

Title:

A Randomized Patient -Blind Controlled Phase III Study to Compare the Efficacy and Safety of Intravenous Ferric Carboxymaltose (Ferinject®) With Placebo in Patients With Acute Isovolemic Anemia After Gastrectomy

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Synopsis

Title	A Randomized Patient -Blind Controlled Phase III Study to Compare the Efficacy and Safety of Intravenous Ferric Carboxymaltose (Ferinject®) With Placebo in Patients With Acute Isovolemic Anemia After Gastrectomy
Protocol Number	FAIRY-01
Date (Version)	08 October 2012
Study Product(s)	Ferric carboxymaltose - Ferinject®
Indication	Acute isovolemic anemia after gastrectomy for gastic cancer
Sponsor & Key Contact Details	Dr. Young-woo Kim National Cancer Center, Goyang, Korea Phone: +82-10-8869-1635 Email: youngwookim082@gmail.com
Anticipated Countries	Republic of Korea
Objectives	This study is designed to evaluate the efficacy of Ferinject® in improving acute isovolemic anemia after gastrectomy for gastric cancer in terms of Quality of life(QOL)and objective measures (Hb and iron parameters). Furthermore, the tolerability and safety of Ferinject® treatment will be evaluated.
Design, incl. Treatment	<p>Randomized patient-blind placebo controlled study.</p> <p>5 - 7 days after gastrectomy for gastric cancer, consented patients with 7g/dl≤Hb<10g/dl will be administered Ferinject® or placebo (normal saline) based on the results of randomization.</p> <ul style="list-style-type: none"> • Study Group <p>Ferinject® to be administered as IV drip infusion or undiluted bolus injection with a minimum administration time of 15minutes (for 1000mg single administration) for body weight ≥50 Kg or 6 minutes (for 500mg single administration) for body weight <50Kg .</p> <p><i><u>Note, Ferinject® should be administered to a maximum of 20mg iron/kg. Therefore in patients with a body weight <50kg, administration of Ferinject® should be limited to 500mg at baseline . All patients with a serum ferritin value <15ng/mL at week 3 visit that a second dose (of 500mg iron or equivalent placebo) will be given.(Study group: Ferinject®500mg, Control Group:Placebo)</u></i></p> <ul style="list-style-type: none"> • Control Group <p>Placebo will be in the form of normal saline administered over same time period as equivalent Ferinject® administration. IV drip infusion or undiluted bolus injection with a minimum administration time of 15 minutes (200mL as infusion or 20mL as bolus injection) for body weight ≥50 Kg or 6 minutes (100mL normal as infusion or 10mL as bolus injection) for body weight <50 Kg.</p>
Inclusion Criteria	<ul style="list-style-type: none"> • ≥20 years old • 7g/dl≤ Hb<10g/dl at 5 – 7 days after gastrectomy for gastric cancer • signed written informed consent
Exclusion Criteria	<ul style="list-style-type: none"> • a concurrent medical condition(s) that would prevent compliance or participation or jeopardize the health of the patient • hypersensitivity to any component of the formulation

	<ul style="list-style-type: none"> • active severe infection/inflammation • History of transfusion, erythropoietin, >500 mg intravenous iron administration within 4 weeks prior to screening. • History of acquired iron overload. • Pregnancy or lactation. • Decreased renal function (defined as creatinine clearance <50 mL/min calculated by Cockcroft-Gault) • Chronic liver disease or increase of liver enzymes (ALT, AST) >3 times the upper limit of normal range. • Participation in any other interventional study within 1 month prior to screening.
Procedures	<p>Post inclusion of eligible patients, follow-up assessment will be performed at 3 and 12 weeks after the baseline procedure.</p> <p>At each visit patients will have:</p> <ul style="list-style-type: none"> • Routine examination, including documentation of any adverse events and concomitant medications • Full blood count assessed at the local hospital laboratory at minimum to include serum ferritin, transferrin saturation(TSAT), Hb, WBC, RBC, Platelets and blood chemistry including AST, ALT,CRP. • QOL assessments will be completed at each visit using the self-reported patient assessment of EORTC QLQ C-30 and Sto-22. These should be completed before any interventional procedure, including blood draw(s). • At baseline: Administration of study medication • Follow-up assessment at the 3th weeks (\pm 7days) and 12th weeks (\pm7days) from the baseline:
Sample Size	Approximately 450 patients (225 per group) from 7 sites.

List of Abbreviation

AE: Adverse Event
AGC: Advanced gastric Cancer
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CRP: C-reactive protein
EGC: Early Gastric Cancer
ESA: Erythropoiesis Stimulating Agent
FCM: ferric carboxymaltose
FU: Fluorouracil
GGT: Gamma-glutamyl transpeptidase
Hb : Hemoglobin
HCG: human chorionic gonadotropin
ID: Iron Deficiency
IDA : Iron Deficiency Anemia
LDH: Lactate dehydrogenase
OS: Overall Survival
PFS: Progression free survival
SAE: Serious Adverse Event
TSAT: Tranferrin Saturation
TIBC: Total Iron Binding Capacity
QOL: Quality of Life

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1. Background information regarding

a. Disease

Peri-operative anemia occurs in 25%-75% of cancer patients, and the prevalence of anemia in the immediate post-operative period after major surgery is as high as 90%. Post-operative acute isovolemic anemia can affect the recovery and QOL of patients by subtly slowing the reaction time, deteriorating memory, increasing heart rate, and decreasing energy levels.

Post-operative transfusion rates for patients with colorectal and gastric cancers have been reported to be 10%-38% and 21%, respectively. Other surgeons prefer observation for post-operative anemia because spontaneous correction occurs within several months if oral intake is adequate (and RBC transfusion has many known risks). However it is difficult for patients to consume a normal diet post-gastrectomy and receive oral iron, which may give rise to gastrointestinal disturbances. As such, some patients do not recover from post-operative anemia.

In a similar retrospective observational study performed at sponsor site (submitted for publication) the role of iron sucrose was assessed. The above issues were all observed. Patients treated with iron sucrose had a faster and more complete Hb response with all patients having anemia corrected at 12 months in the active group versus 10% of patients remaining anaemic at 12 months in the group that had no treatment (observation only).

b. Investigational product

In general, the clinical safety and efficacy studies have been conducted in numerous settings that are representative of underlying diseases that may lead to iron deficiency (ID) i.e., diseases with increased inflammatory status that impairs iron absorption as well as diseases with large losses of iron that cannot be compensated via dietary iron.

To date, over 3,600 subjects have been treated with ferric carboxymaltose in 18 clinical trials. Across these various clinical studies, replenishment of iron stores has been consistently observed. Markers of ID have included both TSAT and serum ferritin. In subjects with more severe or prolonged ID that has led to anemia, correction of ID using FCM has consistently resulted in medically significant increases in Hb values (correction of anemia). This improvement was usually seen within 2 weeks. In addition to the correction of laboratory parameters, iron replacement therapy has demonstrated significant improvements in subject QoL and functional status.

Ferric carboxymaltose was well tolerated by study participants. In Phase 3 studies, approximately 30 to 70% of the subjects experienced at least 1 treatment emergent adverse event (AE), and events considered related to treatment occurred in approximately 3 to 35% of subjects who received either ferric carboxymaltose or ferrous sulphate. Overall, excluding events that were most likely related to the underlying condition, the most commonly reported events in the ferric carboxymaltose group were headache, pyrexia/hyperthermia/body temperature increased, hypertension, hypotension, abdominal pain, muscle cramp/myalgia, nausea/vomiting and rash.

No formal interaction studies have been performed. Except for the reduced uptake of oral iron administered in parallel with parenteral iron, no interactions with other medications are known.

Ferric carboxymaltose has been approved in 39 countries globally including South Korea and has the trade name Ferinject®.

2. Rationale / Purpose

Post gastrectomy, the damage on the gut may impact the ability of the patient to absorb iron from their diet, limiting correction of IDA. However, the sponsor hospital practice is to not intervene unless patient symptomatic, and permit iron and Hb levels to return to normal over time.

