
**An Open-label, Randomised Controlled Multi-centre Study
to Assess the Impact of Ferric Carboxymaltose in Correcting
Iron Deficiency Anaemia Compared to Venofer[®] (Iron
Sucrose) in Chinese Subjects**

Clinical Protocol Number: VIT-IRON-2011-004

Date: 14 August 2017

Version Number: 5.0

Prior Amendments: Amendment 1, 9 April 2014
Amendment 2, 4 May 2016
Amendment 3, 2 September 2016

Co-ordinating Investigator:

[REDACTED]

Sponsor Contact:

[REDACTED]

Sponsor Address:

Vifor International Inc.
Rechenstrasse 37
P.O. Box
9001 St. Gallen
Switzerland

Sponsor Medical Expert

[REDACTED]

Fax: +41 58 851 80 01

[REDACTED]

Clinical Research
Organisation

Tigermed Consulting Ltd.
Fl.15 Dongguan Building
618 Jiangnan Road

Binjiang District
Hangzhou, Zhejiang Prov., 310052,
P.R. China

SIGNATURE PAGE

Declaration of Sponsor

Title: An Open-label, Randomised Controlled Multi-centre Study to Assess the Impact of Ferric Carboxymaltose in Correcting Iron Deficiency Anaemia Compared to Venofer® (Iron Sucrose) in Chinese Subjects

Version Number/Date: Amendment 4, 14 August 2017

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Conference on Harmonisation guidelines on Good Clinical Practice.

[Redacted Signature]

Clinical Representative and
Sponsor Medical Expert
Vifor Pharma

[Redacted Signature]

Date (DD.MMM.YYYY)

[Redacted Signature]

Clinical Representative
Vifor Pharma

[Redacted Signature]

Date (DD.MMM.YYYY)

[Redacted Signature]

Trial Statistician
Vifor Pharma

[Redacted Signature]

Date (DD.MMM.YYYY)

[Redacted Signature]

Regulatory Representative
Vifor Pharma

[Redacted Signature]

Date (DD.MMM.YYYY)

INVESTIGATOR AGREEMENT AND SIGNATURE PAGE

I have read the attached protocol entitled “An Open-label, Randomised Controlled Multi-centre Study to Assess the Impact of Ferric Carboxymaltose in Correcting Iron Deficiency Anaemia Compared to Venofer[®] (Iron Sucrose) in Chinese Subjects”, Amendment 4 dated 14 August 2017, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline on Good Clinical Practice and applicable regulations and guidelines.

I agree to ensure that financial disclosure statements will be completed by:

- me (including, if applicable, my spouse (or legal partner) and dependent children);
- my Sub-investigators

before the start of the study and to report any changes that affect my financial disclosure status for up to 1 year after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Vifor Pharma.

Signature by the Investigator on this Protocol Signature Page documents review, agreement and approval of the requirements contained within this protocol.

Signature

Date (DD.MMM.YYYY)

Name of Principal Investigator

SYNOPSIS

VIT-IRON-2011-004

Title:	An open-label, randomised controlled multi-centre study to assess the impact of ferric carboxymaltose in correcting iron deficiency anaemia compared with Venofer® (Iron Sucrose) in Chinese subjects
Short Title:	China Phase 3 Study
Study Product(s):	Ferinject® (ferric carboxymaltose, FCM)
Indication:	Iron deficiency anaemia (IDA)
Phase:	3
Sponsor:	Vifor Pharma
Study Code:	VIT-IRON-2011-004
Co-ordinating Investigator:	<div style="background-color: black; width: 100%; height: 40px;"></div>
Objectives:	<p><u>Primary Objective(s):</u></p> <ul style="list-style-type: none"> To demonstrate the efficacy of ferric carboxymaltose (FCM) given in a simple dosing regimen in correcting IDA, by demonstrating non-inferiority to treatment with the currently approved intravenous (IV) iron therapy of Iron Sucrose (IS, Venofer) in the Chinese population. <p><u>Secondary Objective(s):</u></p> <ul style="list-style-type: none"> To assess the safety of FCM compared to IS in the Chinese population. To evaluate the effect of FCM compared to IS on relevant laboratory parameters (haematology, chemistry, iron parameters) in the Chinese population.
Design:	<p>Open-label, randomised controlled study to assess the impact of FCM in correcting IDA compared with Venofer (IS).</p> <p>All subjects, after providing written informed consent and meeting the eligibility criteria, will receive a first dose of IV iron as either FCM or IS. A total of approximately 368 subjects (184 per group) will be randomised. All subjects will have IDA as measured by haemoglobin (Hb), serum ferritin and transferrin saturation (TSAT) at screening.</p> <p>Ferric carboxymaltose will be administered as either a diluted infusion or undiluted injection (at Investigator's discretion) at single, maximum daily doses of 500 or 1,000 mg iron) and IS will be administered as an undiluted bolus push injection or diluted infusion (with each single injection/infusion of 200 mg iron). Note, for subjects randomised to receive IS, dosing visits are required three times a week to achieve total iron repletion dosing as calculated using the Ganzoni formula.</p> <p>For subjects randomised to FCM, the total iron requirement will be calculated at baseline based on the screening Hb and body weight (BW). Dosing will be at baseline (Day 1) and, if required, at Day 8 and Day 15..</p>

Design (Cont'd):	All subjects will attend study visits at screening, baseline and thereafter at Weeks 2, 4 and 6. All subjects will attend an end of study visit (at Week 8 – or earlier if discontinued prematurely). Additional dosing visits may be required for subjects receiving IS three times weekly up to Week 4.																														
Treatment:	<div><div>Arm A: Ferric Carboxymaltose</div><div>Dosing to be based on subject Hb and BW at screening as per table below:</div><table><thead><tr><th colspan="6">Total Iron (mg) as FCM</th></tr><tr><th></th><th colspan="2">BW 35-<70 kg¹</th><th colspan="2">BW ≥70 kg</th><th></th></tr><tr><th></th><th>Hb <10 g/dL</th><th>Hb ≥10-<14 g/dL</th><th>Hb <10 g/dL</th><th>Hb ≥10-<14 g/dL</th><th></th></tr></thead><tbody><tr><td>Day 1</td><td>1,000 mg</td><td>1,000 mg</td><td>1,000 mg</td><td>1,000 mg</td><td></td></tr><tr><td>Day8</td><td>500 mg</td><td>No dose</td><td>1,000 mg</td><td>500 mg</td><td></td></tr></tbody></table><div><div>1.</div><div>Notes:</div><div>BW = Body weight; FCM = Ferric carboxymaltose; Hb = Haemoglobin. The maximum single dose that should be given to a subject is 20 mg/kg BW, therefore for subjects with BW 35 - <50kg and Hb ≥ 10 g/dL, the 1,000 mg dose should be split into 2 x 500 mg (one 500 mg dose on Day 1 and one 500 mg dose on Day 8. Subjects with BW 35 - <50 kg and Hb < 10g/dL should receive 3 doses of 500 mg (on Day 1, 8 and 15) .</div></div><div>To be administered as undiluted injection or diluted infusion (500 mg iron diluted in 100 mL 0.9% w/v physiological saline or 1,000 mg iron diluted in 250 mL 0.9% w/v physiological saline) over at least 5 minutes for the 500 mg dose and over at least 15 minutes for the 1,000 mg dose. Administration time should not exceed 30 minutes for either the 500 or the 1,000 mg dose.</div><div>Arm B: Venofer (Iron Sucrose)</div><div>Required total iron dose to be calculated per label (Ganzoni formula):</div><div>Cumulative iron deficit [mg] (calculated from screening values)= BW [kg] x (target Hb⁽¹⁾ - actual Hb) [g/dL]⁽²⁾ x 2.4⁽³⁾ + 500 mg⁽⁴⁾</div><div><div>(1)</div><div>Target Hb for BW >35 kg = 15 g/dL, respectively 9.3 mmol/L</div></div><div><div>(2)</div><div>To convert mmol/L to g/dL: multiply Hb (mmol/L) by the factor 1.61145</div></div><div><div>(3)</div><div>Factor 2.4 = 0.0034 (iron content Hb = 0.34%) x 0.07 (blood volume = 7% of BW) x 10,000 (conversion g/dL to mg/L x 10)</div></div><div><div>(4)</div><div>Storage iron</div></div><div>Note: BW = Body weight.</div><div>The calculated iron dose will be split into doses of 200 mg iron administered by slow intravenous injection at a rate of 1 ml undiluted solution per minute (10 ml of the product in at least 10 minutes; administration time should not exceed 60 minutes) or by drip infusion in a dilution of 1 ml of Venofer in a maximum of 20 ml 0.9% w/v physiological saline (10 ml of the product in maximum 200 ml of saline). The drip infusion rate should be 200 ml solution in at least 30 minutes and should not exceed 60 minutes. The subjects will be administered Venofer three times a week, with an initial dose at baseline and will receive iron, as per approved label, until the subject has received the calculated iron dose. The calculated cumulative Venofer dose will rounded up or down to the nearest 200 mg.</div></div>	Total Iron (mg) as FCM							BW 35-<70 kg ¹		BW ≥70 kg				Hb <10 g/dL	Hb ≥10-<14 g/dL	Hb <10 g/dL	Hb ≥10-<14 g/dL		Day 1	1,000 mg	1,000 mg	1,000 mg	1,000 mg		Day8	500 mg	No dose	1,000 mg	500 mg	
Total Iron (mg) as FCM																															
	BW 35-<70 kg ¹		BW ≥70 kg																												
	Hb <10 g/dL	Hb ≥10-<14 g/dL	Hb <10 g/dL	Hb ≥10-<14 g/dL																											
Day 1	1,000 mg	1,000 mg	1,000 mg	1,000 mg																											
Day8	500 mg	No dose	1,000 mg	500 mg																											
Inclusion Criteria:	<div><div>1.</div><div>At least 18 years of age</div></div> <div><div>2.</div><div>Hb <11 g/dL (females) or Hb <12 g/dL (males) at the screening visit</div></div> <div><div>3.</div><div>Serum ferritin <100 ng/mL for subjects with underlying inflammatory disease (e.g., inflammatory bowel disease (IBD), chronic kidney disease</div></div>																														

