by[ ] we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Investigator Spanioli

presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].**

   When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan and applicable regulations; protecting the rights, safety and welfare of subjects under your care; and ensuring control of drugs under investigation. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator you must adequately supervise those to whom you delegate authority. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were conducted according to the signed investigator statement, and in a manner that protected the rights, safety, and welfare of human subjects. The investigation found that you delegated certain tasks to individuals not qualified to perform such tasks. Specifically,

   a. For [ ] protocol, you delegated the performance of protocol-specified clinical evaluations (e.g., physical examinations, and evaluation of signs and symptoms relating to a DVT or pulmonary embolism) to [ ] According to the [ ] Site Personnel Delegation Log, [ ] was assigned a role of data entry for CRFs. During the inspection, Mr. [ ] indicated that he was not trained or qualified to perform physical examinations, and other required assessments. For example,

      i. For Subject 7013, the Day 65 physical examination and DVT/PE assessment was performed by [ ] during a visit date of March 19, 2007, while you were in England.

      ii. For Subject 7021, the Day 13 assessment records dated February 27, 2007, were initialed by [ ] The DVT/PE assessment was completed by [ ] based on the subject's responses to questions instead of a clinical examination by a qualified individual.

      We note your response letter dated May 18, 2007 states that [ ] is listed as the authorized personnel to perform general study procedures. You also state that [ ] was present at the physical examinations conducted by the PI and acted as a scribe to record results of examinations performed by the PI. You state that [ ] inadvertently checked all other boxes of the physical evaluation for Subject 7013, when the PI was not available. We note that [ ] is listed with the role of data entry on the study delegation log. [ ] is not authorized to

conduct physical assessments of study patients, as it appears he did, when he signed the Day 65 Physical Exam and Assessments form for Subject 7013, or the Day 13 Assessment form for Subject 7021.

2. **You failed to meet the requirements for informed consent, specifically the requirement that information given to the subject or the subject's representative shall be in language understandable to the subject or the representative [21 CFR 50.20].**

   a. The [ ] study Research Subject Information and Consent Form signed by Subject [ ] dated January 3, 2007 is 12 pages long, with the first eight pages written in the English language and the last four pages written in the Spanish language. There was no documentation that this subject is bilingual in both English and Spanish. The section of the consent with seven questions requiring a "yes" or "no" response, appearing in Spanish language text, is not completed. The Research Authorization signed by [ ] on January 3, 2007 consists of the first three pages in English and the signature last page in Spanish. All English language versions of these consent forms dated March 16, 2007 were signed by [ ] however, there is no signature or date relating to the individual discussing the consent. Subject [ ] completed study participation on/or about March 14, 2007.

   b. The [ ] study informed consent document signed by Subject 7003 on October 25, 2006, is in the English language. Records document Subject 7003 was re-consented on the day of surgery, October 29, 2006, using a Spanish language informed consent form. There is no documentation that this subject is bilingual in English and Spanish.

Your May 24, 2007 response letter states that it is unclear why Subject 7003 was re-consented on the day of surgery, since the subject signed the English informed consent form on October 25, 2006, seven days prior to surgery. Your response does not address whether this subject was bilingual, and does not explain why this subject was given an English consent form on October 25, 2006 and a Spanish consent form on October 29, 2006.

3. **You failed to conduct the studies or ensure they were conducted according to the relevant, current protocols [21 CFR 312.60].**

   a. For the [ ] protocol, the required 13 day follow up visit for subject 7010 was not done due to reported scheduling conflicts; however, there is no documentation as to why an alternate date was not scheduled. The protocol required that on day 13, a physical examination with assessment of vital signs be performed, and blood samples be drawn for hematology and clinical chemistry.

   Your response letter dated May 18, 2007, states that several attempts were made to contact this subject, but these attempts were not documented. DSI considers

your response inadequate, as it is the responsibility of the clinical investigator to ensure that correct study procedures are followed.

b. Section 4.5.7 of the [ ] protocol states "Thromboprophylaxis with pneumatic compression is not allowed during the study." Hospital records document that the following 6 subjects received [ ] pneumatic compression therapy during their hospitalization: 7008, 7009, 7014, 7016, 7017, and 7021.

c. Protocol [ ] prohibited the use of pneumatic compression devices. Records for 5 of 62 subjects documented that they received intermittent foot pneumatic compression during hospitalization following total knee replacement: 1018, 1039, 1047, 1050, and 1061.

Your response letter dated May 18, 2007 states that the use of intermittent pneumatic foot compression therapy has been a standard of care for the majority of patients at the [ ] Medical Center, and that the personnel continued using this device with the patients enrolled in these studies. DSI considers your response to be unacceptable. The protocol specifically prohibited the use of intermittent pneumatic compression devices. Furthermore, our investigation found an email exchange of September 26, 2006, between [ ] Senior Medical Research Associate, [ ], and Office Manager, [ ] specifically stating that use of planned intermittent pneumatic compression during active treatment period was an exclusion criteria.

d. Protocol [ ] prohibited the use of drugs known to affect platelet function or coagulation within 7 days prior to surgery and throughout the study treatment period. These included clopidogrel (Plavix) and acetyl salicylic acid (aspirin, Ecotrin). The investigation found that Subject 1061 received both Plavix and aspirin, during his/her participation in the study.