Based on their retrospective observational study, approximately 10% of patients in the 'no intervention' group were still anaemic (defined as Hb < 9 g/dL) at 12 months. The value of 9 g/dL is used due to being a practical trigger for transfusion in many Korean institutes (independent of symptoms). All patients treated with iron sucrose had a response and did not require intervention.

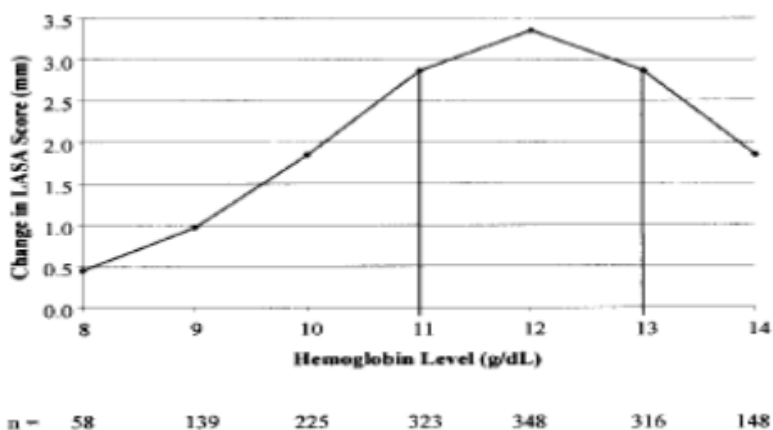
Ferric carboxymaltose (Ferinject®) is believed to have the potential for a more rapid correction of post-operative anemia per published studies and details in Section 1: Investigational product. With the potential of 1-2 administrations to correct deficiency it also offers advantages compared to iron sucrose – benefiting both the patient and the health care system.

AGC patients are especially prone to hemorrhage compared to EGC patients during the surgery, and also receives adjuvant chemotherapy which affects quality of life and treatment outcomes greatly, therefore giving the present study more remarkable clinical significance. Furthermore, the follow up assessment will be conducted in week 3 (before chemotherapy, usually, chemotherapy starts after 4~6 weeks after gastrectomy) and in week 12, which are well before 6th-8th cycle of completion of chemotherapy, so there will be little confounding effect to verify role of the study drug for acute isovolemic anemia.

a. The impact of Hb level on QOL

In addition to the correction of anemia, it is important to confirm the value of treatment to patients. As such, QOL will be assessed at multiple time-points post-surgery where believed that positive influence on patients well-being and recovery.

Figure1. Incremental changes in Linear Analogue Scale Assessment (LASA) overall QOL scores and haemoglobin levels. Based on a longitudinal analysis of community Study 2. Data at baseline, Week 8, and Week 16 were included in the analysis. (Adapted from David Cella and others, *Cancer* 2002; 95: 888–895)¹



According to David Cella and others¹, the maximal incremental gain in QOL occurs when hemoglobin is in the range of 11–13 g/dL. And there are differences in QOL according to the Hb level even in 1 g/dl difference. Therefore, rapid elevation of Hb after giving IV iron could improve QOL.

b. The impact of Chemotherapy on Hb level.

According to results listed below all grade Hb decrease with short term chemotherapy was 12% as summarized in Table 1 and grade 3- 4 Hb decrease due to the chemotherapy appears after an average of 32 days, with the prevalence of 3.1% in Table 2 . Since our study ends at week 12, chemotherapy will not be a significant confounding factor for Hb level in our study.

Table1. Summary of adverse events with an incidence of 10% or more (all grades)in either short- or long-term treatments periods ²

Adverse event	Incidence in all grades		Incidence in grade 3–4	
	Short term (%) ^a (n = 3,758)	Long term (%) ^b (n = 1,605)	Short term (%) (n = 3,758)	Long term (%) (n = 1,605)
Hematological				
Leucopenia	26.9	25.4	2.8	1.5
Neutropenia	21.9	22.7	6.3	5.3
Hemoglobin decreased	12.1	14.8	2.3	2.4
Thrombocytopenia	9.8	8.8	2.0	2.1
Hepatic				
Total bilirubin increased	13.0	20.9	3.9	7.1
AST increased	10.0	16.6	1.4	2.2
ALT increased	8.0	10.7	0.9	1.1
ALP increased	9.9	17.4	2.2	2.9
Gastrointestinal				
Anorexia	37.1	43.2	10.7	10.0
Nausea/vomiting	26.2	25.5	3.8	2.9
Diarrhea	18.4	17.0	2.1	1.1
Stomatitis	12.8	8.8	1.2	0.3
Dermal				
Rash	9.0	5.4	0.9	0.2
Pigmentation	14.7	19.2	1.2	1.0
Other				
Fatigue	27.6	32.8	7.8	7.7

Thrombocytopenia and rash had an incidence of slightly less than 10%, but both are key events and included

^a Incidence of each adverse event that occurred during the first two cycles

^b Incidence of each adverse event that occurred during and after the third cycle

Table2. Distribution of time to onset of grade3-4 adverse events²

Adverse event	Total number of patients throughout study ^a	Distribution of time to first onset ^b (in days), median (quartiles)
Hematological		
Leucopenia	122 (3.2%)	20 (9, 58)
Neutropenia	287 (7.6%)	22 (12, 64)
Hemoglobin decreased	118 (3.1%)	32 (14, 86)
Thrombocytopenia	103 (2.7%)	36 (15, 101)
Hepatic		
Total bilirubin increased	235 (6.3%)	64 (22, 129)
AST increased	87 (2.3%)	68 (21, 137)
ALT increased	48 (1.3%)	52 (14, 127)
ALP increased	121 (3.2%)	38 (8, 106)
Gastrointestinal		
Anorexia	546 (14.5%)	37 (9, 92)
Nausea/vomiting	184 (4.9%)	40 (8, 85)
Diarrhea	96 (2.6%)	19 (12, 57)
Stomatitis	48 (1.3%)	12 (8, 41)
Dermal		
Rash	38 (1.0%)	12 (8, 21)
Pigmentation	49 (1.3%)	16 (10, 46)
Other		
Fatigue	400 (10.6%)	43 (15, 91)
Fluoropyrimidine-related key events ^c	632 (16.8%)	20 (9, 64)
Hematological events^d	500 (13.3%)	22 (10, 71)

^a Percentage in the parenthesis is the proportion to all (3,758) patients

^b Distribution of time to first onset among patients who experienced each adverse event

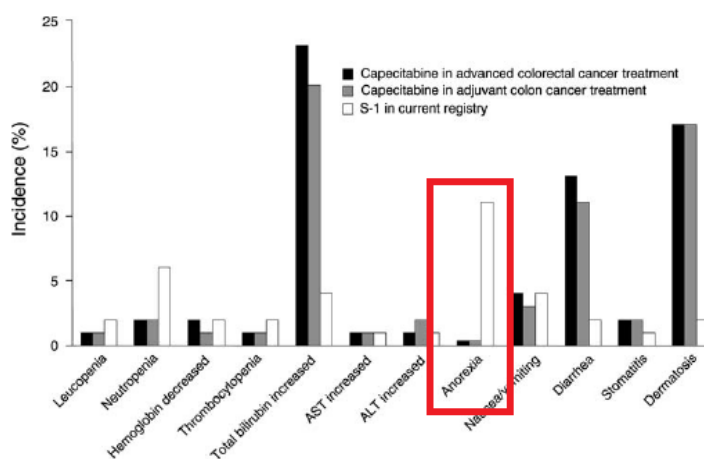
^c Neutropenia, nausea/vomiting, diarrhea, stomatitis, rash, pigmentation

^d Leucopenia, neutropenia, hemoglobin decreased, thrombocytopenia

c. Importance of IV Fe for postgastrectomy patients.