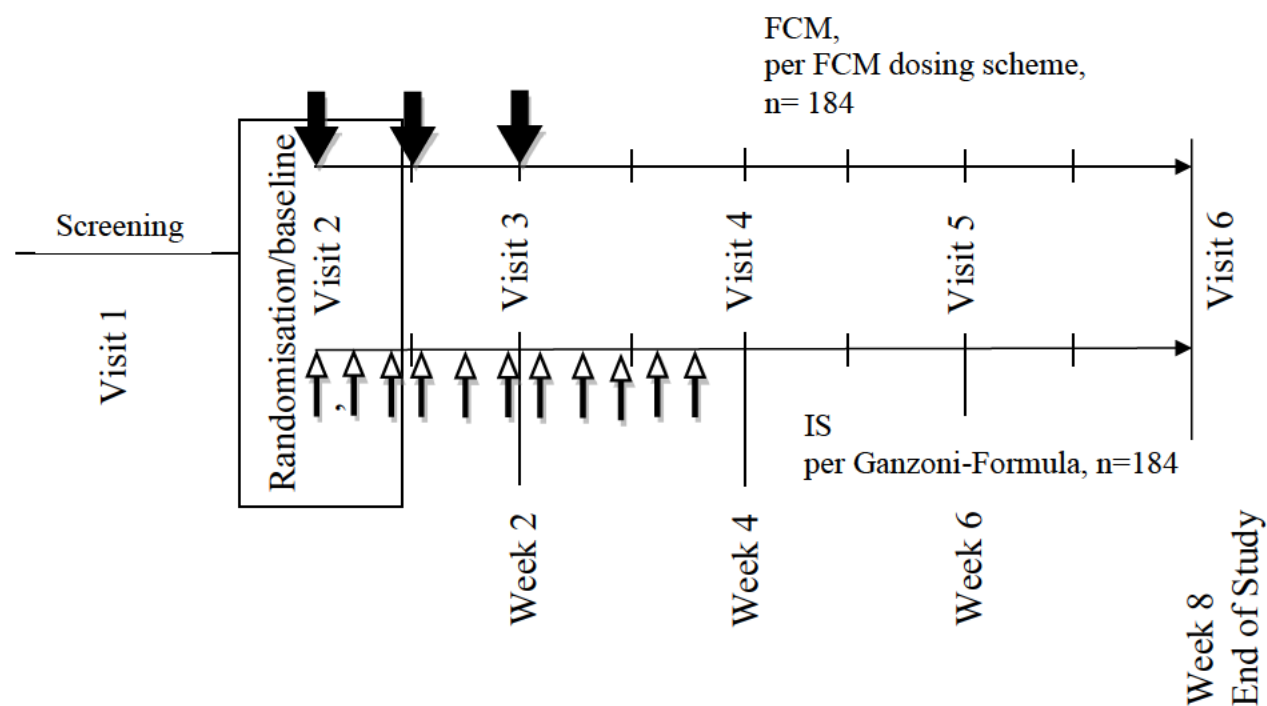
	<p>(CKD) or chronic heart failure (CHF), as determined by high sensitive C-reactive protein [hsCRP] levels above the normal range) otherwise serum ferritin ≤ 14 ng/mL in subjects with no apparent underlying inflammatory disease (as determined by hsCRP levels within normal range) at the screening visit</p> <ol style="list-style-type: none"> 4. TSAT $< 16\%$ (any subject) at the screening visit 5. Microcytic, hypochromic anaemia at the screening visit, defined as: <ol style="list-style-type: none"> a. Mean corpuscular Hb concentration (MCHC) $< 32\%$ b. Mean corpuscular volume (MCV) < 80 fL c. Mean corpuscular Hb (MCH) < 27 pg 6. Subjects with the ability to understand the requirements of the study and abide by the study restrictions, and who agree to return for the required assessments 7. Before any study-specific procedure is conducted, the appropriate written informed consent must be obtained
--	--

Exclusion Criteria:	<ol style="list-style-type: none"> 1. Subject has known hypersensitivity to any of the products to be administered during dosing 2. Any history of iron storage diseases such as haemochromatosis 3. Any history or clinical findings of iron utilisation disorders such as sideroachrestic anaemia 4. Known haemoglobinopathy (e.g. thalassaemia) 5. Any history or clinical findings of anaemia associated with: <ol style="list-style-type: none"> a. Haematuria b. Vitamin B12 or folic acid deficiency that requires treatment (subjects can be included after deficiency is corrected) 6. Any allergic predispositions, i.e. any history of asthma or atopic allergy. This includes drug allergies. 7. Planned surgery with anticipated blood loss (defined as Hb drop >2 g/dL) in the 3 months post randomisation 8. Subject has known malignancy (with or without current treatment), except basal cell or squamous cell carcinoma of the skin or cervical intra-epithelial neoplasia 9. Haemodialysis (current or planned within the next 3 months) 10. History of IV iron therapy, erythropoiesis stimulating agent (ESA) therapy and/or blood transfusion in previous 4 weeks prior to baseline, and oral iron or oral iron-containing products including Chinese herbal medicines (>75mg iron/day) in the 7 days prior to baseline 11. Body weight <35 kg 12. Chronic liver disease and/or screening alanine transaminase (ALT) or aspartate transaminase (AST) above 3 times the upper limit of the normal range 13. Known human immunodeficiency virus infection, acquired immunodeficiency syndrome, tuberculosis 14. Known active hepatitis B or C or other active infection (acute or chronic) 15. Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(ies), or subject is receiving other investigational agent(s) 16. Subject is pregnant or is breast feeding 17. Female subject of childbearing potential not using adequate contraceptive methods during the study and for up to 1 month after the last dose of the study medication. Adequate contraceptive methods are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner. Non-childbearing potential includes being surgically sterilised at least 6 months prior to the study or post-menopausal, defined as amenorrhoea for at least 12 months 18. Male subjects planning to father a child within 7 days from the last study drug administration. 19. Subject has any kind of disorder that compromises the ability of the subject
---------------------	---

	to give written informed consent and/or to comply with study procedures and/or other reason(s) that render subject not appropriate for study participation in the opinion of the treating physician
Primary and Secondary Endpoints:	<p><u>Primary Endpoint:</u></p> <ul style="list-style-type: none"> Percentage of subjects achieving an increase in Hb of ≥ 2 g/dL (responders) from baseline at any time up to Week 8 <p><u>Secondary Endpoints:</u></p> <p>Efficacy:</p> <ul style="list-style-type: none"> Percentage of subjects achieving an increase in Hb ≥ 2 g/dL from baseline at Weeks 2, 4, 6 and 8 Change in Hb from baseline to Weeks 2, 4, 6 and 8 The percentage of subjects with TSAT $\geq 16\%$ and serum ferritin ≥ 100 ng/mL (for subjects with underlying inflammatory disease as determined by hsCRP levels above the normal range) or serum ferritin > 14 ng/mL (in subjects with no apparent underlying inflammatory disease as determined by hsCRP levels within normal range at screening) at Weeks 2, 4, 6 and 8 Change in TSAT from baseline to Weeks 2, 4, 6 and 8 Change in serum ferritin from baseline to Weeks 2, 4, 6 and 8
	<p><u>Secondary Endpoints (Cont'd):</u></p> <p>Safety:</p> <ul style="list-style-type: none"> Change in laboratory parameters (haematology, clinical chemistry and iron status) from baseline over the study duration Summary of all treatment emergent adverse events (TEAE): type, nature, incidence and outcome overall and by underlying disease aetiology Summary of changes in vital signs from baseline to Weeks 2, 4, 6 and 8 <p>Summary of changes in electrocardiogram (ECG) and physical examination (including BW) from baseline to Week 4 (for ECG only) and Week 8</p>
Procedures:	<p>All subjects will be screened (following written informed consent) to assess eligibility for the study.</p> <p>At the screening visit, all subjects will have a physical examination and an ECG performed and blood parameters assessed. If the subject is eligible, they will be randomised at the Baseline visit to receive FCM or IS (with dose as described in the Treatment Section). Study subjects may be hospitalised for study drug application, if needed, at the discretion of the Investigator.</p> <p>Subjects randomised to receive FCM will receive a second and third administration on Day 8 and Day 15, if needed. For subjects randomised to receive Venofer additional dosing visits are required three times a week up to Week 4 to achieve total iron repletion.</p> <p>All subjects will be required to attend follow-up visits at Weeks 2, 4, 6 and an end of study visit at Week 8 (or earlier if discontinued prematurely). At each visit, all subjects will have their vital signs and blood parameters assessed (using central laboratory). An ECG will be performed at Week 4 and Week 8.</p>

	<p>Data will be recorded in the case report form (CRF) after each visit.</p> <p>See Schedule of Events for full details of protocol required procedures and applicable visits (and timings).</p>
Sample Size:	<p>A total of 368 subjects will be randomised (i.e. 184 per treatment group)</p> <p>The sample size is based on showing non-inferiority in the difference in the proportion of subjects achieving an increase in Hb of $\geq 2\text{g/dL}$ at any time up to Week 8 between FCM and IS. Applying a test at a one sided alpha level of 2.5%, and a -15% non-inferiority margin, 147 subjects per-group will have a 80% power to detect whether FCM is non-inferior to IS with an expected IS responder proportion of 70%. The total sample size is 368, which allows for an estimated drop-out rate of 20% of the randomised subjects.</p>
Statistical Methods:	<p>Primary endpoint:</p> <p>Non-inferiority of FCM versus IS will be assessed by the difference in the proportion of subjects achieving an increase in Hb of $\geq 2\text{g/dL}$ at any time up to Week 8. The analysis will be performed for the Per Protocol set (PPS) and tested at a one sided alpha level of 2.5% with a 15% non-inferiority margin. A sensitivity analysis will be performed on the Full Analysis Set (FAS).</p> <p>Secondary endpoints for efficacy:</p> <p>All secondary endpoints will be analysed on the FAS and the PPS. All statistical tests will be performed at a 5% level.</p> <p>Safety analysis</p> <p>All safety analyses will be performed on the Safety Set. Further details will be specified in the Statistical Analysis Plan (SAP).</p>

SCHEMA



↓ = Ferric carboxymaltose administration. Second and third administration only if needed according to dosing table

↑ = Iron Sucrose administration. Subjects will be required to visit the study centre for administration of 200 mg IS three times a week until individually calculated iron dose is achieved.

