STUDY SYNOPSIS

Title:	A randomised double-blind controlled Phase 3 study to compare the efficacy and safety of intravenous ferric carboxymaltose (FCM) (Ferinject®) with placebo in patients with chronic heart failure and iron deficiency.
Short Title:	**FAIR-HF** (**F**erinject® **A**ssessment in patients with **IR**on deficiency and CHF).
Investigator(s):	Professor Stefan D. Anker (Co-ordinating Investigator).
Study Centre(s):	107 sites were initiated of which 75 randomised subjects to this study.
Publication (References):	Anker SD, Colet JC, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:1-13 [1]. Anker SD, Colet JC, Filippatos G, et al. Rationale and design of Ferinject Assessment in patient with IRon deficiency and chronic heart failure (FAIR-HF) study: a randomised, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia. Eur J Heart Fail 2009; 11: 1084-91. Available at: http://eurjhf.oxfordjournals.org.
Studied Period:	2 years
First Subject In:	25 June 2007
Last Subject Out:	9 July 2009
Phase of Development:	3
Objectives:	<u>Primary Objective</u>: • To determine, relative to placebo, the effect of iron-repletion therapy using intravenous (IV) FCM (Ferinject) on self-reported Patient Global Assessment (PGA) and New York Heart Association (NYHA) functional status 24 weeks after initiation of therapy in patients with chronic heart failure (CHF) and iron deficiency. <u>Key Secondary Objectives (Efficacy)</u>: • To evaluate the effect of IV FCM (Ferinject) compared with placebo on exercise tolerance (6-minute walk test (6MWT) distance). <u>Further Secondary Objectives (Efficacy)</u>: • To evaluate the effect of IV FCM (Ferinject) compared with placebo on health related quality of life. • To evaluate resource use and costs associated with the treatment with IV FCM (Ferinject) compared with placebo.

Objectives: (Cont'd)	Safety Objectives: • To evaluate the effect of IV FCM (Ferinject) compared with placebo on: – Estimated glomerular filtration rate (eGFR). – Number and duration of hospitalisations (total and for cardiovascular (CV) conditions). – Mortality. • To evaluate the tolerability and safety of Ferinject compared with placebo.
Methodology (Design of Study):	A randomised, double-blind, placebo-controlled, multicentre, parallel group study.
Number of Subjects (Planned and Analysed):	A total of 576 subjects were initially planned for random assignment to active treatment or placebo. Randomisation 2:1 (i.e., 384 active treatment, 192 placebo). The discontinuation/failure to follow protocol rate was found to be substantially lower than 30%, hence a proportionately lower number of patients were included in the study in order to achieve the sample size as it was stated in protocol. A total of 459 subjects were randomly assigned to FCM or placebo. Randomisation was 2:1 (304 active treatment, 155 placebo).
Diagnosis and Main Criteria for Inclusion:	Patients who met the following criteria at the start of treatment were eligible for the study: 1. At least 18 years of age and signed written informed consent. 2. In NYHA II-III functional class due to stable symptomatic CHF and all of the following: – Two weeks without cardiac hospitalisation. – Patients in NYHA II must have had an acute care admission or emergency room visit for worsening of heart failure (HF) within 24 months prior to randomisation. – On optimal conventional therapy (in general, optimal pharmacological treatment which includes a diuretic, a beta-blocker, and/or an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker as determined by the Investigator, unless contraindicated or not tolerated). – No dose changes of HF drugs during the last 2 weeks (with the exception of diuretics). – No introduction of a new HF drug class during the last 4 weeks.