According to the result below, anorexia was the most significant among the patients treated with chemotherapy with S-1, which leads to a decrease in patient's oral intake (Fig.2) and subsequently affects Hb level recovery. Iron supply via IV might be helpful for post-gastrectomy patients treated with chemotherapy.³ Furthermore, elevation of baseline Hb before starting chemotherapy will be crucial to maintain Hb level during chemotherapy.⁴

Fig. 2 Reported incidence of grade 3–4 adverse events of capecitabine in previous studies (advanced colorectal cancer and adjuvant colon cancer) along with incidence of S-1 in our study. Adverse events of S-1 are those that occurred among patients who had no chemotherapy within 6 months, no major abnormalities in their laboratory parameters, and a good performance status at baseline ($n = 1,365$). Each incidence is rounded off and shown on the vertical axis (Adapted from Takeharu Yamanaka and others)³



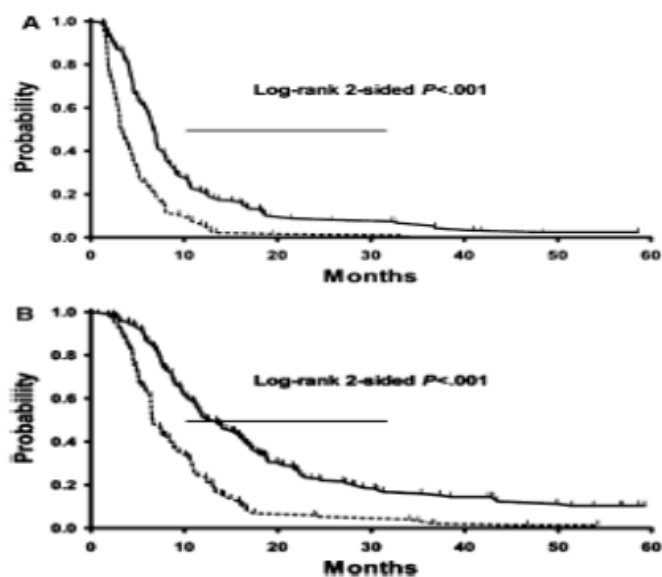
d. The impact of Hb level on Prognosis.

According to study by Se Hoon Park and others: 'Anemia is the strongest prognostic factor for outcomes of 5-fluorouracil-based first-line' ⁶, the association between baseline Hb level, tumor control and survival in 511 patients with AGC who had been treated with FU-based first-line chemotherapy for metastatic disease. Patients with baseline Hb level < 10 g/dl had significantly lower response rate and overall survival than those with Hb 10 g/dl or more.

The response rate that patients who had Hb<12 g/dl and Hb<10 g/dl were significantly less likely to respond to chemotherapy (27%, $P<0.001$ and 9%, $P<0.001$, respectively) compared with those with Hb>12 g/dl (58%) and Hb>10 g/dl (53%) (Fig. 3).

In other words, anemia increases tumor resistance to chemotherapy and decreases responsiveness to treatment in humans. Therefore, in patients with AGC, baseline Hb level was one of the most important adverse prognostic factors for chemotherapy response and survival.³

Figure 3. Progression free survival (a) and overall survival (b). Baseline Hb ≥ 10 g/dl (198 patients, solid line) and Hb < 10 g/dl (136 patients, dotted line) are shown, along with 2-sided P value. (Adapted from Se Hoon Park and others)⁵



3. Trial Objectives

This study is designed to evaluate the efficacy of Ferinject® in improving acute isovolemic anemia after gastrectomy in terms of QOL and objective measures (Hb and iron parameters).

Furthermore, the tolerability and safety of Ferinject® treatment will be evaluated.

4. Trial Design

Randomized patient-blind placebo controlled study.

Hb level of 10 g/dl will be used as a cut-off value for our study based on the guidelines published by American Society of Clinical Oncology and the American Society of Hematology for the treatment of cancer-related anemia, recommending Hb < 10 g/dl as a treatment threshold.

Ferinject® to be administered based on Hb and body weight per approved summary of product characteristics (SmPC). Administration will be as IV drip infusion or undiluted bolus injection with a minimum administration time of 15 minutes (for 1000mg single administrations) or 6 minutes (for 500mg single administrations).

Placebo will be in the form of saline administered over same time period as equivalent administration of Ferinject®.

5. Selection of Subjects

a. Inclusion

- ≥ 20 years old
- $7\text{g/dl} \leq \text{Hb} < 10\text{g/dl}$ at 5 – 7 days after gastrectomy for gastric cancer
- signed written informed consent

b. Exclusion

- a concurrent medical condition(s) that would prevent compliance or participation or jeopardize the health of the patient
- hypersensitivity to any component of the formulation

- active severe infection/inflammation
- History of transfusion , erythropoietin or >500 mg intravenous iron administration within 4 weeks prior to screening.
- History of acquired iron overload.
- Pregnancy or lactation.
- Decreased renal function (defined as creatinine clearance <50mL/min calculated by Cockcroft-Gault)
- Chronic liver disease or increase of liver enzymes (ALT, AST) >3 times the upper limit of normal range.
- Participation in any other interventional study within 1 month prior to screening.

6. Stratification and Randomization

In this trial, patients will be divided into subgroups (strata) based on two factors of patients' stage and study site, to permit to be compared with each other within each stratum.

Patients will be divided into two groups based on their clinical and surgical stages; Stage I group (who do not need adjuvant chemotherapy after gastrectomy), Stage II, III and IV group (who need adjuvant chemotherapy after gastrectomy).

Six study sites will be stratified.

Within each stratum, patients will be randomized through e-Velos system into the study group and the control group.

7. Assessment of Efficacy & Safety

Primary Endpoint:

- Number of responders (Hb increase ≥ 2 g/dL with respect to the baseline Hb value and/or Hb ≥ 11 g/dL) by 12 weeks (independent of alternative anaemia management including transfusion or ESA use). *Note, if patient requires an ESA or blood transfusion by week 12 will be considered a non-responder.*

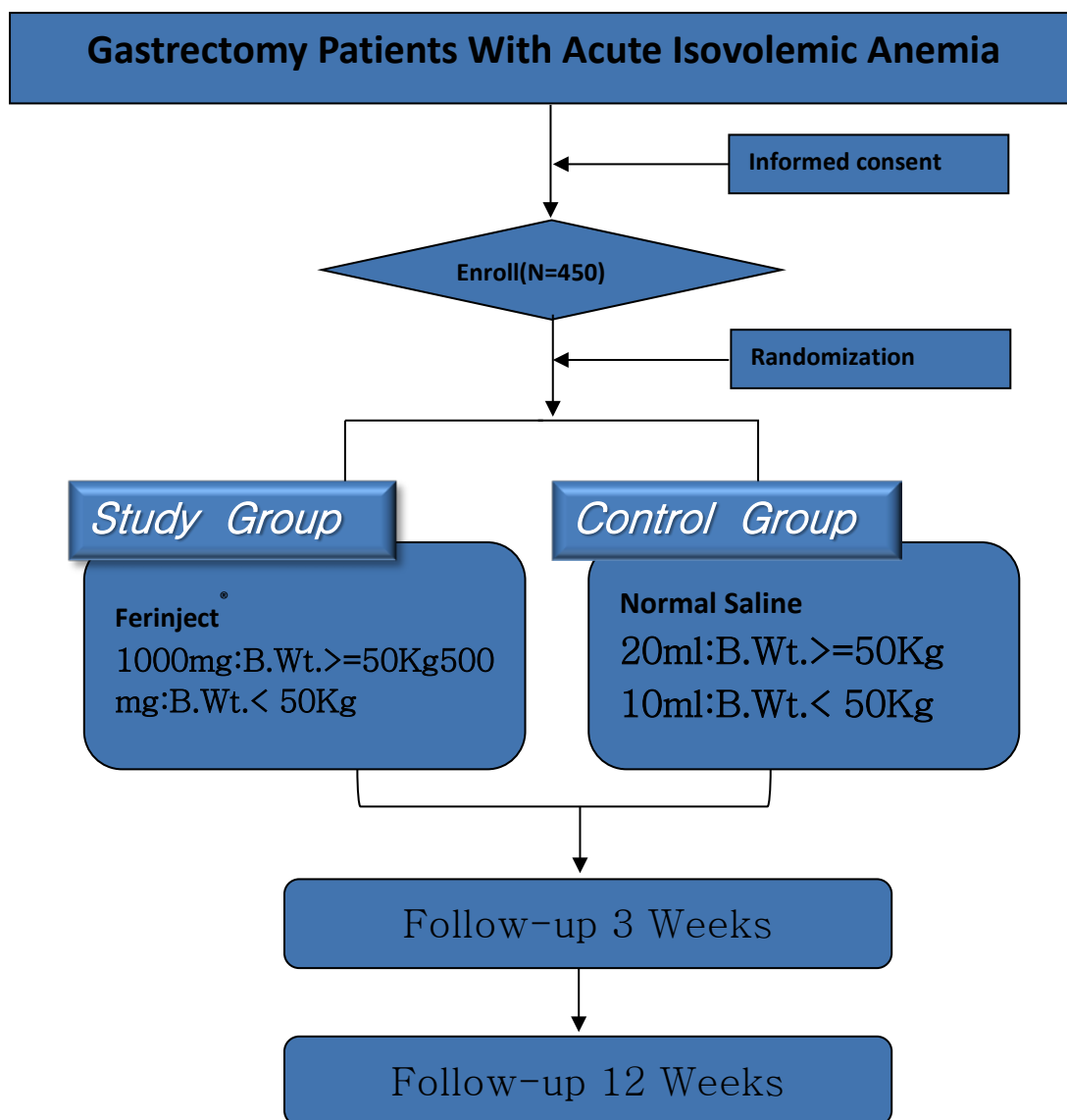
Secondary Endpoints:

- Percentage of patients with Hb ≥ 10 , 11 and 12 g/dL at 3 and 12 weeks (independent of alternative anaemia management including transfusion or ESA use)
- Percentage of patients requiring alternative anaemia management therapy
- Self-reported patient assessment of EORTC QLQ C-30 and Sto-22 at 3 and 12 weeks
- Evolution of Hb, ferritin and TSAT over the study duration (12weeks) independent of alternative anaemia management including transfusion or ESA use
- Safety and tolerability of FCM

8. Trial Procedures

Study visits will be performed at screening, baseline and thereafter at 3 and 12 weeks.

(Both screening and baseline may be performed at 5-7 days after gastrectomy simultaneously.)



Note, Ferinject® should be administered to a maximum of 20mg iron/kg. Therefore in patients with a body weight <50kg, administration of Ferinject® should be limited to 500mg at baseline. All patients with a serum ferritin value <15ng/mL at week 3 visit that a second dose (of 500mg iron or equivalent placebo) will be given.(Study group: Ferinject®500mg, Control Group:Placebo)

Assessment items		Schedule					
Visit		1	2	3	3 ⁻¹	4	
Implementation date		Screening	Baseline	3wks(±7days)		12wks(±14days)	
Medical history		•	•				
Concomitant medication check		•	•	•		•	
Physical examination		•	•	•		•	
Acquisition of informed consent		•					
Randomization			•				
Laboratory	Hematology	Hb	•		•		•
		WBC	•		•		•
		RBC	•		•		•
		Platelets	•		•		•
		Serum Ferritin		•	•		•
		Transferrin Saturation*	Serum Iron		•	•	
	TIBC			•	•		•
	Blood chemistry	AST	•		•		•
		ALT	•		•		•
		CRP	•		•		
		CCR	•				
	Pregnancy Test		○ ¹				
	EORTC QLQ C-30			•	•		•
Sto-22			•	•		•	
Study medication or placebo administration			•		○ ²		
Study medication administration						○ ³	
Adverse event assessment			Continuously throughout study				

1, 2: Screening and baseline procedures may be performed on 5 – 7 days after gastrectomy simultaneously

Transferrin Saturation*: (serum Iron/TIBC)X100%

•: Necessary ○: Only when needed (1:Pregnancy test will be done for women of childbearing age

2. All patients with a serum ferritin value <15ng/mL at week 3 visit that a second dose (of 500mg iron or equivalent placebo) will be given.

3. All patients with a serum ferritin value <15ng/mL at week 12 visit that 500mg iron will be given(Additional medication at 12 weeks is not included in the analysis of the results of the study).

a. Screening

The patients with $7\text{g/dl} \leq \text{Hb} < 10\text{g/dl}$ at 5-7 days after gastrectomy for gastric cancer may be eligible for the study. Prior to any interventional or non-routine assessments of patient eligibility for the study, written informed consent must be obtained. Post consent, patients should be assessed for inclusion.

- written informed consent
- Routine examination, including documentation of all medical history, concomitant medication and physical examination
- Hematology will be assessed at the local hospital laboratory at minimum to include Hb, WBC, RBC, Platelets and blood chemistry including AST, ALT, and CCR, CRP.

Screening should be completed prior to randomization.

The case report form (CRF) should be completed with all relevant details at this visit and coordinating centre informed on the patient screening.

b. Baseline

Post successful screening, eligible patients may complete the Baseline procedure where randomization and drug administration will occur.

At this visit the investigator will administer the study medication to the patients. Ideally the randomization and study drug administration should occur on the same day (although may be completed earlier if required to logistically prepare for administration). (Both will be completed within 5 – 7 days after gastrectomy.) At all times the randomized arm must be kept blinded to the patient to minimise any reporting bias for the QoL assessments.

In addition (and prior) to drug administration, the following assessment should be performed

- Routine examination, including documentation of all medical history, concomitant medication and physical examination. *(if Routine examination, including documentation of all medical history, concomitant medication and physical examination was done at screening, it will be omitted.)*
- Hematology will be assessed at the local hospital laboratory at minimum to include serum ferritin, transferrin saturation((serum Iron/TIBC)X100%), Hb, WBC, RBC, Platelets and blood chemistry including AST, ALT and CRP. *(if CBC and blood chemistry were done a screening, only serum ferritin and TSAT tests are needed)*
- QOL assessments will be completed at each visit using the self-reported patient assessment of EORTC QLQ C-30 and Sto-22. These should be completed before any interventional procedure, including blood draw(s)
- Administration of study medication.

The CRF should be completed with all relevant details of this visit post the baseline visit.

c. Study Visits at Week 3 (± 7 days) and 12 (± 14 days)

At each visit patients will have:

- Routine examination, including documentation of any adverse events, concomitant medications and physical examination.

- Hematology will be assessed at the local hospital laboratory at minimum to include serum ferritin, transferrin saturation, Hb, WBC, RBC, Platelets and blood chemistry including AST, ALT.
- QOL assessments will be completed at each visit using the self-reported patient assessment of EORTC QLQ C-30 and Sto-22. These should be completed before any interventional procedure, including blood draw(s)
- All patients with a serum ferritin value <15ng/mL and Hb <10g/dL at week 3 visit that a second dose (of 500mg iron or equivalent placebo) will be given.(Study group: Ferinject®500mg, Control Group:Placebo)
- All patients with a serum ferritin value <15ng/mL at week 12 visit that 500mg iron will be given(Additional medication at 12 weeks is not included in the analysis of the results of the study)

At all times the randomized arm must be kept blinded to the patient to minimise any reporting bias for the QoL assessments.

The CRF should be completed with all relevant details immediately post each visit.

9. Study Drug

To maintain patient blinding, a curtain or other device to ensure patient does not observe administration of the active drug or placebo.

The investigators will keep adequate records of the receipt, preparation and administration of the study drug.

a. Ferinject® (ferric carboxymaltose)

Drug name:	FERINJECT®.
Active ingredient:	Ferric carboxymaltose.
Dosage form:	5% w/v iron containing 50 mg iron per mL, as sterile solution of FERINJECT® in water for injection. In case of drip infusion FERINJECT® must be diluted only in sterile 0.9% sodium chloride.
Excipients:	Water.
Strength/Packaging:	10 mL vials containing 500 mg iron as iron per vial.
Manufacturer:	Vifor Pharma - Vifor (International) Inc, Switzerland.

b. Placebo

Sterile 0.9% sodium chloride for intravenous infusions will be used as placebo.

c. Study Drug Administration

Study drug may be administered as IV drip infusion or IV undiluted bolus injection.