Table 1: Schedule of Events

Procedures	Visit			
	Visit 1 Screen	Visit 2 Baseline	Visit 3-5	Visit 6 End of study/ Early Termination
	Day -7 to Day -1	Day 1	Weeks 2, 4, 6 ±3 Days	Week 8 ±4 Days
Informed consent	✓			
Eligibility criteria	✓	✓ ⁽¹⁾		
Demographics	✓			
Medical history	✓			
Physical examination and weight	✓			✓
Height	✓			
Vital signs (blood pressure, heart rate, temperature)	✓	✓	✓	✓
Electrocardiogram	✓		✓ ⁽⁶⁾	✓
Laboratory assessments (haematology/ biochemistry/iron parameters) ⁽²⁾	✓	✓	✓	✓
Hepatitis B and C screening ⁽³⁾	✓			
Urinalysis ⁽⁴⁾	✓		✓	✓
Serum pregnancy test ⁽⁵⁾	✓			✓
Adverse events	✓	✓	✓	✓
Prior & Concomitant medications	✓	✓	✓	✓
Randomisation		✓		
Administration of study drug		✓	(✓ ⁽⁷⁾)	

1. Laboratory parameters will be tested at Baseline but will not be used for eligibility because the results will not be available on time. Laboratory parameters taken at screening will be checked for eligibility at Baseline

2. Laboratory assessments include:

- Haematology: Hb, haematocrit, red blood cell count, MCV, MCH, MCHC, reticulocyte count, Hb content in reticulocytes, white blood cell count with differential and platelet count.
- Iron status parameters: serum iron, serum ferritin, serum transferrin, UIBC and TSAT.
- Biochemistry parameters: electrolyte status (sodium, potassium, magnesium, calcium, chloride, phosphorus), AST, ALT, gamma-glutamyl transpeptidase (GGT), glucose, alkaline phosphatase (AP), lactate dehydrogenase (LDH), hsCRP.

3. Hepatitis screening consists of Hepatitis B antigen, Hepatitis B virus DNA and Hepatitis C virus antibody

4. Urinalysis includes: phosphorus, protein, glucose, bilirubin, pH, nitrite, ketone, urobilinogen, blood, leukocytes

5. For women of childbearing potential only.

6. ECG is only performed at Week 4.

7. Subjects randomised to receive FCM will receive a maximum of 1,000 mg at Baseline (Day 1), a second administration of a maximum of 1,000 mg at Day 8 and a third administration of a maximum of 500 mg at Day 15, if applicable. Subjects randomised to Venofer will need to come to the study centre to receive further Venofer dosing three times a week. All study procedures must be conducted prior to dosing.

Notes: ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; hsCRP = high sensitive C-reactive protein; ECG = Electrocardiogram; FCM = ferric carboxymaltose; GGT = gamma glutamyl transpeptidase, Hb = Haemoglobin; LDH =lactate dehydrogenase,MCH = Mean corpuscular Hb; MCHC = Mean corpuscular haemoglobin concentration; MCV = Mean corpuscular volume; TSAT = Transferrin saturation, UIBC= unsaturated iron binding capacity.

TABLE OF CONTENTS

	Page
SIGNATURE PAGE.....	2
INVESTIGATOR AGREEMENT AND SIGNATURE PAGE.....	3
SYNOPSIS	4
SCHEMA.....	10
TABLE OF CONTENTS	13
LIST OF ABBREVIATIONS	18
1. INTRODUCTION AND BACKGROUND.....	20
1.1 Background of the Disease and Treatment Options	20
1.2 Summary of Ferric Carboxymaltose Nonclinical and Clinical Data	21
1.2.1 Pharmacology	21
1.2.2 Preclinical and Pharmacokinetic Studies.....	21
1.2.3 Efficacy.....	22
1.2.4 Safety	23
2. RATIONALE	25
2.1 Design	26
2.2 Dose and Drug Selection	26
2.3 Endpoint and Procedures	27
2.3.1 Primary Endpoint.....	27
2.3.2 Secondary Endpoints	28
2.4 Key Inclusion and Exclusion Criteria.....	28
3. STUDY OBJECTIVES.....	29
3.1 Primary Objective	29
3.2 Secondary Objectives.....	29
4. INVESTIGATIONAL PLAN	30
4.1 Overall Study Design.....	30
4.2 Duration of Subject Participation and Study	30
5. SELECTION AND WITHDRAWAL OF SUBJECTS	31
5.1 Number of Subjects.....	31
5.2 Inclusion Criteria	31
5.3 Exclusion Criteria	31
5.4 Withdrawal of Subjects.....	33
5.4.1 Withdrawal of Subjects from Study Drug	33
5.4.2 Withdrawal of Subjects from Study Visits	33
6. RANDOMISATION, BLINDING AND UNBLINDING PROCEDURES	36
6.1 Randomisation	36

6.2	Blinding.....	36
6.3	Unblinding	36
7.	STUDY TREATMENTS	37
7.1	Dosage Forms/Formulation	37
7.1.1	Ferric Carboxymaltose.....	37
7.1.2	Iron Sucrose	37
7.2	Drug Dosage and Administration	38
7.2.1	Arm A: Ferric Carboxymaltose	38
7.2.2	Arm B: Iron Sucrose	38
7.2.3	IV Administration of Drug (Both Arms)	39
7.3	Package and Labelling	40
7.4	Study Treatment Allocation.....	40
7.5	Site Supply, Storage, Accountability	40
7.5.1	Site Supply	40
7.5.2	Storage	40
7.5.3	Accountability.....	41
7.6	Drug Dose Modification	41
7.6.1	Procedures for Overdose.....	41
7.7	Prohibited Therapy and Concomitant Treatment.....	41
8.	RISKS/PRECAUTIONS	43
8.1	IV irons	43
8.2	Ferric Carboxymaltose.....	43
8.3	Iron Sucrose	44
9.	STUDY PROCEDURES	45
9.1	Description of Study Assessments	45
9.1.1	Vital Signs.....	45
9.1.2	Physical Examination	45
9.1.3	Laboratory Parameters	45
9.1.4	Electrocardiogram.....	46
9.1.5	Urinalysis	46
9.2	Schedule of Assessments	46
9.2.1	Screening and Baseline Procedures	46
9.2.2	Treatment Procedures	47
9.2.3	End of Study (or Early Discontinuation) Procedures	48
9.2.4	Unscheduled Visits	48
10.	EVALUATION, RECORDING AND REPORTING OF AES AND SAES.....	49
10.1	Definitions.....	49
10.1.1	Reference Safety Information	49
10.1.2	Adverse Event.....	49
10.1.3	Adverse Drug Reaction.....	49
10.1.4	Unexpected AE/ADR	49
10.1.5	Serious Adverse Event.....	49

10.1.6	Suspected Unexpected Serious Adverse Reaction.....	50
10.1.7	Special Situations.....	51
10.2	Adverse Event Descriptors	51
10.2.1	Intensity/Severity Categorisation.....	51
10.2.2	Causal Relationship Categorisation	52
10.2.3	Outcome Categorisation	53
10.2.4	Pre-existing Medical Conditions	53
10.2.5	Signs and Symptoms of the Disease Under Study.....	53
10.2.6	Clinical Laboratory Evaluations	53
10.2.7	Special Situations.....	55
10.3	Reporting Procedure for AEs, SAEs, Special Situations and Pregnancy	55
10.3.1	Adverse Events	55
10.3.2	Serious Adverse Events and Special Situations.....	56
10.3.2.1	Elective Surgery/Routine Examination.....	59
10.3.3	Pregnancy.....	59
11.	STATISTICAL ANALYSIS	61
11.1	Statistical Methods.....	61
11.2	Sample Size and Power Calculations.....	61
11.3	Analysis Set	62
11.3.1	Full Analysis Set.....	62
11.3.2	Per-Protocol Set	62
11.3.3	Safety Set	62
11.4	Background and Demographic Characteristics.....	62
11.5	Study Medication	62
11.6	Concomitant Therapy.....	63
11.7	Efficacy Evaluations	63
11.7.1	Primary.....	63
11.7.2	Secondary.....	63
11.8	Safety Evaluations	64
11.9	Interim Analyses	64
11.10	Other Evaluations.....	65
11.10.1	Pharmacokinetics	65
12.	STUDY ETHICAL CONSIDERATIONS	66
12.1	Ethical Conduct of the Study	66
12.2	Informed Consent.....	66
12.3	Institutional Review Board or EC/IEC	66
13.	QUALITY CONTROL AND QUALITY ASSURANCE	67
14.	ADMINISTRATIVE PROCEDURES	68
14.1	Sponsor's Responsibilities	68
14.1.1	Study Supplies	68
14.1.2	Insurance.....	68
14.1.3	Investigator Training.....	68
14.1.4	Study Monitoring.....	68

14.2	Investigator’s Responsibilities	69
14.2.1	Reporting and Recording of Data	69
14.2.2	Source Documentation.....	69
14.2.3	Records Retention.....	70
14.2.4	Site Documentation.....	70
15.	PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY.....	71
15.1	Protocol Waivers, Deviations and Violations.....	71
15.2	Protocol Amendments.....	71
15.3	Study Termination	71
16.	POLICY FOR PUBLICATION AND PRESENTATION OF DATA	72
17.	REFERENCES.....	73

LIST OF TABLES

Table 1: Schedule of Events	11
Table 2: FCM Dosing Schedule.....	38

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BW	Body weight
CFDA	Chinese Food and Drug Administration
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CRF	Case report form
CRO	Contract research organisation
EC	Ethics Committee
ECG	Electrocardiogram
ESA	Erythropoiesis stimulating agent
FAS	Full analysis set
FCM	Ferric carboxymaltose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
hsCRP	High sensitive C-reactive protein
Hb	Haemoglobin
HUB	Heavy uterine bleeding
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Iron deficiency
IDA	Iron deficiency anaemia
IEC	Independent Ethics Committee

IRB	Institutional Review Board
IS	Iron Sucrose
IV	Intravenous
LDH	Lactate dehydrogenase
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
PPS	Per-protocol set
RES	Reticuloendothelial system
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SMC	Standard Medical Care
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TSAT	Transferrin saturation
WMA	World Medical Association

1. INTRODUCTION AND BACKGROUND

1.1 Background of the Disease and Treatment Options

Iron deficiency (ID) is one of the most commonly known forms of nutritional deficiencies. Iron deficiency is a state in which there is insufficient iron to maintain the normal physiological function of tissues such as the blood, brain, and muscles. As iron is present in all cells and, as part of enzymes, is essential for numerous vital functions, such as oxygen transport, transport of electrons in the form of cytochromes, impaired physical condition, cognitive impairment, disturbed thermoregulation and fatigue have been described in patients with ID [1].

Iron deficiency is usually only detected when untreated ID has led to anaemia. Iron deficiency is considered the primary cause of anaemia in approximately 50% of cases [3]. Low haemoglobin (Hb) levels, in conjunction with a decrease in erythrocyte volume and a low erythrocyte Hb concentration (microcytic, hypochromic anaemia), are indicative of iron deficiency anaemia (IDA). Additional assessments include iron makers, such as serum ferritin, a cellular iron-binding protein which is also secreted into the blood, providing the most reliable indirect measure of body iron stores in the absence of infection or inflammation. Serum ferritin levels below 15 ng/mL are highly specific for empty iron stores. Values from 15-30 ng/mL correspond to empty to limited iron stores; values from 30 to 50 ng/mL are borderline and values above 50 ng/mL without coexisting inflammation/infection are evidence of sufficient iron reserves [3].

