DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Biologics Evaluation and Research
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By Facsimile Transmission and Overnight Delivery

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February 16, 2012

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDING AND OPPORTUNITY TO EXPLAIN

Dear Dr. Lasala:

Between February 22, 2011 and March 31, 2011, three Food and Drug Administration (FDA) (hereafter referred to as "FDA" or the "Agency") Investigators conducted an inspection of the following clinical studies involving biological investigational new drugs which you conducted as a clinical investigator:

Study 1: Protocol 2007-02-I: "Phase 1, Single Center, Prospective, Non-Randomized, Open-Label Study of Autologous Bone Marrow-Derived Stem Cells For Utilization and Rescue of Infarcted Myocardium"

Study 2A: Protocol 2007-01-I: "Transfer of Bone Marrow-Derived Mononuclear Cells and Bone Marrow-Derived Mesenchymal Stem Cells into Lower Extremities for the Treatment of Critical Limb Ischemia" (Phase 1 study)

Study 2B: Protocol 2008-01-II: "Transfer of Bone Marrow-Derived Mononuclear Cells and Bone Marrow-Derived Mesenchymal Stem Cells into Lower Extremities for the Treatment of Critical Limb Ischemia" (Phase 2 study)

Study 3A: Protocol 2007-03-I: "Transfer of Bone Marrow-Derived Mononuclear and Mesenchymal Stem Cells Into the Myocardium for the Treatment of Severe Coronary Ischemia" (Phase 1 study)

Study 3B: Protocol 2008-03-II: "Transfer of Bone Marrow-Derived Mononuclear and Mesenchymal Stem Cells Into the Myocardium for the Treatment of Severe Coronary Ischemia" (Phase 2 study)

Study 4: Protocol (b)(4) "Phase 1, Single-Center, Prospective, Non-randomized, Open Label, Safety/Efficacy Study of the Infusion of (b)(4) Autologous Bone Marrow-Derived Mesenchymal Stem Cells, in Patients with Amyotrophic Lateral Sclerosis"

Study 5: Protocol 2009-SCI-I: "Transfer of Autologous Bone Marrow-Derived Mesenchymal Stem Cells for the Treatment of Spinal Cord Injury"

This inspection was conducted as part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products.

At the end of the inspection, the FDA Investigators presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your written response to the Form FDA 483 dated April 19, 2011 ("Response," "Letter"). Your response is insufficient to address the matters outlined in this letter.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as set forth under Title 21 Code of Federal Regulations (CFR), Parts 50 and 312. These regulations are available at http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=201021.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational articles as set forth under 21 CFR § 312.70.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You failed to fulfill the general responsibilities of an investigator. [21 CFR § 312.60 and Part 50].**

   Among other requirements, an investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan and applicable regulations, and for protecting the rights, safety, and welfare of subjects under the investigator's care. You signed the Form FDA 1572, Statement of Investigator, on 9/18/07 and on several occasions thereafter, in which you specifically agreed to conduct the above studies in accordance with the protocol and applicable regulations. You identified several sub-investigators that would assist you in the conduct of the studies, but as the clinical investigator you are responsible for all aspects of the studies.

Our investigation revealed that you failed to fulfill your obligations as the clinical investigator in the use of investigational new drugs in the following ways:

A. The investigational plans for the above studies were limited to the investigational use of **autologous** bone-marrow derived cells. The bone marrow-derived mononuclear cells (BM-MNC) and bone marrow derived mesenchymal cells (BM-MSC) used to conduct the Phase 1 and Phase 2 studies under your INDs were collected and used for autologous infusions. You participated in an End-of-Phase 2 meeting with FDA conducted on November 22, 2010, when the sponsor of your studies, TCA Cellular Therapy, LLC (TCA) proposed the use of autologous BM-MNC combined with **allogeneic** BM-MSC as the investigational product for a Phase 3 study. You were present at the November 22, 2010 meeting when FDA advised TCA that a new IND would be required for the use of the proposed investigational allogeneic product. As documented in the meeting minutes sent to you on December 8, 2010, FDA advised TCA and you that the Agency considered the addition of allogeneic BM-MSC to be a first-in-human Phase 1 study, which would require submission of a new IND, and which should focus on assessment of safety for this new product. In spite of FDA's instructions that a new IND would be required for the use of allogeneic BM-MSC combined with autologous BM-MNC, in violation of the investigational plan, you repeatedly or deliberately administered allogeneic cell products to the following individuals without submitting a new IND:

Identification	**Infusion Date**	**Indication**
(b)(6)		Spinal cord injury
		Spinal muscular atrophy
		Spinal muscular atrophy
		Muscular dystrophy
		ALS
		Progressed muscular atrophy
		Spinal cord injury
		Severe limb ischemia
		Severe limb ischemia
		Spinocerebellar ataxia
		Spinal cord injury
		Spinal cord injury
		ALS
		Spinal cord injury
		Traumatic musculoskeletal injury

During the inspection, you admitted to the FDA investigators that you administered allogeneic cells to patients outside of clinical protocols, conduct that you described as a "compassionate illegal act," "completely wrong," and "completely illegal."

B. You administered, or caused to be administered, an investigational drug to persons not enrolled in clinical research studies. The following individuals were administered an investigational product and were not enrolled in the above-listed clinical research studies:

Study #	IND Indication	Subject #	Primary Bone Marrow Aspiration Date	Infusion Date
1	Myocardial Infarction	(b)(6)		
1	Myocardial Infarction			
2A, 2B	Limb Ischemia			
2A, 2B	Limb Ischemia			
3A, 3B	Coronary Ischemia			
3A, 3B	Coronary Ischemia			
3A, 3B	Coronary Ischemia			
3A, 3B	Coronary Ischemia			
4	ALS			
4	ALS			
4	ALS			
5	Spinal Cord Injury			
5	Spinal Cord Injury			
5	Spinal Cord Injury			

i. Under your authority, (b)(4) infusions of (b)(4) mesenchymal stem cells (MSCs) of autologous origin were administered to myocardial infarction patients identified as (b)(6), who were not enrolled in Study 1. Study 1 is the only approved Sponsor Study that involves the (b)(4) infusion of MSCs of autologous origin for treatment of myocardial infarction.

ii. Under your authority, (b)(4) MSCs and mononuclear cells (MNCs) of autologous origin were administered to limb ischemia patients identified as (b)(6) (b)(6), who were not enrolled in Studies 2A or 2B. Studies 2A and 2B are the only approved Sponsor Studies involving the infusion of (b)(4) (b)(4) MSCs and mononuclear cells of autologous origin to limb ischemia patients.

iii. Under your authority, (b)(4) MSCs and MNCs of autologous origin were administered to coronary ischemia patients identified as (b)(6) (b)(6) who were not enrolled in Studies 3A or 3B. Studies 3A and 3B are the only approved Sponsor Studies involving the infusion

of (b)(4) MSCs and MNCs of autologous origin to coronary ischemia patients.

iv. Under your authority, (b)(4) MSCs of autologous origin were administered to Amyotrophic Lateral Sclerosis (ALS) patients identified as (b)(6) who were not enrolled in Study 4. Study 4 is the only approved Sponsor Study involving the (b)(4) MSCs of autologous origin to ALS patients.

v. Under your authority, (b)(4) MSCs of autologous origin were administered to spinal cord injury patients identified as (b)(6) who were not enrolled in Study 5. Study 5 is the only approved Sponsor Study involving the (b)(4) (b)(4) MSCs of autologous origin to spinal cord injury patients.

In your letter you admit that you chose to treat the fourteen subjects identified above in order to expand access for compassionate use. You explain that you did not realize there was a formal process to obtain expanded access for individuals who did not meet the criteria for an approved IND and a formal process to request compassionate use prior to treatment**.**

C. You failed to perform the following tests or assessments as specified in the protocols:

(b)(4), (b)(6)

In your response regarding item 1.C.i, you explain there was "confusion" regarding this protocol requirement, and you admit that these were protocol deviations and that it was "my mistake by not checking that these tests were performed correctly." Regarding item 1.C.ii, you explain that the subjects in Studies 3A and 3B were often discharged prior to the 24 hours time point specified for the (b)(4) test, and, as a result, the sample was

not drawn by hospital staff. In regard to item 1.C.iii, you state that you did not document the physical exam for the Study 4 subject. Regarding item 1.C.iv, you acknowledge that you assumed, but did not verify, that all baseline tests for Subject (b)(6) had been performed.

D. You failed to report to the IRB the amputation of Subject (b)(6) right foot on (b)(6), fourteen days after administration of the investigational stem cell product (b)(6) in Study 2B. The protocol requires that amputation within 30 days of cell implantation be reviewed by the Investigator and reported to the IRB.

