STUDY SYNOPSIS Protocol Number: FER-CARS-03

Title of the Study:	EFFICACY-HF: EFfect of Ferric Carboxymaltose on exercIse CApacity and Cardiac function in patients with iron deficiencY and chronic Heart Failure
Investigator(s):	Professor Michael Motro, MD, FACC (Co-ordinating Investigator)
Study Centre(s):	41 sites were initiated of which 13 sites randomised 35 subjects to this study.
Publications:	Not applicable
Studied Period (Years):	1
First Subject In:	18 December 2008
Last Subject Out:	31 October 2009
Phase of Development:	3
Objectives:	Primary objective: The primary objective of this trial is to assess, relative to placebo, the effects on the evolution of exercise capacity (i.e., 6-minute walk test (6MWT) and symptomatic status (i.e., New York Heart Association (NYHA) classification) of the addition of intravenous (IV) iron treatment with ferric carboxymaltose (FCM) to the basic regimen of ambulatory subjects with stable symptomatic chronic heart failure (CHF) and iron deficiency (ID). In accordance with this trial's primary objective, the 2 co-primary outcomes are: 1. Evolution from baseline of the distance covered during 6MWT performed 4, 12 and 24 weeks after the start of study treatment. 2. Evolution from baseline in NYHA functional class assessments performed at 4, 12 and 24 weeks after the start of study treatment. Further secondary objectives (efficacy): 1. Evolution from baseline of cardiac function parameters as assessed by 2D Echo/Doppler cardiography 4, 12 and 24 weeks after start of study treatment. 2. Self-reported patient global assessment (PGA) of treatment at 4, 12 and 24 weeks after start of study treatment. 3. Health related quality of life (HRQoL) as assessed by the European quality of life – 5 dimensions and Kansas City cardiomyopathy questionnaire self-administered questionnaires 4, 12 and 24 weeks after start of study treatment.

Objectives: (Cont'd)	Objectives for safety are to evaluate the effect of IV FCM compared to placebo on: 1. Evolution of estimated glomerular filtration rate, vital signs, electrocardiographic findings and laboratory test results (haematology, clinical chemistry, iron status, urinalysis, neurohormone and inflammatory markers). 2. Number and duration of hospitalisations (total and for cardiovascular (CV) conditions). 3. Total and CV mortality. 4. Serious adverse events (SAEs).
Methodology (Design of Study):	Randomised, controlled, observer-blinded Phase 3 clinical trial to compare the effect of IV FCM to placebo on exercise capacity and cardiac function in subjects with CHF and ID. Randomisation is blocked within each centre.
Number of Subjects (Planned and Analysed):	A total of 330 subjects were initially planned for random assignment to active treatment or placebo. Randomisation 1:1 (i.e., 165 FCM, 165 placebo). A total of 35 subjects were randomly assigned to FCM or placebo at time of early termination. 34 subjects commenced study drug (20 FCM; 14 placebo).
Diagnosis and Main Criteria for Inclusion:	The EFFICACY-HF clinical trial investigated stable, CHF subjects with ID. When study treatment was started, each subject included in the trial should have complied with the following inclusion criteria: 1. At least 18 years of age. 2. Signed written informed consent obtained. 3. In NYHA functional Class II or III. 4. Ambulatory and capable of performing a 6MWT. 5. Treated for CHF during at least 1 hospital, emergency room or acute clinic admission within the last 24 months or brain natriuretic peptide ≥100 pg/mL or N-terminal pro-hormone brain natriuretic peptide ≥400 pg/mL, not older than 8 weeks when study treatment is started. 6. Currently treated for CHF for at least 4 weeks with the same combination of at least 2 of the following: (a) diuretic, (b) beta-blocker (including carvedilol), (c) angiotensin converting enzyme inhibitor or angiotensin II receptor blocker. 7. Treated during the last 2 weeks with the same dose of drugs given for CHF (dose changes of diuretics are allowed). 8. Resting cuff blood pressures less than or equal to 160 mm Hg systolic and less than or equal to 100 mm Hg diastolic (at the disappearance of sounds, Korotkoff Phase V). 9. Left ventricular ejection fraction 40% or lower as assessed locally by 2D Echo/Doppler cardiography.

