

TECHNICAL ABSTRACT

A Phase III, Randomised, Controlled, Open Label, Multicentre Study of the Efficacy and Safety of Trinam[®] (EG004); an Assessment of Vascular Access Graft Survival in Hemodialysis Patients (Ark Study 103)

Patients in renal failure on hemodialysis depend on adequate and sustained vascular access; this can be achieved by surgical placement of a synthetic (PTFE) graft. These patients frequently experience graft complications arising from the development of smooth muscle cell (SMC) neointimal hyperplasia in the proximity of the graft-vein anastomosis. Such complications eventually lead to stenosis, access thrombosis and graft failure.

Trinam[®] is being developed to prolong graft survival. It is a combination product consisting of a replication deficient adenovirus containing the human vascular endothelial growth factor D (Ad-VEGF-D) gene and a biodegradable local delivery device (collar) made of collagen. At the end of the surgical procedure to insert the PTFE graft the collagen collar is applied around the anastomosis and sealed with a collagen surgical sealant. This procedure creates a reservoir between the site of anastomosis and the collagen collar. The adenoviral vector is then injected into this reservoir, localizing the expression of the transgene to the site of the anastomosis. Expression of VEGF-D has been shown to have a vascular protective role and inhibit SMC neointimal proliferation, therefore expression of VEGF-D should prolong graft survival(1).

The mechanism for this vasculoprotective effect of VEGF, as distinct from its more widely appreciated 'angiogenic' role, is that VEGF interacts with endothelial cell surface receptors to increase production of nitric oxide and prostacyclin. These entities diffuse into the media of the blood vessel wall and counter the tendency for intimal hyperplasia to develop.

The safety and efficacy of Trinam[®] was evaluated in a porcine model in which a PTFE loop-graft was used to join the pig carotid artery to the ipsilateral internal jugular vein. No safety concerns were raised in this study and Trinam[®] and ultrasound assessments showed that treatment with Trinam[®] enhanced the patency of the graft compared to control animals.

Trinam[®] has also been evaluated in a Phase II dose escalation study (Ark Study 102) in patients with end stage renal disease. No safety concerns have been reported to date and there was little or no evidence for systemic biodistribution of the adenoviral vector containing the VEGF-D gene or wild-type virus. Preliminary data from this study indicates that Trinam[®] may extend the life expectancy of grafts.

The objective of the proposed Phase III, randomised, controlled, open label, multicenter study is to assess the efficacy and safety of Trinam[®] when applied to the graft-vein anastomosis site in patients with end-stage renal disease who require vascular access for hemodialysis.

At the beginning of the study, after staff at each hospital have been trained, the site will be evaluated to ensure they have the necessary expertise to administer Trinam[®]. This will involve treating a patient who receives an end-to-side graft placement with Trinam[®]. The surgical data and short term safety data from this patient will be evaluated by the chair of the Data Safety Monitoring Board (DSMB) before the site can recruit patients into the main part of the study. If the data are not satisfactory the site may be allowed to treat one additional patient in the evaluation phase. Long term safety and efficacy data will be collected from these patients, however the efficacy data from these patients will not be used in the evaluation of the efficacy of Trinam[®]. This phase of the study will be termed Site Evaluation.

In the main phase of the study 250 patients will be randomized in a 1 to 1 ratio to the active group (end-to-side or end-to-end graft with Trinam[®]) or the control group (graft placement surgery only). Patients in both treatment groups will be stratified according to placement of an initial or replacement (after failure of a previous vascular access) arm graft and end-to-side or end-to-end anastomosis. After the study has been open for 15 months, a blinded sample size review will be performed in order to assess the overall survival pattern of study grafts. If necessary the sample size or the follow-up period of the study will be increased.

After randomization, patients will attend routine study visits until the end of the study, which will either be based on the results of the sequential analysis and a recommendation from the DSMB or 18 months after the last patient was randomized into the study (assuming an 18 month recruitment period). In case of graft failure or kidney transplantation, further follow-up will be limited to safety variables only.

After the completion of the main study all patients who were treated with Trinam[®] will be followed for a further 4-years to comply with current Gene Therapy Patient Tracking System guidelines (CBER November 2006). The long-term follow-up will be conducted each annually after the study has been completed and will involve assessing the general health of the patients who received Trinam[®] by questionnaire.

References:

1. Zachary I, Mathur A, Yla-Herttuala S. Vascular protection. A novel nonangiogenic cardiovascular role for vascular endothelial growth factor. *Arterioscler Thromb Vasc Biol* 2000;20:1512-1520.