Diagnosis and Main Criteria for Inclusion: (Cont'd)	3. Left ventricular ejection fraction (LVEF) 40% or lower for patients in NYHA II and 45% or lower in NYHA III as assessed according to local methodology by 2-D echocardiography, radionuclide ventriculography, cardiac magnetic resonance imaging, or X-ray contrast ventriculography within 6 months prior to randomisation. For patients treated with beta-blockers or with cardiac resynchronisation, LVEF assessment for eligibility must be performed at least 3 months after stable beta-blocker therapy or device implantation. 4. Screening haemoglobin (Hb) at least 9.5 g/dL but below or equal to 13.5 g/dL (average of 2 Hb concentrations as measured locally by HemoCue® analyzer). 5. Screening ferritin below 100 mcg/L, or below 300 mcg/L when transferrin saturation (TSAT) is below 20%. 6. Resting 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). 7. Adequate veins for repeated blood sampling and IV administration of investigational drug. 8. Negative pregnancy test and use of adequate contraceptive methods for women of childbearing potential. 9. Patient must be able to perform the 6MWT according to Investigator judgement.
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 >16.0 g/dL at any stage of treatment, iron treatment was discontinued and placebo was administered instead.
Batch Number (FCM):	514210 and 701010
Duration of Treatment:	26 weeks
Reference Therapy, Dose and Mode of Administration:	Placebo: Normal saline (0.9% weight/volume sodium chloride) administered in analogy to active treatment procedures (both for dose and mode of administration).
Batch Number (Placebo):	6162C13 and 8024C15
Criteria of Evaluation:	Primary Efficacy: • Self-reported PGA score and change in NYHA class from baseline to Week 24 visit after start of investigational drug, taking into account subjects who are hospitalised at that time or have died.

Criteria of Evaluation: (Cont'd)	<u>Secondary Efficacy</u>: • Patient Global Assessment score at Week 4 and Week 12 visits. • Change in NYHA class from baseline to Week 4 and Week 12 visits. • Change in 6MWT distance from baseline to Week 4, Week 12 and Week 24 visits. • Health related quality of life: – Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline to Week 4, Week 12 and Week 24 visits (overall summary score and symptom frequency score). – Change in European Quality of Life – 5 Dimensions (EQ-5D) questionnaire total score from baseline to Week 4, Week 12 and Week 24 visits. <u>Safety and Related Efficacy Endpoints</u>: • Days alive and out of hospital. • Hospitalisation rate (total hospitalisation, hospitalisation due to CHF, other CV hospitalisation). • Time to the first hospitalisation for worsening of CHF. • Total mortality. • Change in eGFR. • Adverse events: Type, nature, incidence. • Vital signs (blood pressure, pulse rate and body weight). • 12-lead electrocardiogram (ECG). • Change in clinical laboratory panels (haematology, clinical chemistry, iron status, urinalysis).
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 effect of treatment was tested by using ordered polytomous regression with PGA at Week 24 as dependent variable and treatment as independent variable. For NYHA at Week 24, the overall treatment effect was tested by ordered polytomous regression with treatment and baseline NYHA class as independent variables. Alpha adjustment was made using the method of Benjamini-Hochberg. Supportive per-protocol analyses were performed on those subjects who have participated in the trial without major protocol violations. 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.

Summary of Efficacy:	Of the 459 subjects randomised and starting treatment, 304 subjects were assigned to the iron-repletion group (and received FCM) and 155 were assigned to the control arm (and received placebo). Subjects were well matched for baseline clinical and laboratory characteristics and the use of CV medications at the time of enrolment (for all individual parameters). The study had 2 co-primary efficacy endpoints, PGA at Week 24 and change in NYHA class at Week 24 (compared to baseline). For PGA, 50% versus 28% of subjects reported that they were "much or moderately improved" for FCM and placebo groups respectively (odds ratio (OR), 2.51; 95% confidence interval (CI), 1.75 to 3.61; $p<0.001$). 47% versus 30% of subjects at Week 24 were in NYHA functional Class I or II, in the FCM and placebo groups, respectively (OR after adjustment for the baseline value, 2.40; 95% CI, 1.55 to 3.71; $p<0.001$). The benefits of iron therapy for the 2 co-primary endpoints were consistent in all subgroup analyses, including those by sex, age, renal function, NYHA class, LVEF, heart failure aetiology, diabetes status, body mass index, Hb level (<12.0 g/dL, signifying anaemia, versus >12.0 g/dL) and median ferritin level (<39 mcg/L versus. >39 mcg/L). Statistical significance was observed for both PGA and NYHA class in favour of FCM, also at Week 4 and 12 ($p<0.001$ for both comparisons). In addition to the co-primary efficacy endpoints, statistical significance in favour of the FCM group was seen for the 6MWT, quality of life (when evaluated using the EQ-5D visual assessment score and also for the overall KCCQ score) at Weeks 4, 12, and 24 ($p<0.001$ for all comparisons).
Summary of Safety:	From the 459 subjects randomised, 392 subjects (267 (87.8%) (FCM) and 125 (80.6%) (placebo)) completed 24 weeks of therapy. Study treatment was stopped prematurely in 37 (12.2%) subjects assigned to FCM and 30 (19.4%) subjects that received placebo. The most common withdrawal reason from the therapy in both treatment groups was withdrawal of subject consent (13 (4.3%) FCM versus 10 (6.5%) placebo). Over half of the subjects in both groups reported at least 1 adverse event (AE) (165 subjects (54.1%) in FCM versus 78 subjects (50.6%) for placebo). The maximal intensity of the AEs reported was considered to be either mild or moderate (141 for FCM versus 60 for placebo). Overall, AE considered (by Investigator) as having a certain or probable/possible relationship to study medication was 25 subjects from the FCM group and 11 subjects from the placebo group.