Your May 31, 2007 response is insufficient. Subject 1061 was screened on January 24, 2007, and entered the active treatment phase on January 31, 2007. Your letter refers to a Drug Dispensing Record that documents clopidogrel and acetyl salicylic acid for Subject 1061 were discontinued on January 31, 2007, the same day that active study treatment began, and not seven days before as the protocol required.

e. The [ ] protocol states that to ensure the blindness of the study the investigator should not measure any coagulation parameter at the local health care facility. The investigation found that coagulation testing for PT INR and PTT, Activated, was performed for Subject 7009 at the December 21, 2006 visit, and the PT, PT INR and APPT coagulation tests were done for Subject 7002 on October 24 and 26, 2006. These subject results were available for review by the Clinical Investigator.

In your letter dated May 18, 2007, you state that these tests were ordered in error.

f. For the [ ] study, the Screening (Day 0) chemistry lab test for Subject 7012 was collected on December 13, 2006. These lab results documented, among other things, a Lactate Dehydrogenase (LDH) value of 1612 U/L (reference range 100-220 U/L), stamped as "not clinically significant." This entry did not contain dates or signatures of the responsible person. The associated 'screening' hematology report contained your signature and was dated January 5, 2007, approximately three weeks after this subject's hip replacement surgery on December 19, 2006. No documentation was found explaining the determination that the LDH value was "not clinically significant."

Your response dated May 18, 2007, states that you chose not to require repeat testing because blood work would be performed prior to the subject's surgery as part of the pre-operative hospital procedure. You also noted that it appeared that the initial blood sample was unreliable based on the NSA potassium results, and that chronic or acute tissue damage would have been noted in the subject if the initial LDH value was accurate. You also state that blood collection was performed on the day after surgery, and that the lab values were within normal range. This response is unacceptable. An LDH value of 1612 U/L is clearly out of range, and clinic records should document why you considered this as "not clinically significant." Furthermore, you did not explain why you reviewed the screening chemistry lab results on January 5, 2007, almost three weeks after the subject's surgery.

g. The [ ] protocol required that blood samples be drawn twice on Day 6, to measure coagulation parameters. The protocol specified the times for these blood draws as shortly before intake of the tablet (at trough) and 2-4 hours after intake of tablet (at peak). For Subject 7021, for the Day 6 sample, the drug administration records document that study drug was administered at 21:21 on February 19, 2007. The post-dose blood collection record documents a time of 22:30, or slightly more than 1 hour later. For Subject 7002, drug administration records document that study drug was administered at 10:19 AM on October 30, 2006, and the blood collection records document a time of 16:00, or almost 8 hours later.

We acknowledge in your letter dated May 18, 2007, you state that the times entered by the nurse were erroneous, and that the Study Coordinator [ ] was present during the period of drug administration and firmly recalls the sample collection times as being done within the timeframes specified by the protocol. DSI considers this response to be inadequate because you provided no documentation to support your contention.

h. The [ ] study protocol states that "in case of premature discontinuation during the treatment phase, all assessments as described for Visit Day 13 have to be performed. Records document that Subject 7014 received investigational drug from January 12-14, 2007 (four tablets and 5 injections), and was removed from the study because the rehabilitation center declined to administer study

medication. The investigation found that remaining doses of study medication were returned on February 20, 2007, and that the Day 6 and other safety follow up visits and blood draws were not performed, and the assessments required for the Day 13 follow-up Visit were not done.

We note in your letter dated May 18, 2007 that you include a Note to File, dated April 12, 2007, that documents you contacted this subject for follow-up evaluation. DSI considers this response to be inadequate because it does not explain why your follow-up with this subject occurred approximately 3 months after the subject was discontinued from the study.

i. Protocol[ ]required the exclusion of subjects with a 12-lead electrocardiogram (ECG) demonstrating QTc>450 msec and/or clinically significant abnormalities at screening. Records document that Subject 1019 had a prolonged QTc of 457 msec on September 25, 2006, and signed an Informed Consent document on September 25, 2006 at screening.

Your May 31, 2007 response letter states that the ECG tracings were sent to a core ECG laboratory for interpretation. DSI considers your response to be inadequate to explain why you enrolled a subject into the study who did not meet eligibility requirements at study entry.

j. The[ ]protocol required that all adverse events be fully recorded on the subject's Case Report Form. The investigation found clinic records that documented loss of memory, and isolated nonobstructive thrombus in the common femoral vein on the right side for Subject 7002, on November 28, 2006; left foot drop for Subject 7008 on December 7, 2006; and urinary incontinence for Subject 7016 on January 12 and 14, 2007. These adverse events were not documented onto the subjects' Case Report Form.

