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Date: 25 January 2005

To all investigators in the TACT trial:

RE: SAE Report # 10002, Serious Adverse Event: CARDIAC FAILURE CONGESTIVE

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 the TACT trial, "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 congestive heart failure. This 74 year old caucasian male had a history of angina pectoris, myocardial infarction with angioplasty, congestive heart failure, valvular heart disease, severe aortic stenosis, type II diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, gout, osteoarthritis, atrial fibrillation/flutter, transuretheral prostatectomy, pneumonia and left leg cellulitis.

The patient was randomized to EDTA chelation or placebo on 10 December 2003 and received a total of 32 IV infusions. The patient received weekly infusions from 18 December 2003 through 08 July 2004 and maintenance infusions on 12 August 2004 and 09 September 2004. The last dose of study drug was Infusion 32, administered on 09 September 2004 from 07:25 to 11:04 hours. The patient was seen in April 2004. His ejection fraction was 40%, BUN was 28 mg/dL and his creatinine was 1.3 mg/dL. Doses of his diuretics were increased, and the patient developed worsening renal function felt by his physicians to be related to pre-renal azotemia. On 09 April 2004, echocardiogram results revealed left atrial dilation of 5.2 cm, left ventricle concentric hypertrophy, apical hypokinesis, inferior hypokinesis, right ventricle and right atrial dilatation, aortic valve thickening with peak gradient of 67.2 mmHg with mean of 40.2 mmHg, aortic valve area of 0.6 cm squared, mild aortic insufficiency, mild tricuspid insufficiency, mild pulmonic insufficiency, mild mitral insufficiency, and severe aortic stenosis. On 09 September 2004, during Infusion 32, the investigator noticed evidence of gross lower extremity edema and administered an extra dose of Bumex 2 milligrams followed by as needed treatment. On 16 September 2004 at 11:00 hours, the patient presented to the emergency room with the chief complaints of severe back pain, fluid retention unresponsive to diuretics, and the inability to urinate or defecate. His BUN was 109 mg/dL and his creatinine was 3.9 mg/dL. The two blood pressures reported during the admission were 90/56 mmHg and 80/50 mmHg. The patient was diagnosed with

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severe congestive heart failure, lack of perfusion to the kidneys and bowels, and back pain. The patient was treated with intravenous dopamine and dobutamine, but his blood pressure slowly declined and his urine output remained very poor. On 17 September 2004 at 06:00 hours, the patient expired in the emergency room while awaiting admission to the intensive care unit. The death certificate, received on 07 October 2004, stated the causes of death as congestive heart failure and aortic stenosis.

The investigator assessed the causal relationship between the study drug and the serious adverse event as not associated stating that the cause of the congestive heart failure was due to concomitant disease and his clinical impression, as well as other treating physicians, during the course of therapy was the subject's critical aortic stenosis was resulting in heart failure symptoms that required increasing doses of diuretics. This then resulted in increasing creatinine that he felt was due to pre-renal azotemia. The investigator was aware of the increasing creatinine and felt that pre-renal azotemia was the etiology given the fact that some fluctuation in creatinine was seen.

While the investigator has determined that this event is not drug related, we feel obligated to report this event based on the source documents and clinical information forwarded to us. Each of the three following clinical scenarios/summaries are possible:
1) The patient's death is related to congestive heart failure that occurred as a result of progressive aortic stenosis. In this clinical scenario, his fluctuating and subsequently increasing creatinine is related to prerenal azotemia that occurred as a result of his increasing diuretic requirement. This is supported by the clinical impressions of the physicians caring for the patient as well as the greater than 20 to 1 ratio of BUN to creatinine and hypotension that were present at his ER presentation.
2) The patient's death is related to congestive heart failure that was caused by the infusion of crystalloid fluids given during the course of the study. This is somewhat supported by a rise in weight that occurred during the infusions that occurred in the two months following April 2004. However, clinically it does not provide an etiology for his concurrent renal failure. His creatinine rose from 1.3 to 2.0 in July when he was back at his baseline weight. This would imply that his renal function declined as a result of another process (such as prerenal azotemia as suggested in scenario #1 or due to an intra-renal toxicity such as study drug as described in #3).
3) The patient's death was related to congestive heart failure that was caused by volume overload related to progressive renal insufficiency. While the cause of this patient's renal insufficiency is unknown, it was felt by his treating physicians to be related to prerenal azotemia. Of note, the use of study drug has been associated with renal failure. Given this, this is a plausible clinical scenario.

While we believe that the clinical scenario detailed in #1 is most supported by the source documents available, the documents do not provide sufficient evidence to be

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able to refute the latter two scenarios as possibilities. Because of this and the likelihood that these scenarios are not separate and distinct (meaning that aortic stenosis, cardiomyopathy with EF of 40%, crystalloids related to study drug infusion, and intrinsic renal failure [if present] could all have contributed in some manner), we feel it is appropriate to report this event with our interpretation that the first scenario is most likely.
This serious, unexpected, not associated adverse event was reported to the Food and Drug Administration on 19 October 2004. The event was not reported to the site investigators because it was assessed as not associated to the drug under investigation by the site investigator. We are reporting the event today at the request of the National Heart, Lung, and Blood Institute. 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/IEC for review. Please file a copy of this letter, along with any response, in your regulatory binder. If your IRB/IEC 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