Although a modern diet and the use of iron supplements have reduced the incidence and degree of ID in industrialised countries, iron supply is still a problem in certain subgroups of the population, namely young children, pregnant and menstruating women. The prevalence of iron deficiency that resulted in iron deficiency anaemia (IDA) in China, is estimated to range from 19.9% to 28.9%, dependent on the population studied, and considered a moderate public health concern [3]. Additionally, ID may be observed in patients with chronic diseases where hepcidin is upregulated and appears to decrease absorption of iron from the gastrointestinal tract (e.g., chronic kidney disease (CKD), chronic heart failure (CHF) or inflammatory bowel disease (IBD)). For instance, it has been demonstrated that ID alone is an independent risk factor for mortality in patients with CHF [4].

Mild ID (i.e., plasma ferritin <30 ng/mL, transferrin saturation (TSAT) <20% [5]) can be prevented or corrected by eating iron-rich foods. However, as ID can have serious health consequences that diet may not be able to quickly correct, iron supplementation may be necessary. Initial treatment options usually include oral iron replacement therapies. Unfortunately, there is a subset of patients where oral iron is ineffective or cannot be tolerated and intravenous (IV) iron replacement is required.

Typically, oral iron is not effective in populations that have an underlying chronic disease that may be impairing absorption of iron from food (or other oral supplements)

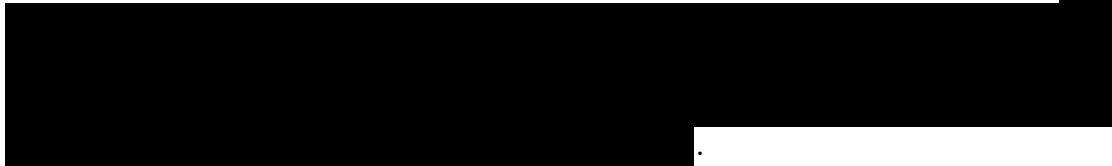
or where the loss is greater than amount that can be replaced or there is a need for a more rapid repletion than can be achieved with oral iron. Diseases that may lead to impaired absorption have resulted in numerous international guidelines being developed to aid in guiding physicians for appropriate correction measures. Examples of where IV iron is recommended include CKD [6], IBD [7] and oncology [8].

Iron Sucrose (IS, Venofer[®]) is an IV iron replacement therapy approved in China. This was first approved in China in 2008 and is used in patients in whom the results following oral administration of iron preparations are not good and who require IV iron therapy. It is recommended that the iron deficit is calculated with the Ganzoni formula [9] and thereafter corrected with individual bolus IV injections/ infusions of up to 200 mg iron administered.

1.2 Summary of Ferric Carboxymaltose Nonclinical and Clinical Data

1.2.1 Pharmacology

Ferric carboxymaltose (FCM, Ferinject[®]) is a polynuclear iron(III)-hydroxide carboxymaltose complex with a molecular weight of about 150,000 Daltons.



1.2.2 Preclinical and Pharmacokinetic Studies

In pharmacokinetic (PK) studies after IV administration in Caucasian subjects, iron provided by FCM was rapidly cleared from the serum and efficiently incorporated into erythrocytes [10]. Iron from FCM was distributed predominantly to the liver, spleen and bone marrow [11]. Non-clinical studies showed that, in the liver, which is a primary site for iron storage, IV administration of FCM resulted in iron localisation predominantly in cells of the reticuloendothelial system (RES), with minor amounts in the parenchyma [12]. The deposition of iron in the RES (phagocytes/monocytes) is preferred as it minimises the potential for iron-induced oxidative damage to the parenchyma, as described in mice with different IV iron preparations [13].

It is to be considered that the findings observed in the various toxicological studies resulted from iron overload in healthy iron-replete animals. Iron accumulation could be seen predominantly in the liver, spleen and kidneys when repeated high doses were administered to rats and dogs. Repeated-dose toxicity studies in rats and dogs indicate that in terms of total iron dose, there is about a 3- to 8-fold safety margin to the human dose based on the no observed adverse effect level.

Data from reproductive and developmental toxicity studies indicate that there is a minimal risk associated with administration of FCM during pregnancy and lactation. Nonclinical studies suggested that there is limited placental or milk transfer of iron

from FCM after maternal exposure to FCM. Therefore, the use of FCM is contraindicated in the first trimester of pregnancy, and the potential risks and benefits should be carefully balanced when considering use of FCM in pregnant women in the second and third trimester, or lactating women.

Ferric carboxymaltose did not demonstrate genotoxic potential in a standard battery of tests.

Ferric carboxymaltose did not exhibit cross reactivity with anti-dextran antibodies in a guinea pig passive cutaneous anaphylaxis model. Administration of a challenge dose of FCM to previously treated rats did not result in a hypersensitivity reaction.

Based on these nonclinical studies, FCM is considered to have a suitable pharmacologic, toxicologic and safety profile for IV dosing in humans for the treatment of ID/IDA.

1.2.3 Efficacy

In general, clinical safety and efficacy studies have been conducted in numerous settings representative of underlying diseases that may lead to ID; i.e., diseases with increased inflammatory status impairing iron absorption as well as diseases with increased losses of iron that cannot be compensated via dietary iron. Single iron doses administered to subjects ranged from 100 mg to 1,000 mg iron, with cumulative iron doses of up to 6,500 mg administered for repletion and maintenance of iron stores. More specifically, studies have been conducted in conditions leading to ID/IDA using distinct populations in nephrology, women's health, gastroenterology, cardiology, and neurology, as well as combinations of various populations. Data of 7,300 subjects treated with FCM in 38 clinical trials have been generated so far. No studies have been performed in healthy volunteers due to the fact that FCM is designed to replenish deficient iron deposits, and as iron cannot be excreted, administration to healthy non-iron deficient volunteers may be toxic.

Across the various clinical studies performed, effective 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 with associated anaemia, correction of ID using FCM has consistently resulted in significant increases in Hb values (correction of anaemia). An increase in Hb values was usually seen within 4 weeks of FCM administration. In addition to the correction of laboratory parameters, iron replacement therapy has demonstrated significant improvements in quality of life and functional and symptomatic status in some patient populations. Of importance, these latter improvements were also seen when FCM was administered to ID subjects without anaemia, with no significant changes (either increase or decrease) to Hb values.

Ferric carboxymaltose first received marketing authorisation in The Netherlands in July 2007, and since then, in over 60 countries worldwide. The total exposure of

patients since the introduction of FCM into the market up to 1 January 2015 corresponds to over 2,179,768 patient years. The total number of adverse drug experience cases reported is considered small with respect to the overall drug exposure. The reports confirm the known adverse event (AE) profile and the positive benefit/risk ratio of FCM.

1.2.4 Safety

Ferric carboxymaltose was well tolerated by study participants. In completed clinical studies, up to 1 January 2015, approximately 50% of the subjects experienced at least one treatment-emergent adverse event (TEAE), and events considered related to treatment occurred in 17.5% of subjects who received FCM. Overall, the most commonly reported adverse drug reactions (ADR) in the FCM group were nausea, headache, dizziness, hypertension, injection/infusion site reactions, hypophosphataemia and flushing. Only 1.7% of subjects had severe TEAEs.

In relation to laboratory parameters recorded in clinical studies, no consistent pattern of clinically meaningful changes requiring intervention have been observed. However, mild and transient changes of liver enzymes, such as aspartate aminotransferase (AST and alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT and alkaline phosphatase (AP, have been reported in some studies.

A transient decrease in blood phosphorus levels was frequently observed. The nadir occurred approximately 2 weeks after dosing and resolved without treatment in most subjects within the follow-up period of up to 12 weeks. Severe hypophosphataemia (i.e., <0.3 mmol/L) was only observed in very few cases, and was of short duration.

A human breast milk excretion sub-study suggests a low toxic potential for infants breastfed by mothers receiving FCM (Study VIT-IV-CL-009). Higher iron levels in breast milk were measured 24 and 48 hours after IV administration of FCM compared with ferrous sulphate, however all levels of iron measured were considerably lower than toxic levels that could result in iron intoxication of the newborn. Transfer of iron from FCM to human milk was $\leq 1\%$. Based on limited data on nursing women, it is unlikely that FCM represents a risk to the nursing child.

The safety profile of FCM in the first trimester of pregnancy has not been demonstrated in a clinical trial. There is, however, a limited amount of data from a recent clinical study (FER-ASAP-2009-01) in which no new safety signals were observed for mother and child after administration of FCM (n=123) for the treatment of IDA in the second and/or third trimester of pregnancy. A careful benefit/risk evaluation is required before FCM use during pregnancy. If the benefit of FCM treatment is judged to outweigh the potential risk to the foetus, it is recommended that treatment be confined to the second and third trimester of pregnancy.

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly. No formal interaction studies have been performed.

Refer to the Investigator's Brochure (IB) for further details.

2. RATIONALE

Ferric carboxymaltose has been developed by Vifor Pharma – Vifor International Inc. as a formulation enabling the application of high iron doses of up to 20 mg/kg body weight as infusion, and as undiluted injection of up to 15 mg/kg body weight. Ferric carboxymaltose has a low immunogenic potential and does not exhibit cross-reactivity to anti-dextran antibodies. The application of high doses of IV iron in 1 single administration with the potential to replenish the iron stores has multiple advantages over multiple smaller doses. Compared to other IV iron products, FCM can be given in a short time (6 minutes instead of 3.5 hours for a 500 mg iron dose) and in iron doses of up to 1,000 mg, which reduced the need for the subject for multiple and long stays at the hospital. This reduces hospital costs [5]. Also, especially in rural regions, a single administration for replenishing the iron stores may help to increase subject compliance, and might make long journeys to the hospital unnecessary. A single administration versus multiple infusions additionally reduces the risks associated with the administration procedure, such as phlebitis, infection, extravasation, of other infusion-related AEs [5].

It has been seen that interethnic variability in PKs of certain drugs can cause unexpected outcomes, such as therapeutic failure, adverse effects, and toxicity in subjects of different ethnic origin, which can be both due to genetic and environmental factors. The International Conference on Harmonisation (ICH) published a guidance to facilitate the registration of drugs among ICH regions (European Union, Japan, the United States), recommending a framework for evaluating the impact of ethnic factors on efficacy and safety of drugs at a particular dosage and dosage regimen. Especially drugs metabolised via the Phase 1 enzymes of the cytochrome group are prone to ethnical and/or genetic variability [14]. Ferric carboxymaltose is not metabolised via cytochrome and constitutes a delivery system for the trace element iron. Based on limited data from Asian subjects who participated in the global registration studies conducted in Europe, genetic or interracial differences are not expected.

