



**Duke Clinical Research Institute**  
**DUKE UNIVERSITY MEDICAL CENTER**

**SAFETY SURVEILLANCE**

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Date: 28 November 2005

To all investigators in the TACT trial:

RE: SAE Report # 10006, Serious Adverse Event: CONSTIPATION

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 CONSTIPATION. This 63 year old male with a history of angina pectoris, congestive heart failure, diabetes mellitus, peripheral vascular disease, hypertension, hypercholesterolemia, cigarette smoking, percutaneous coronary intervention, and coronary artery bypass graft surgery was randomized to either EDTA chelation or placebo on 09 September 2005. The patient had received a total of 2 IV infusions of chelation solution or placebo from 13 October 2005 through 20 October 2005. The last dose of study drug was Infusion 2, administered on 20 October 2005 from 10:10 hours to 13:10 hours. Prior to the serious adverse event, the patient was seen on 20 October 2005. As noted, Infusion 2 was administered at that time. The pre-infusion blood pressure was 145/60 mm/Hg and the patient reported experiencing a headache on 13 October 2005 which resolved the same day. The serious adverse event of constipation occurred on 23 October 2005. The patient reported being constipated for 2 weeks. The patient was admitted to the hospital and found to be impacted. On 24 October 2005, the patient was discharged from the hospital.

The site investigator has assessed the causal relationship between the study drug and the serious adverse event as not associated stating the constipation was related to the use of the vitamin therapy. However, I have reviewed the information provided by the site principal investigator and the study coordinator. As per this information, the subject feels that this SAE was related to his participation in the trial. A relationship is supported by the timing of this event relative to study initiation. While the site investigator feels that this event is related to the use of vitamin therapy, I am of the opinion that our ability to discern whether the event was related to either vitamin therapy or chelation therapy is not possible. This ability to discern between therapies is further hampered by the fact that vitamins are not regulated substances in the United States and there is no available package insert or investigator brochure to consult. For this



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reason and based on the temporal relationship between study participation and event, I am of the opinion that this event to a reasonable possibility could be related to chelation therapy. Of note, I remain blinded to the arm to which the patient was randomized.

We are distributing an investigator alert, since CONSTIPATION is not specifically mentioned in the TACT Investigator 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/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 the clinical coordinating center at Mt Sinai Medical Center 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](mailto:szcze001@mc.duke.edu) (e-mail), or (919) 668-7128 (fax).

Yours sincerely,

A handwritten signature in cursive script, appearing to read 'L. Szczech'.

Lynda Szczech, MD  
DCRI Medical Monitor