Duke Clinical Research Institute
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SAFETY SURVEILLANCE
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Date: 19 January 2005

To all investigators in TACT:

RE: SAE Report # 10004, Serious Adverse Event: CARDIO-RESPIRATORY ARREST

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to inform you of an unexpected, serious adverse event which occurred in TACT, "A multi-site, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of EDTA (ethylene diamine tetra-acetic acid) chelation therapy in individuals suffering from Coronary Artery Disease (CAD)".

The current case concerns a patient in the above trial who experienced CARDIO-RESPIRATORY ARREST. This 59 year old female presented to the study with a history of Angina Pectoris, Congestive Heart Failure, Hypertension, Hypercholesterolemia, and PCI.

The patient was randomized to EDTA chelation or placebo on 28 January 2004 and received a total of 33 IV infusions of chelation solution or placebo to date, with the most recent infusion on 11/30/2004. Patient was receiving maintenance infusions.

On 01 December 2004, the patient experienced cardiopulmonary arrest and death. When the patient missed the scheduled maintenance Infusion # 34 visit, an attempt to contact the patient was made. It was discovered that the patient had died on 01 December 2004. On 30 November 2004, the patient presented for maintenance infusion 33. The patient denied any significant medical problems, hospitalizations, myocardial infarctions, strokes, percutaneous coronary interventions, coronary artery bypass graft surgeries, implantable cardioverter defibrillator or pacemaker placements since the last visit. The patient weighed 187.1 pounds. Her infusion was complete at 1:05 PM. The next day, on 01 December 2004, the patient presented at the local emergency room via ambulance and paramedics at 2:44 AM with the chief complaint of shortness of breath at home with decreased respirations, dyspenic with a heart rate 20-30 beats per minute. The patient was unresponsive, intubated with cardiopulmonary resuscitation in progress. Initial assessment revealed pupils of 5 millimeters with sluggish reaction. The patient was unresponsive and flaccid. The patient had an irregular heart rhythm, peripheral pulses were thready and no edema was present. The patient was intubated with frothy sputum on 100% FIO2 with a pulse oximetry of 82% saturation. Lung auscultation revealed rales. The patient's abdomen was obese and soft. The patient was treated with 100 % oxygen, epinephrine, atropine, sodium bicarbonate, Lasix, Bumex and ringer's lactate intravenous solution. All attempts to resuscitate the patient failed, and the patient was pronounced dead by the emergency room physician at 03:40 hours with a clinical impression of unsuccessful cardiopulmonary resuscitation, acute myocardial infarction, and congestive heart failure / cardiogenic shock. The official cause of death was listed as cardiopulmonary arrest. Other pertinent laboratory information includes serum creatinine between 0.9- 1.0 mg/dL during the months of January through April of 2004, rising to 1.1-

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1.2 during May through July of 2004, 1.4 mg/dl in September of 2004, and 1.8 mg/dl on the day of her death.

The site investigator has assessed the causal relationship between the study drug and the serious adverse event as not associated stating the cardiopulmonary arrest was due to progression of the disease under study. However, because the time from study infusion to presentation to the emergency room was 13 3/4 hours, no note of clinical deterioration was made prior to infusion, and available clinical information does not provide a clear cause of death, I feel reporting of this case as associated is indicated as a conservative measure. Differential diagnoses include pulmonary embolism, congestive heart failure, myocardial infarction, and malignant dysrhythmia.

We are distributing an investigator alert, since cardio-pulmonary arrest is not specifically mentioned in the TACT Investigator's Brochure. We will keep you informed if further relevant information becomes available on this type of adverse event. Please submit a copy of this letter to your IRB for review. Please file a copy of this letter, along with any response, in your regulatory binder. If your IRB requests that the informed consent be changed, please do so and submit a copy of the new consent to your site manager or monitor for approval before implementing.

If you have any questions or further concerns regarding this SAE, please contact me at (919) 688-8008 (phone), szcze001@mc.duke.edu (e-mail), or (919) 668-7138 (fax).

Yours sincerely,

Lynda Szczech, MD
DCRI Medical Monitor