According to the “Reform Plan for Chemical Drug Registration Classification ([2016] No. 51)” issued by the China Food and Drug Administration (CFDA) and effective since 04 March 2016, FCM constitutes a Category 5.1 drug, Originators marketed overseas under application for being listed in China. And according to requirement of clinical trials for products that are marketed overseas but not in China (CFDA order 28, Provisions for Drug Registration), a PK study should be conducted together with a 100-pair phase 3 study. This Phase 3 bridging study is designed to assess safety of FCM in the Chinese population, and to show efficacy by demonstrating non-inferiority to IS (Venofer), an IV iron product which is currently available on the Chinese market. A Phase 1, ascending dose study, VIT-IRON-2011-003, will be conducted in parallel to this Phase 3 study. The objective of this study is to evaluate the PK and pharmacodynamics of FCM in Chinese subjects with IDA.

2.1 Design

An efficacy study in Caucasian subjects by Evstatiev et al, 2011 [15] demonstrated that FCM administered using a simplified dosing formula (as proposed in this study) was superior to IS dosed using the Ganzoni formula (at multiple 200 mg iron doses). However, since no data are available on the use of FCM in Chinese patients, a non-inferiority design has been chosen for this study, assuming that FCM treatment is at least as good as IS in Chinese subjects. A randomised design was chosen to reduce bias in baseline differences between the treatment groups.

Due to the differences in posology between the study drug (FCM) and the comparator (IS) additional administrations may be required for subjects receiving IS. In a 65 kg subject with Hb of 9 g/dL at screening, FCM would require 2 individual doses of FCM (1,000 mg iron followed by a single dose of 500 mg iron 1 week later). However, if the same subject was randomised to receive IS, the cumulative dose required (as per label) would be 1,436 mg iron which would require 7 individual 200 mg iron doses (i.e., bi-weekly dosing) starting on Day 1.

Therefore, this study will utilise an open-label design to avoid unnecessary IV placebo injections. This reduces the burden of requiring additional subject visits to both groups (as subjects receiving IS will need more dosing visits than subjects in the FCM group) as well as removing the potential for infection and other side-effects that may result from an IV placebo injection.

IV iron products are designed to deliver, in a controlled way, iron to the body and to replenish iron stores and as a consequence increase Hb concentration. Therefore, the study primary endpoint is the percentage of subjects achieving an increase in Hb \geq 2g/dL (responders) from baseline at any time up to Week 8. Since knowledge of the study drug will not impact this objective parameter, in addition to the fact that all subjects will be receiving IV iron, the open-label design is considered to be the most appropriate design for this study.

2.2 Dose and Drug Selection

Ferric carboxymaltose is an IV iron preparation which, in Europe, is indicated for subjects with ID when oral iron preparations are ineffective or cannot be used. It is a Type 1 iron complex with a low risk of toxicity as Type 1 iron complexes are stable and robust complexes [13]. As such, FCM provides iron for the endogenous iron transport and storage proteins in a controlled manner. This permits FCM to be administered in individual dosing at up to 1,000 mg iron at relatively short time intervals. Moreover, being free of dextran or dextran derivatives, FCM has no risk of dextran-induced immunogenicity. Nevertheless, as with all IV iron preparations, FCM may induce hypersensitivity reactions (see Section 8.1).

The IB summarises data from over 30 completed clinical trials with FCM which supports the administration of doses of up to 1,000 mg per administration, with an approved maximum single dose of 20 mg iron/kg BW.

Traditionally the Ganzoni formula has been used to calculate total iron requirements [9]. However, Evstatiev et al, 2011 [15] have recently demonstrated that FCM dosed using a simplified dosing formula (as proposed in this study) is superior in efficacy to dosing using the Ganzoni formula (using Venofer at multiple 200 mg iron doses). The simplified dosing formula (Table 2) is calculated based on subject BW and Hb. Using this standard formula, the heaviest subjects with low Hb receive the highest cumulative iron doses.

As such, FCM will be administered using this simplified formula for calculating the total iron dose to achieve appropriate repletion of iron requirements.

An IV iron preparation is deemed most appropriate as a comparator arm within this study. Iron Sucrose (Venofer) manufactured by Vifor Pharma is an IV iron preparation available on the Chinese market and was selected as the comparator product. Iron Sucrose has a favourable and well documented safety profile. Alternative products at higher doses are all dextran-based with risk of dextran-induced anaphylactic reactions and other non-dextran based IV irons were less stable than IS and therefore would have required lower maximal single iron doses with an additional visit burden on subjects and participating sites. Additionally, there are numerous studies comparing FCM and IS that confirm the choice as an appropriate comparator. For subjects randomised to the IS arm, dosing (including calculation of the total dose) will be per the approved Chinese label.

2.3 Endpoint and Procedures

2.3.1 Primary Endpoint

As IV iron products are designed to deliver, in a controlled way, iron to the body and to replenish iron stores, and as a consequence increase Hb concentration, the study primary endpoint is the percentage of subjects with an increase in Hb $\geq 2\text{g/dL}$ (responders) from baseline at any time up to Week 8.

The aim is to demonstrate non-inferiority of FCM given in a standardised dosing regimen to the currently approved formulation (IS) given according to the Ganzoni formula with respect to increase in Hb $\geq 2\text{g/dL}$ from baseline at any time up to Week 8. As IS is given in doses of 200 mg iron, it might take longer for the subject to receive the complete iron dose (e.g., 3 weeks with 3 injections per week if 1,800 mg are needed), as compared to FCM. To allow for the control subjects to respond to IV iron treatment, an 8 week study duration is chosen, which is expected to be within 5 weeks after the last treatment received for the majority of the control subjects.

2.3.2 Secondary Endpoints

In addition to demonstrating an increase in Hb ≥ 2 g/dL (responders) from baseline at any time up to Week 8, the study will summarise the absolute and change from baseline of key laboratory parameters, such as Hb, TSAT and serum ferritin as well as the percentage of subjects achieving TSAT ≥ 16 % and serum ferritin ≥ 100 ng/mL (for subjects with underlying inflammation) or serum ferritin > 14 ng/mL (for subjects with no underlying inflammation). This will permit for confirmation of the replenishment of iron stores as well as to document if Hb will increase to values above the normal range and will allow the physician to determine appropriateness of medication.

2.4 Key Inclusion and Exclusion Criteria

The inclusion criteria match the key population where the drug could be utilised. The excluded population reflects known and/or theoretical high-risk populations and/or those with ID due to other causes and are hence excluded from this study.

Due to the wide number of underlying diseases or general population that may suffer from IDA, there are no specific criteria for disease aetiology. However, when including subjects and summarising safety aspects, the underlying disease will be included as a key variable due to the significant impact it may have on serum ferritin levels (inclusion criteria and known to be elevated in subjects with chronic disease) and on the AEs that are reported (as the underlying disease may increase the risk of events including risk of morbidity). Note, all safety events will have physician assessed relationship to study drug recorded to permit distinguishing between events due to disease and those related to drug – with drug related events also presented for the overall population.

Subjects with IDA (defined as Hb < 11 g/dL for females and < 12 g/dL for males, serum ferritin < 100 ng/mL (if subject has concomitant inflammation) or ≤ 14 ng/mL (in non-inflamed subjects), TSAT $< 16\%$, mean corpuscular Hb concentration (MCHC) $< 32\%$, mean corpuscular volume (MCV) < 80 fL, and mean corpuscular Hb (MCH) < 27 pg) will be included. Success of IDA treatment will be assessed by comparing change from baseline in Hb as well as serum ferritin (as marker for iron stores) and TSAT (as marker for circulatory iron pool) between treatment groups. Subjects with hypersensitivity to FCM or any of its excipients, subjects with evidence of iron overload or disturbances in utilisation of iron (i.e. sideroachrestic anaemia) and subjects with anaemia not attributed to ID are excluded as IV iron administration is contraindicated.

3. STUDY OBJECTIVES

3.1 Primary Objective

- To demonstrate the efficacy of FCM given in a simple dosing regimen in correcting IDA, by demonstrating non-inferiority to treatment with the currently approved IV iron therapy of IS (Venofer) in the Chinese population.

3.2 Secondary Objectives

- To assess the safety of FCM compared to IS in the Chinese population.
- To evaluate the effect of FCM compared to IS on relevant laboratory parameters (haematology, chemistry, iron parameters) in the Chinese population.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open-label, randomised controlled study to assess the impact of FCM in correcting IDA compared to Venofer (IS) in Chinese subjects. The study will randomise approximately 368 subjects (184 per group) suffering from different underlying diseases leading to IDA. It is expected that approximately 850 subjects need to be screened to randomise 368 subjects.

After an initial screening period (up to 7 days), eligible subjects will undergo baseline assessments and will be randomised (1:1) to receive either FCM or IS at study Day 1.

In the FCM group, study drug administration will occur on Day 1 and, if needed, on Day 8 and Day 15. Subjects randomised to IS will receive injections/infusions of a maximum of 200 mg iron three times a week until the calculated total iron dose is administered.

All subjects will return for assessment of efficacy and safety at Weeks 2, 4, 6 and 8. The schedule of assessments is provided in Table 1: Schedule of Events.

Randomised subjects who terminate their study participation for any reason regardless of whether the study drug was taken or not, will retain their randomisation number. The next subject will be given the next randomisation number.

The Investigator is responsible for ensuring that consideration is given to the post study care of the subject's medical condition.

4.2 Duration of Subject Participation and Study

The expected duration of subject participation is a maximum of 10 weeks: Screening period duration is up to 1 week; treatment period duration including follow up is 8 weeks (± 4 days).

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Number of Subjects

Approximately 368 subjects will be randomised into this study. It is expected that approximately 850 subjects will need to be screened to achieve 368 randomised subjects. For detailed justification of the sample size please refer to Section 11.2, Sample Size and Power Calculations.

5.2 Inclusion Criteria

Investigators will be expected to maintain a screening log of all potential study candidates that includes minimum key information about the potential candidate, date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or refused to participate). The following inclusion criteria must be met for each subject:

1. At least 18 years of age.
2. Hb < 11 g/dL (females) or <12 g/dL (males) at screening visit
3. Serum ferritin <100 ng/mL for subjects with underlying inflammatory disease (e.g. IBD, CKD or CHF, as determined by high sensitive C-reactive protein (hsCRP) levels above the normal range) otherwise serum ferritin \leq 14 ng/mL in subjects with no apparent underlying inflammatory disease (as determined by hsCRP levels within normal range) at the screening visit
4. TSAT <16% (any subject) at the screening visit.
5. Microcytic, hypochromic anaemia at the screening visit, defined as:
 - a. MCHC < 32%
 - b. MCV < 80 fL
 - c. MCH < 27 pg
6. Subjects with the ability to understand the requirements of the study and abide by the study restrictions, and who agree to return for the required assessments
7. Before any study-specific procedure is conducted, the appropriate written informed consent must be obtained.