- Ferinject® 1000mg iron dose:
 - As IV infusion, 20mL Ferinject® should be diluted in a maximum of 250mL normal saline and administered over at least 15 minutes.
 - As IV bolus injection, 20mL Ferinject® to be administered over at least 15 minutes

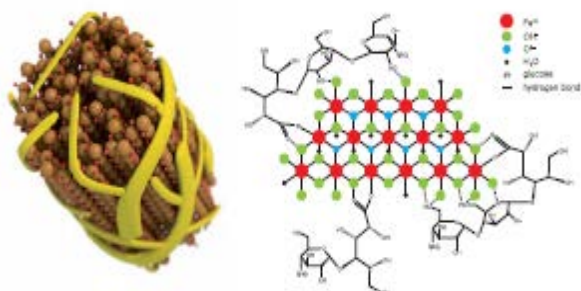
- Ferinject® 500mg iron dose
- As IV infusion, 10mL Ferinject® should be diluted in a maximum of 100mL normal saline and administered over at least 6 minutes.
- As IV bolus injection, 10mL Ferinject® to be administered over at least 6 minutes

Note, Ferinject® should be administered to a maximum of 20mg iron/kg. Therefore in patients with a body weight <50kg, administration of Ferinject® should be limited to 500mg at baseline . All patients with a serum ferritin value <15ng/mL at week 3 visit that a second dose (of 500mg iron or equivalent placebo) will be given.(Study group: Ferinject®500mg, Control Group:Placebo)

Placebo will be in the form of normal saline. Administration should be over same time period as equivalent Ferinject® administration but without the Ferinject® component. i.e., as 250mL IV infusion or 20mL IV bolus injection over at least 15 minutes OR 100mL IV infusion or 10mL IV bolus injection over at least 6 minutes.

d. Characteristics of Study Drug(FERINJECT®)

d-1. Structure of Ferric carboxymaltose



Therapeutic indications: FERINJECT is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

d-2. Determination of the cumulative iron dose

	<50kg	≥50kg
Ferinject	500mg	1,000mg

d-3. Method of administration

FERINJECT must be administered only by the intravenous route: by bolus injection.

FERINJECT	Iron	Amount of Sterile 0.9% m/V Sodium Chloride Solution	Minimum Administration Time
2 to 4 mL	100 to 200 mg	50 mL	No minimum administration time
≥4 to 10 mL	≥200 to 500 mg	100 mL	6 minutes
≥10 to 20 mL	≥500 to 1,000 mg	250 mL	15 minutes

d-4. Clinical Pharmacokinetics

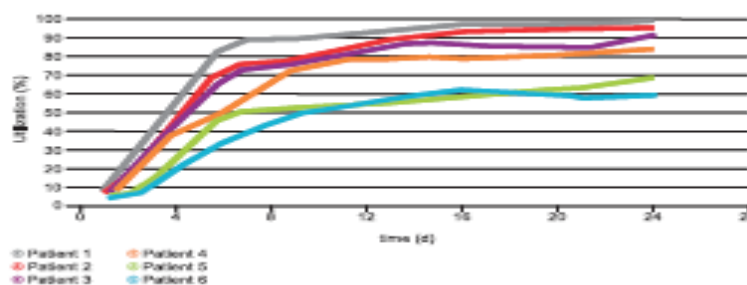


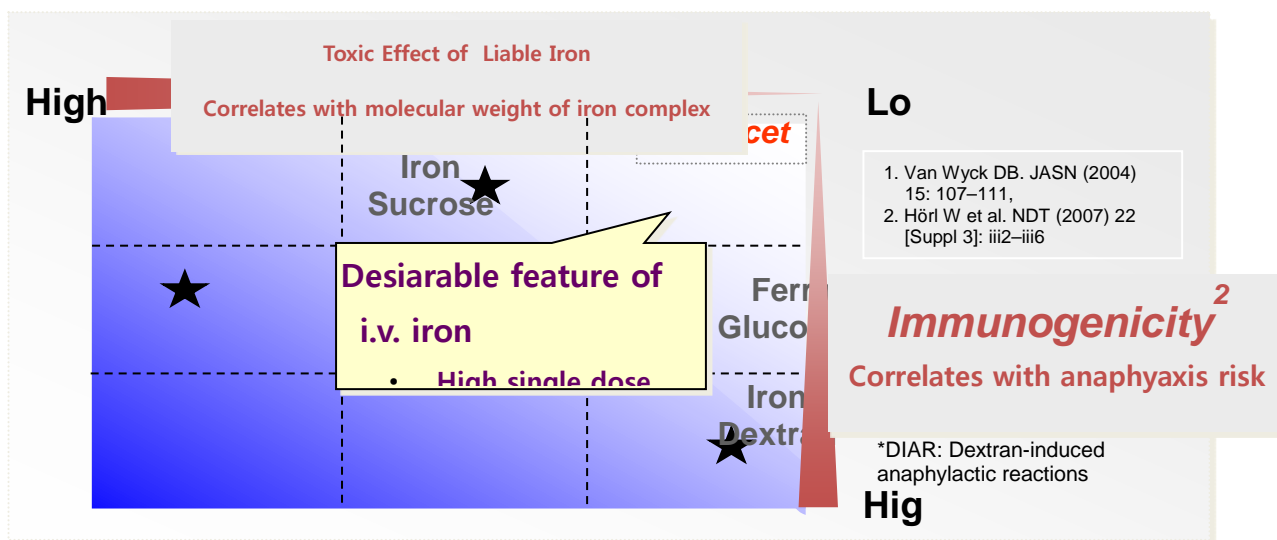
Fig.4 Red cell utilisation of ⁵²Fe/⁵⁹Fe labelled ferric carboxymaltose following a single i.v. administration in patient with iron deficiency, renal anemia or functional iron deficiency (modified from Beshara et al.)⁶

d-5. Contraindications

The use of FERINJECT is contraindicated in cases of:

- known hypersensitivity to FERINJECT or to any of its excipients
- anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
- evidence of iron overload or disturbances in utilisation of iron

d-6. Safety and Tolerability of Ferric carboxymaltose



It combines the positive characteristics of iron dextran and iron sucrose but is not associated with dextran induced hypersensitivity reactions and can be given in much higher doses than iron sucrose or iron gluconate. The chemical characteristic of the iron carbohydrate complex means that iron is released slowly, avoiding toxicity and oxidative stress.⁷

- **Undesirable effects**

Adverse Event				
System Organ Class	Very Common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Immune System Disorders	–	–	Hypersensitivity	Anaphylactoid reactions
Nervous System Disorders	–	Headache, dizziness	Paraesthesia, dysgeusia	–
Cardiac Disorders	–	–	Tachycardia	–
Vascular Disorders	–	Hypertension	Hypotension, flushing	–
Respiratory, Thoracic and Mediastinal Disorders	–	–	Dyspnoea	–
System Organ Class	Very Common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (≥1/10,000, <1/1,000)
Gastrointestinal Disorders	–	Nausea	Vomiting, dyspepsia, abdominal pain, constipation, diarrhoea	–
Skin and Subcutaneous Tissue Disorders	–	–	Pruritus, urticaria, erythema, rash ¹	–
Musculoskeletal and Connective Tissue Disorders	–	–	Myalgia, back pain, arthralgia, muscle spasms	–

General Disorders and Administration Site Conditions	-	Injection site reactions ²	Pyrexia, fatigue, chest pain, oedema peripheral, pain, chills	Rigors, malaise
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Adverse drug reactions (ADRs) reported from clinical trials are summarised in the table above.