Summary of Safety: (Cont'd)	Headache was the most commonly reported AE (15 events in 11 subjects (3.6%) from the FCM group versus 13 events in 9 subjects (5.8%) from the placebo group). The next 2 most common events were influenza (14 events in 13 subjects (4.3%) from the FCM group versus 11 events in 8 subjects (5.2%) from the placebo group) and chronic cardiac failure (10 events in 10 subjects (3.3%) from the FCM group versus 13 events in 10 subjects (6.5%) from the placebo group). The most common AEs when defined by system organ class occurred in infections and infestations (55 events in 49 subjects (16.1%) in FCM group and 32 events in 24 subjects (15.6%) in placebo group) and cardiac disorders (46 events in 38 subjects (12.5%) in FCM group and 49 events in 33 subjects (21.4%) in placebo group; p=0.012). No severe or serious allergic reactions related to the study treatment were reported. Fifty-one subjects had a serious adverse event (SAE) during the study (31 (10.2%) subjects in FCM versus 20 (13.0%) subjects in placebo group). The most common SAE reported was for cardiac disorder and statistical significant differences between groups were observed for this event (11 subjects in FCM versus 14 subjects in placebo group, p=0.0122). All other Investigator-reported SAEs had no significant difference between groups. Additionally, there were no significant differences in rates of death or of hospitalisation for any cause, any cardiovascular cause, or worsening heart failure. In relation to laboratory assessments, increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed at Week 4 in the FCM group. Over the study duration, the number of subjects with ALT or AST outside the normal range was 40 (13.1%) FCM subjects versus 12 (7.8%) placebo subjects for AST and 33 (10.8%) FCM subjects versus 8 (5.2%) placebo subjects for AST. Of note, only 2 subjects had values of AST and ALT greater than 3 times the upper limit of normal (1 at Week 4 and 1 at Week 24), both occurring in the FCM group. Increases in liver enzymes are well documented with IV iron. Additionally, transient decreases in phosphate levels (hypophosphataemia) were observed for the FCM group. This effect was most pronounced at Week 4. No clinical consequence, sequelae or intervention were associated with this serum phosphate change and this effect was again expected and is well documented in the Investigator's Brochure for Ferinject. There were no significant differences between the 2 study groups with respect to 12-lead ECG parameters (ventricular rate, PR interval, QRS interval, QTC interval) at any study visit post baseline. The overall safety evaluation in this study indicates a positive benefit/risk ratio for Ferinject. There were no new safety signals and no new information that necessitates update of the safety specification.

Conclusions:	Iron replenishment (per Ganzoni formula) and maintenance using intravenous FCM for 24 weeks in subjects who had CHF and iron deficiency (measured by serum ferritin and TSAT) with or without anaemia (assessed by Hb) improved symptoms (improvement in NYHA class), functional capacity (increased walking distance as measured by 6MWT), and quality of life (per PGA, KCCQ, and EQ-5D assessment tools). On average, subjects received 1,850 mg iron and the overall safety profile of treated subjects was similar to the placebo group confirming the favourable benefit/risk profile of FCM.