5.3 Exclusion Criteria

1. Subject has known hypersensitivity to any of the products to be administered during dosing.
2. Any history of iron storage diseases such as haemochromatosis.

3. Any history or clinical findings of iron utilisation disorders such as sideroachrestic anaemia
4. Known haemoglobinopathies (e.g. thalassaemia).
5. Any history or clinical findings of anaemia associated with:
 - a. Haematuria
 - b. Vitamin B12 or folic acid deficiency that requires treatment (subjects can be included after deficiency is corrected)
6. Any allergic predispositions, i.e. any history of asthma or atopic allergy. This includes drug allergies.
7. Planned surgery with anticipated blood loss (defined as Hb drop >2 g/dL) in the 3 months post-randomisation.
8. Subject has known malignancy (with or without current treatment), except basal cell or squamous cell carcinoma of the skin or cervical intra-epithelial neoplasia.
9. Haemodialysis (current or planned within the next 3 months).
10. History of IV iron therapy, erythropoiesis stimulating agent (ESA therapy and/or blood transfusion in previous 4 weeks prior to baseline, and oral iron or iron-containing products including Chinese herbal medicines (>75 mg iron/day) in the 7 days prior to baseline.
11. Body weight <35 kg.
12. Chronic liver disease and/or screening ALT or AST above 3 times the upper limit of the normal range.
13. Known human immunodeficiency virus infection, acquired immunodeficiency syndrome, tuberculosis.
14. Known active hepatitis B or C or other active infection (acute or chronic).
15. Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(ies), or subject is receiving other investigational agent(s).
16. Subject is pregnant or is breast feeding.

17. Female subject of childbearing potential is not using adequate contraceptive methods during the study and for up to 1 month after the last dose of the study medication. Adequate contraceptive methods are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner. Non-childbearing potential includes being surgically sterilised at least 6 months prior to the study or post-menopausal, defined as amenorrhoea for at least 12 months.
18. Male subjects planning to father a child within 7 days from the last study drug administration.
19. Subject has any kind of disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures and/or other reason(s) that render subject not appropriate for study participation in the opinion of the treating physician.

5.4 Withdrawal of Subjects

5.4.1 Withdrawal of Subjects from Study Drug

Study drug must be stopped if the subject experiences any kind of hypersensitivity reaction related to the study drug during administration. The subject may remain in the study and continue to attend study visits. Whether the subject will receive additional doses of study drug will be discussed with the Medical Monitor and will be decided on a case by case basis.

Subjects may be withdrawn from the study drug if in the opinion of the Medical Monitor or the Investigator there would be a risk to the subject's safety if they received any further dose of study drug. If the subjects are withdrawn from study drug they may remain in the study and continue to attend study visits.

Subjects discontinuing study drug will not be replaced.

5.4.2 Withdrawal of Subjects from Study Visits

Subjects may voluntarily withdraw from study participation at any time without having to provide a reason. Subjects may be withdrawn because of the appearance of a new health condition which may require care or medications prohibited by the protocol, unacceptable AEs, refusal to continue treatment, or at the Investigator's discretion if it is in the subject's best interest.

If a subject withdraws from the study at any time either at his or her request or at the Investigator's discretion, the reason(s), including the primary reason for withdrawal, if provided by the subject, should be recorded. Subjects who discontinue the study prematurely should undergo all End of Study assessments, if possible.

Subjects may be withdrawn by the Investigator and their study participation discontinued prematurely for several reasons. Discontinuation from the study is **mandatory** in the following circumstances:

- The subject requires blood transfusion or ESA treatment (e.g. for excessive acute bleeding) or intake of iron preparations other than the study drug. If possible, discontinuation assessments should take place before transfusion or treatment. The reason for discontinuation and the date must be recorded on the appropriate page of the case report form (CRF). The date on which the procedure actually took place should also be recorded on the CRF.
- Surgery with expected significant blood loss.
- Development of an illness, condition, or procedural complication, which would interfere with the subject's continued participation.
- The Investigator/study physician feels it is medically in the best interest of the subject to discontinue the subject's participation in the study.
- Pregnancy (to be recorded on the specific pregnancy reporting form).

Subjects may be discontinued from the study for the following reasons (reason to be recorded on the appropriate page of the CRF):

- Subject does not comply with study procedures.

Appropriate documentation will be kept for all subjects who are enrolled into the study (i.e., who provide written informed consent). All subjects who discontinue from the study will be strongly encouraged to have all assessments for the End of Study visit (Visit 6) performed.

If a subject refuses to continue in the study, the reason for refusal must be fully documented in the subject's source document and recorded in the study-specific CRF. It is the subject's right to withdraw from the trial without providing a reason. In this case, the source documents and the CRF must document the reason for discontinuation as "withdrawal by subject".

It is essential to obtain follow-up data on any subject withdrawn because of an AE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If a subject is discontinued due to an AE, the event must be followed-up by the investigator through contact with the subject until resolution or stabilisation has occurred. All AEs must be followed-up until resolution, stabilisation or the subject is lost to follow-up and cannot be contacted.

Reasons for discontinuations will be documented in the CRFs. Subjects who discontinue prematurely will not be replaced.

The Sponsor may discontinue the study for any reason at any time. In this case, all subjects, after a final visit, will be withdrawn from the study and study treatment discontinued.

6. RANDOMISATION, BLINDING AND UNBLINDING PROCEDURES

6.1 Randomisation

An Interactive Response Technology (IRT) system will be used in the study. A separate user manual that outlines the details of IRT will be provided to the sites.

All subjects screened must be identifiable throughout the study and will be given a unique study subject number. Each site will be identified by a 3 digit number, and subject numbering will be assigned by IRT. The Investigator will maintain a list of subject numbers and subject names to enable records to be matched at a later date.

Randomisation of eligible subjects will be performed before start of treatment with study drug. Randomisation will be performed based on a pre-defined, computer generated randomisation list. The subjects will be randomised 1:1 to receive either FCM administration(s) or IS. IRT will be contacted for treatment assignment following confirmation of eligibility at the Baseline visit.

6.2 Blinding

Due to the differences in posology between the study drug (FCM) and the comparator (IS) more injections/infusions may be required for subjects receiving IS.

Therefore, the study will utilise an open-label design to avoid unnecessary IV placebo injections/infusions. This reduces the burden of requiring additional subject visits to both groups as well as removing potential infections and other side-effects that may result from a placebo IV injection/infusion.

6.3 Unblinding

As this is an open-label study, unblinding procedures are not applicable.

7. STUDY TREATMENTS

7.1 Dosage Forms/Formulation

All investigational medicinal products used in this study have been manufactured in accordance with current Good Manufacturing Practice (GMP).

7.1.1 Ferric Carboxymaltose

Ferric carboxymaltose will be provided by Vifor Pharma – Vifor (International) Inc. for this study.

Strength:	Sterile FCM solution as a 5% w/v iron solution in water for injection.
Excipients:	
Appearance:	Dark brown, non-transparent aqueous solution.
Dosage Form:	10 mL vials containing 500 mg iron per vial.
Manufacturer:	Vifor Pharma – Vifor (International) Inc., Switzerland.
Storage:	
Note:	For drip infusions, FCM must be diluted only in sterile 0.9% sodium chloride solution.

7.1.2 Iron Sucrose

Iron Sucrose (Venofer) will be provided by Vifor Pharma – Vifor (International) Inc. for this study.

Strength:	Sterile solution for injection containing 2% w/v iron. 1 mL of Venofer contains 20 mg of iron.
Excipients:	Water for injection, sodium hydroxide (for pH adjustment).
Appearance:	Dark brown, non-transparent aqueous solution.
Dosage Form:	5 mL ampoules containing 100 mg iron per ampoule.
Manufacturer:	Vifor Pharma – Vifor (International) Inc., Switzerland.
Storage:	Store between 4°C and 25°C. Do not freeze.

7.2 Drug Dosage and Administration

7.2.1 Arm A: Ferric Carboxymaltose

Study drug should be administered in doses based on subject BW and Hb value at screening as per Table 2.

Subjects will receive study drug as undiluted injection or infusion. The individual dose requirement (in mg of iron) per visit is described below:

Table 2: FCM Dosing Schedule

	Total Iron (mg) as FCM				
	BW 35 - <70 kg ¹		BW ≥70 kg		
	Hb <10 g/dL	Hb ≥10- <14 g/dL	Hb <10 g/dL	Hb ≥10- <14 g/dL	
Day 1	1,000 mg	1,000 mg	1,000 mg	1,000 mg	
Day 8	500 mg	No dose	1,000 mg	500 mg	

Notes: BW = Body weight; FCM = Ferric carboxymaltose; Hb = Haemoglobin.

1. The maximum single dose that should be given to a subject is 20 mg/kg BW, therefore for subjects with BW 35 - <50kg and Hb ≥ 10 g/dL, the 1,000 mg dose should be split into 2 x 500 mg (one 500 mg dose on Day 1 and one 500 mg dose on Day 8. Subjects with BW 35 - <50 kg and Hb < 10g/dL should receive 3 doses of 500 mg (on Day 1, 8 and 15).

For IV injection, the required amount of FCM solution will be drawn from the vial into a syringe and injected as an undiluted solution.

For drip infusion, FCM solution must be diluted only in sterile 0.9% m/V sodium chloride solution (500 mg iron diluted in 100 mL 0.9% w/v physiological saline, for a total volume of 110 ml or 1,000 mg iron diluted in 250 mL 0.9% w/v physiological saline, for a total volume of 270 ml). For stability reasons, dilutions to concentrations less than 2 mg iron/mL are not permitted.

From a microbial point of view, FCM preparations for parenteral administration must be used immediately after dilution with sterile 0.9% m/V sodium chloride solution.

For both injection and infusion, FCM should be administered up to a maximum single dose of 1,000 mg iron (up to a maximum of 20 mg/kg BW) over at least 5 minutes for the 500 mg dose and over at least 15 min for the 1,000 mg dose. Administration time should not exceed 30 minutes for either the 500 or the 1,000 mg dose.