▪ **Tolerability**

Ferinject® vs oral iron			Ferinject® vs iron sucrose	
MedDRA SOC-preferred term, n (%)	FCM (n = 147)	Oral iron (n = 103)		
≥1 adverse event	64 (43.5)	61 (59.2)		
Gastrointestinal disorders	12 (8.2)	40 (38.8)		
Constipation	2 (1.4)	18 (17.5)		
Diarrhoea	2 (1.4)	4 (3.9)		
Faeces discoloured	0 (0.0)	3 (2.9)		
Gastrointestinal haemorrhage	0 (0.0)	3 (2.9)		
Nausea	2 (1.4)	5 (4.9)		
General disorders and administration site conditions	18 (12.2)	6 (5.8)		
Infusion site reactions	3 (2.0)	0		
Oedema peripheral	9 (6.1)	2 (1.9)		
Infections and infestations	20 (13.6)	8 (7.8)		
Bronchitis	3 (2.0)	0		
Upper respiratory tract infection	2 (1.4)	4 (3.9)		
Urinary tract infection	5 (3.4)	1 (1.0)		
Metabolism and nutrition disorders	10 (6.8)	3 (2.9)		
Hyperkalaemia	6 (4.1)	1 (1.0)		
Nervous system disorders	6 (4.1)	7 (6.8)		
Headache	3 (2.0)	2 (1.9)		
Vascular disorders	9 (6.1)	2 (1.9)		
Hypotension	3 (2.0)	0		

FCM, ferric carboxymaltose; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class

Table 3. Adverse events experienced by ≥2% of subjects in either treatment group (safety population)³



Adverse Event related with Ferinject®: Comparison of Incidence of adverse events after Ferinject® vs iron sucrose administration to hemodialysis patients⁹

d-7. Interaction with other medicinal products and other forms of interaction

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. Therefore, oral iron therapy should not be started during the study.

d-8. clinical Trial

Title	A multicenter comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anemia in patients undergoing major elective surgery
Published	Br J Anaesth. 2011;107(3):477-8 Impact factor:4.2
Author	E. Bisbe, others
Objective	Evaluation of efficacy & safety for ferric carboxymaltose in preoperative patients
Method	The patients who has pre-operative anemia <ul style="list-style-type: none"> - Ferric carboxymaltose(FCM;n=76): 500-1000mg(Ganzoni calculation) - Iron sucrose(IS;n=84): 100-200mg injected patient in pre-operation
Result	<ul style="list-style-type: none"> • Ferric carboxymaltose: Higher Hb level & lower transfusion rate than iron sucrose in pre-operation • Ferric carboxymaltose vs Iron sucrose - Injection Frequency: 1time vs 2 times(p=<0.001) - Final Hb level: 12.5 vs 12.1(p<0.05) - Transfusion rate : 9% vs 24%

Title	FERGIcor, a Randomized Controlled Trial on Ferric Carboxymaltose for Iron Deficiency Anemia in Inflammatory Bowel Disease												
Published	GASTROENTEROLOGY 2011[Epub-ahead]												
Author	RAYKO EVSTATIEV et al												
Objective	In this study, compared the efficacy and safety of a novel fixed-dose ferriccarboxymaltose regimen (FCM) with individually calculated iron sucrose (IS) doses in patients with inflammatoryboweldisease (IBD) and IDA.												
Method	<p>Open, multi-center, randomized comparison clinical study.</p> <p>Study subjects: 485 patients with mild to severe or terminated IBD who also suffer from Iron Deficiency Anemia(ferritin < 100 g/l, Hb 7-12 g/dl(female), 7-13 g/dl(male)).</p> <p>Administration method:</p> <ol style="list-style-type: none"> 1. Ferric carboxymaltose(n=240): inject 1,000 or 500mg iron into patients in 15 minute span at maximum 3 times. If the patient weight is less than 67kg, maximum amount of 500mg iron is to be injected. 2. Iron sucrose (n=235): Using Ganzoni formula, calculate insufficient amount of iron for each patient, then inject 200mg iron at maximum of 11 times for at least 30 minutes span and twice a week for 30 minute span (calculate with goal Hb value of 15 g/dl) 												
Result	<p>1. Hb increase over 2 g/dl % Ferric carboxymaltose: 65.8%, iron sucrose 53.6% (p=0.004)</p>  <table border="1"> <thead> <tr> <th>Treatment</th> <th>Hb increase over 2 g/dl %</th> </tr> </thead> <tbody> <tr> <td>Ferric carboxymaltose</td> <td>65.8</td> </tr> <tr> <td>Iron sucrose</td> <td>53.6</td> </tr> </tbody> </table> <p>2.Hb normalization(Female: ≥12 g/dl, male: ≥13 g/dl) Ferric carboxymaltose: 72.8%, iron sucrose: 61.8% (p=0.015).</p>  <table border="1"> <thead> <tr> <th>Treatment</th> <th>Hb normalization %</th> </tr> </thead> <tbody> <tr> <td>Ferric carboxymaltose</td> <td>72.8</td> </tr> <tr> <td>Iron sucrose</td> <td>61.8</td> </tr> </tbody> </table>	Treatment	Hb increase over 2 g/dl %	Ferric carboxymaltose	65.8	Iron sucrose	53.6	Treatment	Hb normalization %	Ferric carboxymaltose	72.8	Iron sucrose	61.8
Treatment	Hb increase over 2 g/dl %												
Ferric carboxymaltose	65.8												
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Treatment	Hb normalization %												
Ferric carboxymaltose	72.8												
Iron sucrose	61.8												
Conclusion	FERGI’s Ferric carboxymaltose is more efficacy & tolerance than iron sucrose of Ganzoni , is simiar with iron sucrose for safety.												

Title	Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency
Published	<i>The new england journal of medicine</i>
Author	Stefan D. Anker, M.D., Ph.D., et al
Objective	to determine whether treatment with intravenous iron (ferric carboxymaltose) would improve symptoms in patients who had heart failure, reduced left ventricular ejection fraction, and iron deficiency, either with or without anemia.
Method	<p>e. Enrolled: 459 patients with chronic heart failure of New York Heart Association (NYHA) functional class II or III, a left ventricular ejection fraction of 40% or less (for patients with NYHA class II) or 45% or less (for NYHA class III), iron deficiency (ferritin level <100 µg /L or between 100 and 299 µg/L, if the transferrin saturation was <20%), and a hemoglobin level of 95 to 135 g /L.</p> <p>f. Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of I.V. iron (ferric carboxymaltose) or saline (placebo).</p> <p>g. The primary end points were the self-reported Patient Global Assessment and NYHA functional class, both at week 24. Secondary end points included the distance walked in 6 minutes and the health-related quality of life.</p>
Result	<ol style="list-style-type: none"> 1. patients receiving ferric carboxymaltose, 50% reported being much or moderately improved, as compared with 28% of patients receiving placebo, according to the Patient Global Assessment (odds ratio for improvement, 2.51; 95% confidence interval [CI], 1.75 to 3.61). 2. patients assigned to ferric carboxymaltose, 47% had an NYHA functional class I or II at week 24, as compared with 30% of patients assigned to placebo (odds ratio for improvement by one class, 2.40; 95% CI, 1.55 to 3.71). 3. Results were similar in patients with anemia and those without anemia. 4. Significant improvements were seen with ferric carboxymaltose in the distance on the 6-minute walk test and quality-of-life assessments. 5. The rates of death, adverse events, and serious adverse events were similar in the two study groups.
Conclusion	Treatment with intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life; the side-effect profile is acceptable. (ClinicalTrials.gov number, NCT00520780.)

10.Safety Stopping Rules for an Individual Patient

As only a single administration of Ferinject® is planned, no safety stopping rules apply to this study.

11.Premature Discontinuation of an Individual Patient

Patient may withdraw from the study at any time. However, if the patient intends to withdraw from the study he or she must notify the investigators, and they will discuss alternate treatment if needed. If study medication is ceased for any reasons, patients should be encouraged to attend all visits per section detailing Trial Procedures .