Your May 24, 2007 response states these adverse events were documented in the subject's medical history and physical examination report. This response is insufficient, as these adverse events were required to be documented on the subjects' Case Report Form.

k. The[ ]protocol excluded female subjects who "are not using adequate birth control method." The protocol lists birth control pills or barrier method as the only acceptable means for birth control. The investigation found that Subject 7010, who was 18 years of age at the time, was "encouraged" to practice abstinence for at least three months after having the surgical procedure (December 2006). Furthermore, the investigation found that this subject had been previously scheduled to undergo surgery (May 15, 2006), but was found to have become pregnant and underwent abortion.

Your response letter dated May 18, 2007 states that you received sponsor approval for allowing this subject to use abstinence as a form of birth control. This response is unacceptable. An email dated April 5, 2007 from[ ]Medical

Research Associate [ ] instructed the staff to discuss only the protocol- specified birth control options with this subject.

1. Protocol [ ] required that each subject be instructed to take 4 capsules of study medication once a day, at the same time of day during the treatment period; and that the dose was to be administered with 240 mL of water. The investigation found no documentation that such instructions were given and no record confirming that these requirements were met.

   Your May 31, 2007 response states the protocol did not provide instructions of how to ensure that 240 ml of water was consumed, or how to document this fact. This response is unacceptable. It is the responsibility of the clinical investigator to ensure that protocol specified procedures are followed and documented.

4. **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].** For example:

   a. For the [ ] protocol, the concomitant medications required to be entered on the Concomitant Medication eCRF were not entered, and some source records were inconsistent with eCRF entries. Specifically,

      i. Source records document that Subject 7014 received Benicar, acetaminophen with codeine, rosiglitazone maleate with glimepiride (4 mg/2 mg), Premarin 1 g, oxybutynin 5 mg, and Toprol XL, whereas the Case Report Form documents only Benicar, Toprol XL, metformin and oxybutynin 5 mg. Furthermore, the Date Started column is not completed, and initials of the reviewing physician are not recorded.

      ii. Source records document that Subject 7010 received concomitant medications aspirin, folic acid, iron, Darvocet, naproxen, and vitamins. The CRF lists codeine as the only concomitant medication, and there are no entries for the Date Started.

      iii. For Subject 7021, the Summary of Medications form for the hip surgery hospitalization (February 12 – 19, 2007) documents the administration of aspirin and several other drugs that are not entered in the Concomitant Medication eCRF. Start and stop dates are not entered for 10 of the 13 drugs listed in this eCRF.

   We note that in your response letter dated May 24, 2007, you state that these inconsistencies were due to documentation of information in various sources. We also acknowledge your action to implement a Standard Operating Procedure to establish a standard procedure to ensure consistent documentation of study data.

b. For the [ ] protocol, for Subject 7014, The End of Treatment eCRF states that premature termination was due to "consent withdrawn," whereas source records document that the subject was taken off the study because the rehabilitation center refused to continue patient on study drug.

In your letter dated May 24, 2007, you explain the transfer of this subject to a rehabilitation center in West Palm Beach after her hip replacement surgery. Your response does not clarify if the subject withdrew consent, or if she was discontinued from the study by the rehabilitation center.

c. For Protocol [ ] the source records for Subject 1061 document concomitant medications of fenofibrate and carbamazepine. The Concomitant Medication eCRFs for this subject does not record these concomitant medications. Your May 31, 2007 response letter states this documentation was inadvertently omitted in the eCRF for this subject. Your response is insufficient as it is your responsibility to ensure correct and completed documentation during the conduct of this study.

5. You failed to maintain adequate drug disposition records [21 CFR 312.62(a)].

Protocol [ ] Section 4.5.8, states "Drug administration will be documented (date, time, dose and signature of dispensing person). Drug account of the unused study medication will be performed." The investigation found that the Drug Dispensing log entries for 14 subjects who completed the study as of March 2007 contained incomplete information and did not adequately account for subject compliance. For example:

a. For Subject 7003, the Drug Dispensing log documents that the amount of drug used was "unknown" with no explanation provided for the lack of drug accountability.

b. For Subject 7004, the Drug Dispensing log documents the number of tablets and injections administered as unknown and that the patient never returned study medication.

c. For Subject 7008, the drug Dispensing log documents that 21 tablets and 16 injections were administered to the subject and that the subject returned 19 tablets, with no explanation provided in the "discrepancy" column.

d. For Subject 7011, the Drug Dispensing Log documents that the number of tablets used was "unknown" and that 16 injections were administered, whereas the CRF documents that all doses were administered.

e. For Subject 7012, the Drug Dispensing Log documents that 29 tablets and 14 injections were administered, and 11 tablets and 2 injections were returned, but the "discrepancy explanation" column is left blank.

> In your letter dated May 18, 2007, you refer to the complexity of the study with limited instructions regarding assuring administration of investigational drug by various caregivers. This response is unacceptable. Due to the inaccurate drug disposition records, we are unable to accurately assess compliance with the protocol.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Tejashri Purohit-Sheth, M.D. at (301) 796-3402 FAX (301) 847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
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/s/

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