7.2.2 Arm B: Iron Sucrose

For subjects in the individually calculated IS dosage regimen group, the individual iron deficit will be calculated using the formula of Ganzoni [9]:

Cumulative iron deficit [mg] =

$$BW [kg] \times (\text{target Hb}^{(1)} - \text{actual Hb}) [g/dL]^{(2)} \times 2.4^{(3)} + 500 \text{ mg}^{(4)}$$

⁽¹⁾ Target Hb for BW >35 kg = 15 g/dL, respectively 9.3 mmol/L

⁽²⁾ To convert mmol/L to g/dL: multiply Hb (mmol/L) by the factor 1.61145

⁽³⁾ Factor 2.4 = 0.0034 (iron content Hb = 0.34%) x 0.07 (blood volume = 7% of BW) x 10,000 (conversion g/dL to mg/L)

⁽⁴⁾ Iron storage depot

Note: BW = Body weight.

The calculated cumulative IS dose is to be rounded up or down to the nearest 200 mg.

Subjects will receive single doses of IS of up to a maximum single dose of 200mg iron three times a week. Depending on the calculated iron deficit, up to 11 IS injections will be given.

Iron Sucrose (Venofer) will be administered by slow IV push injection at a rate of 1 ml undiluted solution per minute (10 ml of the product in at least 10 minutes; administration time should not exceed 60 minutes) or by drip infusion in a dilution of 1 ml of Venofer in maximum 20 ml 0.9% w/v physiological saline (10 ml of the product in maximum 200 ml saline). Venofer must be used immediately after dilution. The drip infusion rate should be 200 ml solution in at least 30 minutes, and should not exceed 60 minutes.

7.2.3 IV Administration of Drug (Both Arms)

Study personnel responsible for study drug application will apply a tourniquet, seek a suitable vein, disinfect injection site and perform the vein puncture. It is recommended to use a blue catheter 22 gauge (or pink catheter 20 gauge) and secure it with duct tape. The use of blue butterfly needle is possible.

After the puncture, the correct position of the needle can be reviewed in the vein by flushing with 10 mL NaCl 0.9%. Connect the syringe or infusion set to the needle and slowly inject or infuse the FCM (see Section 7.2.1, Arm A: Ferric Carboxymaltose) or IS (see Section 7.2.2, Arm B: Iron Sucrose). The vein should then be flushed with 5-10 mL saline.

Study medication should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. Each subject should be observed for adverse effects during and for at least 30 minutes following each injection. Hospitalisation for study drug administration is not a requirement of the study. However, Investigators might choose to hospitalise subjects while they receive study drug as a precautionary measure. Hospitalisation for this purpose does not fulfil the criteria of a serious adverse event (SAE) and will not be recorded as such. If an AE/SAE occurs before, during or after administration of study drug during

hospitalisation, this shall be assessed and recorded as per seriousness criteria for AE/SAEs.

Since FCM has a physiological pH, pain at the injection site is very unlikely, therefore caution should be given to avoid paravenous injections. The choice of an appropriate needle for the IV access should minimise the potential risk of a paravenous injection of FCM or IS. Iron Sucrose has a basic pH and therefore, if paravenous leakage occurs, a burning sensation is felt by the subject.

Treatment administration of FCM or IS must be discontinued immediately if swelling (paravenous injection) is observed, which can cause irritation and a brown discolouration of the skin which can be long-lasting. No rinsing or pressure bandage should be used, in order to prevent distribution and extension of extravasations. Study treatment can be re-administered in a different location (i.e. other arm).

7.3 Package and Labelling

Both FCM and IS will be supplied to each site already packaged and labelled. All packaging and labelling operations will be performed according to GMP and Good Clinical Practice (GCP) guidelines. Labelling will be in accordance with local study site regulations for investigational products. Ferric carboxymaltose will be packaged in kits containing 1 labelled FCM vial (500 mg per 10 ml). Venofer will be packaged in kits containing 2 ampoules of Venofer (100 mg per 5 ml). Kits will be numbered for tracking purposes. The kit box as well as the vial/ampoule in the kit box will be labelled with the same kit number.

7.4 Study Treatment Allocation

Each eligible subject will be assigned to 1 of the treatment arms using IRT.

7.5 Site Supply, Storage, Accountability

7.5.1 Site Supply

Once a site has been approved to receive study drug, the site will be supplied with an initial stock of study drug. The need for drug resupply will be assessed on a regular basis taking into account the number of subjects enrolled, and the number of subjects in screening, at the site.

7.5.2 Storage



Use of a calibrated thermometer and maintenance of a temperature log is mandatory. The log should be updated by site personnel at least once weekly with the minimum and maximum temperatures for the week being recorded. This log must be available for review by the Monitor during on-site monitoring visits. Should the storage

temperature be outside the range, the medication must be quarantined immediately and the Sponsor must be contacted for guidance.

7.5.3 Accountability

The Investigator at each site is responsible for study drug supplies. The Investigator will ensure that adequate records of the receipt, preparation, administration and return of the study drug are kept and that the study drug is used only for subjects enrolled in the study. All data regarding the study drug must be recorded on the relevant forms provided.

Each study site will maintain a drug inventory/dispensing record for all drugs dispensed and returned. At the end of the study, 1 copy of the drug inventory/dispensing record should be sent to the Sponsor for the central study file. The original will be kept in the site files.

After completion of the study, or if it is prematurely terminated, all materials will be returned to the Sponsor. If the study medication is destroyed at site, the Investigator will forward the certificate of destruction to the Sponsor. The decision to destroy study medication at site must be made by the Sponsor.

7.6 Drug Dose Modification

If extravasation is noted during administration of FCM or IS, dosing should be ceased immediately. Study drug administration may be completed using a different injection site to complete the required dosage. If it is not possible to administer the full dose to a subject, the amount of actual dose administered must be documented on the relevant page of the CRF.

In case of severe anaemia (Hb <6 g/dL), the subject is to be discontinued from the study. Further management of anaemia is at the Investigator's discretion.

7.6.1 Procedures for Overdose

If an inadvertent overdosing of a subject (e.g., by a calculation error of the required iron dose) is detected, this must be reported as an AE (see Section 10, Evaluation, Recording and Reporting of AEs and SAEs).

Post-baseline iron parameters will be assessed at each visit using the central laboratory. In the case of iron accumulation the Investigator at the site will initiate corrective measures according to local guidelines for treatment of iron overload, if necessary.

7.7 Prohibited Therapy and Concomitant Treatment

Prohibited therapies in this study will include the following drugs:

- Oral or other IV iron therapy (other than the study medication). Note: Ongoing use of multivitamins or nutritional supplements containing iron are permitted when doses are lower than 75 mg per day. If the dose of iron in these products is unknown, they should not be administered during the study.
- ESAs
- Blood transfusions

Note: Blood transfusions and ESAs might be used as rescue medication if the subject requires such treatment for symptomatic anaemia therapy. In this case, the subject must be withdrawn from the study and end of study procedures must be completed before transfusion or treatment. The reason for discontinuation and the date must be recorded on the appropriate page of the CRF. The date on which the procedure actually took place must also be recorded in the CRF.

If symptoms of acute iron intoxication occur, treatment will be according to standard medical practice, e.g. consider the use of an iron chelator such as deferoxamine mesylate.

In case of hypersensitivity reactions (including anaphylactoid reactions) or signs of intolerance, an appropriate therapy will be started according to the Investigator's judgement.

Any concomitant treatment given for any reason during the course of the study must be recorded on the CRF and in the subject's medical records, including dosage, start and stop dates and reason for use.

8. RISKS/PRECAUTIONS

8.1 IV irons

Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be fatal. Therefore, facilities for cardiopulmonary resuscitation must be available. If allergic reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Hypersensitivity reactions have also been reported after previously uneventful doses of any parenteral iron complexes, including FCM and IS. Each subject should be observed for adverse effects during and for at least 30 minutes following each study drug (FCM or IS) application.

In subjects with liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Parenteral iron administration should be avoided in subjects with hepatic dysfunction where iron overload is a precipitating factor, in particular porphyria cutanea tarda. Careful monitoring of iron status is recommended to avoid iron overload.

Parenteral iron must be used with caution in cases of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FCM or Venofer be stopped in subjects with ongoing bacteraemia. In subjects with chronic infection, a benefit/risk evaluation has to be performed, taking into account the suppression of erythropoiesis (due to chronic infection).

Paravenous leakage must be avoided because leakage of FCM or IS solution at the injection/infusion site may lead to irritation of the skin and potentially long-lasting, brown discolouration at the site of injection/infusion. In the event of paravenous leakage, administration of FCM or IS must be stopped immediately. Study treatment may be re-administered in a different location (i.e. other arm), but extra care needs to be taken to make sure that paravenous leakage does not occur again. This also needs to be clearly documented in the CRF and the source data. If a subject did not receive the full dose, this also needs to be recorded.

8.2 Ferric Carboxymaltose

One mL of undiluted FCM solution contains up to 5.5 mg (0.24 mmol) of sodium. This has to be taken into account in subjects on a sodium-controlled diet.

To date, over 7,300 subjects have received FCM in completed clinical studies. The most commonly reported ADRs that have occurred in 1% to 10% of subjects were headache, dizziness, hypertension, nausea, injection/infusion site reactions, flushing and hypophosphataemia. No reported ADRs were very common ($\geq 10\%$).

Please refer to the latest version of the IB for a full list and description of risks and precautions.

8.3 Iron Sucrose

Subjects administered IS commonly (between 1% and 10%) experience dysgeusia, hypertension, hypotension, nausea, injection/infusion site pain.

Hypotensive episodes following administration of IS have been reported and will be caused if injection/infusion is administered too rapidly. For further details on risks and precautions, please refer to the currently approved Insert Sheet for China.

9. STUDY PROCEDURES

9.1 Description of Study Assessments

9.1.1 Vital Signs

To be performed per Table 1: Schedule of Events. Body temperature, resting blood pressure (systolic and diastolic) and heart rate will be measured with the subject in a sitting position.

9.1.2 Physical Examination

To be performed per Table 1: Schedule of Events.

A full physical examination will be performed at screening and End of Study/ Early Withdrawal visit. Any clinically significant abnormalities occurring before signature of informed consent should be recorded on the medical history page of the CRF and any clinically significant abnormalities occurring or worsening after signature of informed consent should be recorded on the AE page.

9.1.3 Laboratory Parameters

All blood samples (total blood volume approximately 46ml) will be analysed at a central laboratory, Teddy Clinical Research laboratory,
3rd floor, Building 12
Xiangyin Road No 128
Yangpu District
Shanghai 200433
China.

Blood for clinical chemistry and haematology does not have to be drawn under fasting conditions.