12.Patient Identification and Randomization

All patients enrolled must be identifiable throughout the study. The investigator will maintain a personal list of patient numbers and patient names to enable records to be found at a later date. This must be kept confidential and remain at the study site during and after completion of the study.

Patients eligible for randomization will receive a randomization number. Randomized patients who terminate their study participation for any reason regardless whether the study drug was taken or not, will retain their randomization number. The next patient will be given the next randomization number.

13.Safety Reporting

13.1. Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH definition).

An AE is any adverse, noxious or pathological change as compared to pre-existing conditions that occurs during a clinical study, whether considered drug-related or not.

An AE is considered associated with the use of the drug if the causality is possible, probable or certain.

13.2. Adverse Drug Reaction

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs). The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

13.3. Unexpected Adverse Drug Reaction

An ADR, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or patient information leaflet [PIL] or summary of product characteristics [SPC] for an approved product).

Expected ADRs are defined as any ADR mentioned in the IB (or PIL/SPC), provided that the severity and/or frequency of the ADR concerned does not exceed that reported in the IB (or PIL/SPC).

Unexpected ADRs are defined as any ADR not reported in the IB (or PIL/SPC), or reported at a lower severity and/or frequency.

13.4. Definition of Serious Adverse Events or Serious Adverse Drug Reaction

A SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

(Note: the term life-threatening in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect,
- Other situations when the above definitions are not met, but the event may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above

Medical and scientific judgement should be exercised in deciding whether a case is serious, such as important medical events that may not be immediately life-threatening or result in hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above. These should also usually be considered as serious.

Additionally, pregnancies and symptomatic study medication overdose will also be reported.

13.5. Adverse Event Recording and Reporting

AEs will be recorded throughout the study from study drug administration after signing the Informed Consent Form until the end of study.

Each AE occurring to a patient, either spontaneously revealed by the patient, observed by the investigator/study physician, or elicited by asking a non-leading question such as “How are you feeling?”, and whether believed by the investigator/study physician to be related or unrelated to the study medication, must be recorded on the AE information page of the CRF and on the patient’s records. The investigator/study physician will also determine the relationship of any AE to study medication and record it on the appropriate section of the CRF.

13.6. Adverse Event & Serious Adverse Event Reporting

The investigator will report SAEs to the IRB per local regulations. A copy of each event must be sent to the co-ordinating Investigator.

Prompt reporting of serious adverse reactions to health authorities or IRB, for example suspected unexpected serious adverse reactions (SUSAR), will be performed in accordance with national regulatory requirements and laboratory guidelines.

Any adverse, significant or non-significant adverse events that occurred during the trial period (from the time of attainment of the subject consent to 1 month of F / U visit) should be recorded in the subject's medical record and in the appropriate eCRF / SAE reporting form.

Each recorded AE and SAE describes "start date, end date, CTCAE rating, treatment need, result, significance" and so on. The tester shall determine the causal relationship to the clinical trial procedure for all adverse events.

All AEs / SAEs that occurred between the time of writing the consent form and the one month F / U visit are recorded and reported regardless of the causal relationship. Between one month F / U and the last F / U visit, all AEs are collected but SAE reports only when relevant to the test procedure. After the last follow-up visit, report only SAEs that are deemed relevant to the test drug or test procedure.

Time period	Report
Consent to 1-mo. F/U	All AEs and SAEs regardless of relevance, including deaths
1-mo. F/U to last F/U	All AEs and trial-related SAEs Deaths not associated with the trial will not be recorded as a SAE.
After last F/U	Trial-related SAEs Deaths not associated with the trial will not be recorded as a SAE.

The occurrence of SAEs will be notified by the investigator/study physician by fax within 24 hours after becoming aware of their occurrence. In case of difficulties or questions an additional phone contact will be useful.

At the time of the initial telephone call/fax, the investigator/study physician will supply the following information:

- Identifiable health-care professional reporter.
- Patient/subject demographics.
- Suspected substance (drug code or name, start and end date, dose - if known).
- Suspected nature of the AE including date of onset, duration and treatment (including hospitalisation).
- Protocol number or title.
- Action taken with respect to test drug.
- Severity of event.
- Relationship to test drug in the opinion of the investigator/study physician.
- Seriousness.
- Concomitant drug therapy at the time of the AE.
- Outcome (if available).

- Recovery date (if available).
- In the case of death, the cause and post-mortem findings (if available).

If applicable the investigator can attach copies of CRF pages to the SAE report form being faxed to avoid double documentation.

The relevant Independent Ethics Committee (IEC) will also be informed of the occurrence of a SAE, if appropriate, within the required time frames.

Additional information will be requested as necessary. SAEs will be followed up for a period of 30 days after last intake of study medication or date of last contact with the patient. Pregnancies will be followed up for 3 months after delivery or termination of the pregnancy. Any effect on either mother or foetus should be determined, if possible.

Any AE that is serious, associated with the use of the study drug, and unexpected (suspected unexpected serious adverse reaction [SUSAR]) has additional reporting requirements, as described below:

- If the SUSAR is fatal or life-threatening, associated with the use of the trial drug, and unexpected, regulatory authorities and IECs will be notified within 7 calendar days after the Primary investigating site learns of the event. Additional follow-up information may be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening, regulatory authorities and IECs will be notified within 15 calendar days after the Primary investigating site learns of the event.

Follow-up information may be submitted if necessary. Primary investigating site will notify the central EC in a timely fashion.

The Primary investigating site will also provide annual safety updates to the regulatory authorities and IECs responsible for the trial. These updates will include information on SUSARs and other relevant safety findings.

13.7. Pregnancy

When a female subject becomes pregnant during the study and study treatment has been administered to the subject, the outcome of the pregnancy needs to be monitored and the safety of the mother and unborn child need to be safeguarded (as per protocol, pregnancy is an exclusion criteria).

Women of child-bearing potential should have a negative serum pregnancy test. Study medication should not be initiated by the Investigator until a report of a negative pregnancy test has been obtained.

Effective contraception must be used (in both male and female subjects) before beginning study medication, during study dosing, and for 5 days following discontinuation of study medication.

A female subject must immediately inform the Investigator if she becomes pregnant during the study. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

14. Sample Size and Statistics

14.1. Sample size consideration

The sample size is based on a superiority design assuming an FCM response (per primary endpoint definition) of 75% by week 12 and a response of 60% in the control group.

For patients with intervention, the improvement is expected to be at least 15% higher (ie., 75% responders). This change would also be considered medically significant and warrant early intervention.

Using these estimates, 400 patients are required to have a 90% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure from 60% in the control group to 75% in the experimental group.

Calculation based on the formula (Pocock): $n = f(\alpha, \beta) \times [p1 \times (100 - p1) + p2 \times (100 - p2)] / (p2 - p1)^2$ where p1 and p2 are the percent 'success' in the control and experimental group respectively and $f(\alpha, \beta) = [\Phi^{-1}(\alpha/2) + \Phi^{-1}(\beta)]^2$.

To account for potential patient drop-outs over the 12 week study period, the sample size is estimated at 450 patients (225 per group).

The parameters will be analyzed by a Pearson chi-square test or Fisher's exact test (patient age and gender, clinicopathologic data, and morbidity), and Student's t-test (Hb level before treatment and hospital days after treatment). The Z test will be used to determine whether or not a significant difference existed between two groups with respect to the slopes for changes in the Hb level during follow-up. (Pocock SJ. Clinical Trials: A Practical Approach. Wiley; 1983)

14.2. Analysis set

A. Efficacy Analysis Set

- 1) Intention to Treatment: That participants in the trials should be analysed in the groups to which they were randomized
- 2) Full analysis set (FAS): That participants who have results of at least one post baseline Hb value among the safety set
- 3) Per-Protocol set: The participants who fulfil the protocol in the terms of the eligibility, interventions, and outcome assessment.