Diagnosis and Main Criteria for Inclusion: (Cont'd)	10. Screening haemoglobin (Hb) value equal to or above 9.5 g/dL (5.9 mmol/L), and below or equal to 13.5 g/dL (8.4 mmol/L). 11. Screening ferritin below 100 mcg/L (224.7 pmol/L), or below 300 mcg/L (674.1 pmol/L) when transferrin saturation (TSAT) is below 20%. 12. Adequate veins for repeated blood sampling and IV administration of study treatment. 13. Use of adequate contraceptive methods for women of childbearing potential.
Test Product, Dose and Mode of Administration:	Ferric carboxymaltose solution (Ferinject®) for parenteral application, 50 mg/mL iron. Medication was given as an IV bolus of 4 mL (could be 2 mL for last injection in correction phase). Total dose required was calculated using the Ganzoni formula (and administered in first 12 weeks) with a maintenance dose administered from Week 12 at 200 mg every 4 weeks until Week 24. If ferritin >800 mcg/L, or ferritin >500 mcg/L when TSAT >50%, or Hb >16 g/dL at any stage of treatment, iron treatment was discontinued and placebo was administrated instead. Once the serum ferritin was found to be <400 mcg/L, and TSAT to be <45%, and Hb to be <16 g/dL, study treatment with FCM was restarted.
Batch Number (FCM):	820200
Duration of Treatment:	26 weeks.
Reference Therapy, Dose and Mode of Administration:	Placebo: Normal saline (0.9% w/v NaCl) administered in analogy to active treatment procedures (both for dose and mode of administration).
Batch Number (Placebo):	8024C15
Criteria of Evaluation:	<u>Efficacy</u> The co-primary endpoints for efficacy of the EFFICACY-HF trial are to determine, relative to placebo, the effect of IV FCM on: 1. Change from baseline in the 6MWT performed at 4, 12 and 24 weeks after the start of study treatment – taking into account subjects who had died or were hospitalised. 2. Change from baseline in NYHA functional class assessments performed at 4, 12 and 24 weeks after the start of study treatment – taking into account subjects who had died. The secondary endpoints for efficacy are: 1. Change from baseline of cardiac function parameters as assessed by 2D Echo/Doppler cardiography 4, 12 and 24 weeks after start of study treatment. 2. Self-reported PGA of treatment at 4, 12 and 24 weeks after start of study treatment. 3. HRQoL endpoints.

Criteria of Evaluation: (Cont'd)	<u>Safety</u> Endpoints for safety are the following: 1. Change from baseline for: • e-GFR • Vital signs • Electrocardiographic findings and laboratory test results • Haematology • Clinical chemistry • Iron status • Urinalysis • Neurohormone and inflammatory markers. 2. Number and duration of hospitalisations (total and for CV conditions). 3. Total and CV mortality. 4. SAE.
Statistical Methods:	Primary efficacy analyses were performed according to the intention-to-treat principle on all subjects who were randomised and in whom investigational drug treatment was started. Subjects were analysed in the treatment group which corresponds to the treatment they were randomly assigned to, i.e., irrespective of actual treatment received. The 6MWT distance at baseline, Week 4, Week 12 and Week 24 and the 6MWT change from baseline at Week 4, Week 12 and Week 24 were summarised by treatment group as continuous variables. The number and percentage of subjects in each of the NYHA ranks were tabulated at baseline, Week 4, Week 12 and Week 24. The change from baseline at Week 4, Week 12 and Week 24 was summarised as a categorical variable by treatment group. Change was also characterised at each time point as better/same/worse. Safety analyses were performed on all subjects who were started on investigational drug. Subjects were analysed in the treatment group which corresponds to the treatment they actually received. For all endpoints, no statistical analyses were performed.
Summary - Conclusions:	<u>Summary of Efficacy</u> Of the 35 subjects randomised, 20 subjects were assigned to the iron-repletion group and received FCM. 15 subjects were assigned to the control arm and 14 of them received placebo. On average, subjects in the FCM group received 1,640 mg iron (32.8 mL) with similar dosing equivalent (33.3 mL) in the placebo group. The study had 2 co-primary efficacy end points, 6MWT at Week 24 and change in NYHA class at Week 24 (compared to baseline). No formal statistical testing was applied to efficacy endpoints due to the early termination of the study.

Summary - Conclusions: (Cont'd)	Summary of Safety No formal statistical testing was applied to endpoints due to the early termination of the study. Of the 35 subjects randomised, 28 subjects completed the study (17 (85.0%) (FCM) and 11 (78.6%) (placebo)). Study treatment was stopped prematurely in 3 (15.0%) subjects assigned to FCM and 3 (21.4%) subjects that received placebo. Most subjects reported at least 1 adverse event (16 subjects (80.0%) in FCM versus 12 subjects (85.7%) for placebo). Adverse event considered (by Investigator) as having a "certain" or "probable/possible" relationship to study medication was reported for 9 (45.0%) subjects from the FCM group and 3 (21.4%) subjects from the placebo group. 13 subjects experienced at least 1 SAE during the study in total, 8 (40.0%) subjects in FCM versus 4 (28.6%) subjects in placebo group. One subject experienced "left heart failure worsening" in the screening phase (no randomisation). 2 subjects died during the study (1 (5.0%) in FCM and 1 (7.1%) in placebo) and 1 subject (in placebo group) required a heart transplant. There were no new safety signals and no new information that necessitates update of the safety specification from this study.
Conclusions:	Due to poor recruitment of the study only 35 subjects were randomised of a planned 330 subjects. Hence no formal statistical testing was applied and no conclusions can be drawn. No new safety signals or information necessitating an update of the safety specification resulted from this study.