In your letter you admit that you were aware of the amputation, and that you signed the serious adverse event report but that you did not know that it was not reported to the IRB.

2. You failed to assure that an Institutional Review Board (IRB) would be responsible for the initial and continuing review and approval of the clinical studies by failing to adhere to the conditions of approval imposed by the IRB, and you failed to promptly report to the IRB all changes in the research activity, all unanticipated problems involving risk to human subjects and others, and to not make changes in the research without IRB approval. [21 CFR § 312.66].

A. You failed to adhere to the conditions of approval imposed by the IRB in that there is no documentation of training for all study staff on Human Subject Protection (HSP) and Good Clinical Practice (GCP) requirements as certified in the Initial Review Submission Forms that were submitted to the IRB**.** The IRB specifically required you to provide and document HSP training, and on the Initial Review Submission form you indicated that the training had indeed been performed.

In your letter you stated that the education of staff regarding the protection of human subjects "typically occurred at the initiation visit after IRB approval."

B. You failed to adhere to an IRB requirement that you not make any changes in research activity without prior IRB approval, and to promptly report to the IRB all changes in research activity, in that you failed to seek IRB approval (as instructed in the IRB approval letter dated 2/19/2010) for the infusion of allogeneic mesenchymal stem cells to Study 4 Subject (b)(6), or for any of the fifteen subjects listed in item 1. A., above.

In your response, you admitted that it was your decision to treat the subjects with allogeneic cells in order to create expanded access for compassionate use. You also stated that you did not realize that this would be considered as a planned protocol deviation with a requirement of IRB submission and approval.

C. You failed to adhere to the IRB conditions of approval for study 3A by making changes to research activity prior to IRB approval. Specifically, on 3/19/08 you eliminated the physical examination requirements at the infusion visit (Visit 4), you eliminated the study

visits at months 9 and 10, (b)(4) (b)(4) of which was done approximately 11 weeks prior to IRB approval.

D. You failed to adhere to the IRB's conditions of approval for your studies, in that you did not obtain a translated consent form for a non-English speaking study subject, Study 4 Subject (b)(6) in accordance with the IRB's requirements for a written certified translation of the informed consent document in the prospective subject's first language.

   In your letter you acknowledged that you understood that the consent needed to be translated for a non-English speaking individual, but you did not understand that it had to be a written translation.

E. You failed to obtain IRB approval prior to making changes to the research, in that you did not seek IRB approval for the use of the "Standard Release Form" signed by study subjects in Studies 2A, 2B, 3A, 4 and 5.

   In your letter you admitted that this form was given to a few subjects before obtaining photographs, videotaping, or using personal information in news articles or other media, and stated that you did not realize that this form required IRB approval.

F. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects and others, in that you failed to report to the IRB that (in Study 2B) Subject (b)(6) was amputated on (b)(6), fourteen days after administration of the investigational stem cell product (b)(6)) in Study 2B. The protocol requires that amputation within 30 days of cell implantation be reviewed by the Investigator and reported to the IRB. See item 1.D. above.

   In your letter you admit that you were aware of the amputation, and that you signed the serious adverse event report but that you did not know that it was not reported to the IRB.

G. You failed to promptly report to the IRB all changes to the research, in that you did not report to the IRB at any time that you administered the investigational product to the (b)(6) in addition to the protocol-specified target region of the (b)(6) for Subject in Study 2B. This protocol deviation was never reported to the IRB as required in the IRB approval letter.

   In your response you explain that you performed these injections to "remove an immediate hazard to the patient." You acknowledged your responsibility for the event and stated that you did not know that it was not reported.

This letter is not intended to contain an all-inclusive list of deficiencies with your clinical studies of investigational new drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations. Accordingly, the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated findings, including an explanation of why you should remain eligible to receive investigational articles and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR § 312.70(a).

Within fifteen (15) business days of receipt of this letter, write me to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) business days of receipt of this letter. If you do not write to me to arrange a conference time within fifteen (15) business days, the right to file a response will be waived.

Your reply should be sent to:

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1488

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents. A representative of your choosing may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational articles. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (available at the Internet address identified on page 1 of this letter) and 21 CFR § 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer who has not participated in this matter will conduct the hearing. The Commissioner will determine whether or not you will remain entitled to receive investigational articles. You should be aware that neither entry into a consent agreement nor

pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure: Proposed consent agreement