B. Safety Analysis Set:

That participants in the trials should be analyzed in the groups to they were randomized and who took study medication

15.Safety Analyses

15.1 Adverse events

Safety Analyzes shall be performed for all adverse events and adverse drug reactions occurring during the course of the study. If the trial must be discontinued due to AEs, the mechanism between the AE and the experimental drug will be investigated in order to establish a causal relationship. Analysis of AEs will be conducted using the Chi-square and Fisher's exact tests to determine whether the experimental drug is statistically more effective than the control group. The AEs will be coded using the NCI CTCAE version 4.03 Dictionary for Drug Regulatory Affairs (MedDRA).

15.2 Concomitant medication

In the event of an AE that requires treatment, the frequency and percentage of administered combinatorial agents will be calculated and recorded. Again, the frequency and percentage of each therapeutic agent will be clinically tested. Analysis of these combinatorial therapies will be

conducted using the Chi-square and Fisher's exact tests to determine whether these agents are statistically effective.

16. Access to Trial Data/Documents

15.1. Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centres, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits by the appointed Clinical Research Associate(CRA). The CRA will review CRFs for accuracy and completeness during on-site monitoring visits and after their release to the clinical study database where the central data monitor will verify for accuracy and any discrepancies will be resolved with the investigator or designees, as appropriate.

Primary investigating site's Clinical Quality Assurance department or an independent Clinical Quality Assurance group may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a Licensing Application. The investigator should immediately notify the Primary investigating site if they have been contacted by a regulatory agency concerning an upcoming inspection.

16.2. Case Report Forms and Source Documentation

It is the responsibility of the investigators to ensure the completeness and accuracy of CRFs, and that they are compiled in a timely manner. One CRF must be compiled for each patient participating in the study. All CRF corrections are to be made by the investigator or other authorised study site personnel. The investigator must authorize changes to the recorded safety and efficacy data.

Data must be entered into CRFs. The AE page of the CRF must be signed as well as dated by the investigator.

The CRFs are to be completed within approximately 5 working days after the patient's visit including the results of tests performed outside the investigator's office, so that they always reflect the latest observations on the patients participating in the study.

Completed CRFs will be reviewed by the monitor to determine their acceptability. If necessary, queries will be generated and transmitted to the study site for resolution.

16.3. Access to Source Data

Primary investigating site will aim to perform at least one on-site monitoring visit per site. The dates of the visits will be recorded by the monitor in a centre visit log to be kept at the site. The first post initiation visit will usually be made as soon as possible after enrolment has begun. At these visits, the monitor will compare the data entered in the CRF with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AE, administration of concomitant medication, drug receipt/dispensing/return records, and study drug administration information. Specific items required as source documents will be reviewed with

the investigator prior to the study. Findings from this review of CRFs and source documents will be discussed with the investigator.

During monitoring visits, the investigator (and as appropriate the study coordinator) will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

17. Ethical Considerations

17.1. Ethical Conduct of the Study

The study will be conducted according to the principles of the World Medical Association's (WMA) Declaration of Helsinki (as amended by the 59th WMA General Assembly, Seoul, October 2008), and the ICH guidelines for GCP. The Primary investigating site will ensure that the study complies with all local, federal or country regulatory requirements. If full compliance with all declarations, guidelines and regulations is not planned, the exceptions must be noted here and an explanation provided as to the acceptability of the data generated from the clinical trial.

The Investigator must ensure the anonymity of all subjects participating in the study. Each subject will be assigned a unique subject number and this should be used on all forms associated with the subject's documents or samples that will be supplied to the primary investigating site or any party completing testing on behalf of the Primary investigating site (e.g., blood for central laboratory assessments).

17.2. Informed Consent

The informed consent form (ICF) used for the study must comply with the Declaration of Helsinki, federal regulations, and ICH guidelines; and must have been approved by the IRB/EC/IEC prior to use. The Investigator or an authorised associate must explain orally and in writing the nature of the study and the treatment in such a manner that the subject is aware of potential benefits and risks. Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects must be provided sufficient time to consider participation, including discussion with family members prior to signing the ICF. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Subjects must give informed consent in writing.

A guideline on how to administer informed consent should be followed by all site staff administering informed consent to subjects when an equivalent process is not available at his/her site.

17.3. Institutional Review Board or EC/IEC

The protocol, any protocol amendments and consent form for the proposed clinical study and any other documents required by the local IRB/EC/IEC must be submitted by the Investigator for review and approval to the IRB/EC/IEC. The Investigator must also ensure that the IRB/EC/IEC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis.

18. Insurance and Financing

The Primary investigating site confirms that it carries liability insurance which protects non-employee physicians or Investigators against claims for which they may become liable as a result of damages caused by products used in this clinical study.

Insurance coverage is not extended to damages that the Investigators or third parties may suffer by reason of acts of commission or omission on the part of such Investigators and that are not in accordance with accepted common medical practices (*lege artis* procedures).

The Primary investigating site will reimburse the subject for all study related injuries provided that the injury does not arise from the subject's misuse of the study drug or failure to follow the Investigator's instructions.

19. Publication Policy

The Primary investigating site will form a publication committee and this committee will propose and develop appropriate scientific manuscripts or abstracts from the study data. Investigators may not present or publish partial or complete study results individually. Any manuscript or abstract proposed by the Investigators must be reviewed and approved in writing by the Primary investigating site before submission for publication. Names of all Investigators participating in the study will be included in the publication.

The publication committee for a study will comprise of authors selected in adherence with the International Committee of Medical Journal Editors criteria for authorship. That is, all authors must meet each of the following 3 criteria:

- Substantial contribution to conception and design or acquisition of data, or analysis and interpretation of data.
- Drafted the article or revised it critically for important intellectual content.
- Approved the final version for publication.

20. Planning of monitoring co-investigation site

After approval from each institution IRB, research start-up meeting will be conducted.

Each research site will be visited on a monthly basis to monitor for confirm the completeness of the subject records and accuracy of case records, and examine whether study protocol properly followed the regulation.

21. Data safety monitoring committee (DSMC)

In order to meet the requirement set forth by Food and Drug Administration, One bio statistician and one oncology expert, both of whom do not participate in the present study, must be chosen to form and run the Data Safety Monitoring Board (DSMB)

- At the critical time period such as the start and end of the research, DSMB will inspect the overall progress of the study and research data management, and conduct interim analysis.

22. References

1. Relationship between Changes in Hemoglobin Level and QOL During Chemotherapy in Anemic Cancer Patients Receiving Epoetin Alfa Therapy: David Cella, Ph.D., and others
2. Safety evaluation of oral Fluoropyrimidine S-1 for short- and long-term delivery in advanced gastric cancer: analysis of 3,758 patients: Takeharu Yamanaka and others.
3. Safety evaluation of oral Fluoropyrimidine S-1 for short- and long-term delivery in advanced gastric cancer: analysis of 3,758 patients: Takeharu Yamanaka and others
4. A randomized trial of anemia correction with two different hemoglobin targets in the first-line chemotherapy of advanced gastric cancer, Se Hoon Park and others
5. Anemia is the strongest prognostic factor for outcomes of 5-fluorouracil-based first-line: Se Hoon Park and others
6. Beshara S, Sorensen J, Lubberink M, Tolmachev V, Langstrom B, Antoni G, Danielson BG, Lundqvist H. Pharmacokinetics and red cell utilization of ⁵²Fe/⁵⁹Fe-labelled iron polymaltose in anaemic patients using positron emission tomography. *Br J Haematol* 2003;120:853-859 **12** Rummyantsev V. A multi
7. Peter Geisser **Vifor (International) Inc. St. Gallen, Switzerland.** The pharmacology and safety profile of ferric carboxymaltose (Ferinject®): structure/reactivity relationships of iron preparations
8. Wajeh Y. Qunibi¹ and others, A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. *Nephrol Dial Transplant* (2011) 26: 1599–1607 doi: 10.1093/ndt/gfq613 Advance Access publication 7 October 2010
9. Schaefer R. et al. Intravenous ferric carboxymaltose or iron sucrose to treat iron deficiency anemia in hemodialysis patients. Poster no. MP375.XLV ERA-EDTA congress Stockholm, Sweden, May 10-13, 2008