Haematology parameters to be analysed are Hb, haematocrit, red blood cell count, MCV, MCH, MCHC, reticulocyte count, Hb content of reticulocytes, white blood cell count with differential (absolute and percentage) and platelet count.

Iron status parameters include serum iron, serum ferritin, serum transferrin, UIBC and TSAT.

Clinical chemistry parameters to be analysed are electrolyte status (sodium, potassium, magnesium, calcium, chloride, phosphorus), glucose, AST, ALT, GGT, AP, lactate dehydrogenase and hsCRP.

Blood for safety laboratory assessments will be collected at screening, baseline, Weeks 2, 4, 6 and 8. Blood samples must always be collected prior to study drug administration.

A serum pregnancy test (for women of childbearing potential only) will be performed at screening and End of Study visit.

9.1.4 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed locally at each participating site at screening, Week 4 and End of Study visit/Early Withdrawal. Heart rate, QT, QTcF, RR interval, QRS complex duration and PR interval values will be assessed. Absolute and change from baseline data will be analysed for interval data, any clinically significant abnormal findings will be recorded in the source documents and as an AE in the CRF. QT and QTc will be analysed in accordance with ICH E14 guidance [16].

The 12-lead ECGs will be recorded and assessed according to local clinical practice. All original ECG traces must be stored in the subject's medical record as source documents. In cases where thermal paper will be used for ECG traces an ECG copy on permanent paper must be produced and also stored in the subject's medical record.

9.1.5 Urinalysis

A urine sample will be collected during the study visits as per Table 1: Schedule of Events, and analysed in the central laboratory to measure urine phosphate, protein, glucose, bilirubin, pH, nitrite, ketone, urobilinogen, blood, leukocytes.

9.2 Schedule of Assessments

For detailed schedule of assessments (including all protocol required assessments, visits and visit windows) please refer to Table 1: Schedule of Events.

9.2.1 Screening and Baseline Procedures

After signing the informed consent and within 7 days prior to the initial treatment administration, relevant demographic (including age, sex and race), key information on IDA (including underlying cause for IDA and date of diagnosis, and previous treatments), and baseline medical history data, including concomitant medications will be collected. Study procedures will be performed per

Table 1: Schedule of Events, to assess subject eligibility for the study.

Consent must be received prior to any procedure completed only for the study and before randomisation or administration of study drug.

Screening laboratory values will be used to assess for subject eligibility (including serum pregnancy tests for females at screening) on relevant blood parameters. Laboratory assessments will be repeated at the baseline visit but not assessed to confirm eligibility criteria.

Eligible subjects will be randomised at the baseline visit to one of the two treatment arm.

Subjects failing to meet eligibility will be considered screen failures and will discontinue study participation. Subjects may be re-screened once. Any subject that is rescreened must have all tests and procedures completed to permit inclusion into the study (i.e., all screening tests and procedures must be completed as per the Schedule of Events with the exception of any inclusion criteria, exclusion criteria and procedures that can use historical results. In case of re-screening, documented informed consent must be obtained again, and the date of informed consent must be a minimum of 4 weeks after the date when the subject was declared a screen failure. The subject will keep their unique subject number.

9.2.2 Treatment Procedures

Subjects randomised to receive FCM will receive the first administration of FCM at baseline (Day 1), and the second and third dose at Day 8 and Day 15, if needed according to the dosing matrix (see Table 2, Section 7.2.1, Arm A: Ferric Carboxymaltose).

Subjects randomised to IS will have their iron deficit calculated according to the Ganzoni formula (see Section 7.2.2, Arm B: Iron Sucrose). The doses will be split into injections of 200 mg iron and administered three times a week until the calculated dose has been given to the subject. The cumulative Venofer dose is to be rounded up or down to the nearest 200 mg. During these dosing visits, no additional data will be collected or procedures performed, except for ongoing information on AEs or change in concomitant medications, including dose. Note: Application of IS and FCM at any visit should be done after all assessments as per Schedule of Event, Table 1, especially blood draw for laboratory assessments, have been performed.

For both treatment groups, time of start and end of administration (including any interruptions) and volume administered (i.e. incomplete dose including reason) must be recorded.

During post-baseline visits at 2, 4 and 6 weeks (± 3 days), the following assessments will be performed:

- Vital signs
- Laboratory assessments (haematology, chemistry, iron parameters, urinalysis)
- AEs and concomitant medications
- ECG (only Week 4)

See

Table 1: Schedule of Events for full details of protocol required procedures and applicable visits (and timings).

9.2.3 End of Study (or Early Discontinuation) Procedures

On completion of the study (i.e., last study visit – Week 8 \pm 4 days), or if subject is discontinued/withdrawn early, all assessments for Week 8 per

Table 1: Schedule of Events should be performed. This includes the following:

- Physical Examination + BW
- Vital signs
- ECG
- Laboratory assessments (haematology, chemistry, iron parameters, urinalysis)
- Pregnancy test (for women of childbearing potential only)
- AEs and concomitant medications

9.2.4 Unscheduled Visits

Subjects may be seen at the out-patient clinic for a medical reason related to the VIT-IRON-2011-004 study outside the scheduled visits defined by the protocol. Data collected during such visits must be recorded on the Unscheduled Visit eCRFs designed for this purpose. If the reason for performing an extra visit constitutes a (serious) AE, this information must be documented on the AE pages of the CRF (see Section 10).

10. EVALUATION, RECORDING AND REPORTING OF AEs AND SAEs

10.1 Definitions

10.1.1 Reference Safety Information

The reference safety information (RSI) is a document covering information relating to safety, indications, dosing, pharmacology, warnings, precautions, contraindications and other information concerning the product. As a minimum, it contains the Company Core Safety Information, which consists of the information on contraindications, warnings and precautions, use in special populations, undesirable effects and overdose from the Company Core Data Sheet. For this study, the current version of the IB is considered the RSI for FCM and for Venofer the Chinese SmPC is considered the RSI.

10.1.2 Adverse Event

Any untoward medical occurrence in a subject 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.

10.1.3 Adverse Drug Reaction

In the pre-approval clinical experience with a new medical 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 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.

10.1.4 Unexpected AE/ADR

An AE/ADR, the nature (i.e., specificity/seriousness/outcome/frequency) or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational product, or package insert/SmPC for an approved product). Reports which add significant information on the specificity, increase in the rate of occurrence, or severity of a known, already documented adverse reaction also constitute unexpected events.

10.1.5 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening (the term “life-threatening” in the definition of “serious” refers to an event in which the subject 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 was more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation (unless elective surgery (a planned, non-emergency medical procedure)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (i.e., medically significant)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Conversely, some hospitalisations, particularly those which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not automatically be classed as SAEs. In addition, hospitalisation for the purpose of study drug administration, should not be recorded as an SAE.

Any worsening of a pre-existing medical condition or any new medical condition that meets the above SAE criteria should be considered as an SAE.

Any suspected transmission of any infectious agent via a medicinal product should be considered as an important medical event (i.e., medically significant) and therefore documented as an SAE.

The Investigator is encouraged to discuss with the CRO/Sponsor any AEs for which the issue of seriousness is unclear or questionable.

10.1.6 Suspected Unexpected Serious Adverse Reaction

Any ADR that is both serious and unexpected (per the RSI) that, based on the opinion of the Investigator or Sponsor, is felt to have a reasonable suspected causal relationship to a medicinal product.

10.1.7 Special Situations

The following are defined as special situations:

- Exposure of a medicinal product during pregnancy
- Medication error: any unintentional error in the prescribing, dispensing or administration of a medicinal product during the study
- Medication overdose: the administration of a quantity of study medication given per administration or per day which is above the protocol maximum permitted dose
- Occupational exposure: An exposure to a medicinal product for human use as a result of one's professional or non-professional occupation
- Drug interaction
- Unexpected therapeutic or clinical benefit from product use

Suspected adverse reactions associated with medication errors of the investigational medicinal product or use outside that foreseen in the protocol (e.g., overdose) are also considered as ADRs. Any special situation occurring with/without ADR/AE shall be recorded in the study specific documentation.

10.2 Adverse Event Descriptors

10.2.1 Intensity/Severity Categorisation

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); however the event itself may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

In general, the intensity of a particular AE to be recorded is the worst intensity experienced by the subject during the course of the event. The medical assessment of intensity will be determined by using the following definitions:

- Mild: The AE is easily tolerated and does not interfere with usual activity.
- Moderate: The AE interferes with daily activity, but the subject is still able to function.
- Severe: The AE is incapacitating and the subject is unable to work or complete usual activity.

10.2.2 Causal Relationship Categorisation

An Investigator who is qualified in medicine must make the determination of relationship to investigational product for each AE and SAE. The Investigator should decide whether, in his or her medical judgement, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE/SAE should be classified as unrelated. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a cause-and-effect relationship between the investigational product and the occurrence of the AE/SAE, then the AE/SAE should be considered as certainly, probably/likely, or possibly related. For SAEs, the Investigator must provide a brief comment explaining the rationale of his/her assessment of causal relationship on the SAE reporting form.

The following additional guidance may be helpful:

Term	Relationship	Definition
Certain	Yes	<ul style="list-style-type: none"> Event or laboratory test abnormality, with plausible time relationship to drug intake Cannot be explained by disease or other drugs Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) Rechallenge satisfactory, if necessary
		<ul style="list-style-type: none"> Event or laboratory test abnormality, with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required

Possible	Yes	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake
		<ul style="list-style-type: none"> • Could also be explained by disease or other drugs
		<ul style="list-style-type: none"> • Information on drug withdrawal may be lacking or unclear
Unrelated	No	<ul style="list-style-type: none"> • Event or laboratory test abnormality which is clearly related to circumstances not connected with the drug intake.

If the causal relationship between an AE/SAE and the investigational product is determined to be ‘certainly, probably/likely or possibly related’ , the event will be considered to be related to investigational product for the purposes of expedited regulatory reporting. In circumstances where the Investigator is not providing his/her assessment about the relationship, the event will be considered as “related” and qualify for expedited regulatory reporting.

10.2.3 Outcome Categorisation

Outcome may be classified as recovered/resolved (i.e., without sequelae), recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal or unknown. If the outcome is reported as recovered/resolved with sequelae, the Investigator should specify the kind of sequelae on the AE/SAE form. If the outcome of an AE/SAE is reported as unknown, the Investigator should specify (on the AE/SAE form) the rationale why unknown was selected.

10.2.4 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study (such as IDA or the underlying cause for IDA (i.e. heavy menstrual bleeding or IBD)). Such conditions should be recorded on the medical history CRF page. A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE CRF page, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”, “worsening of back pain”).

10.2.5 Signs and Symptoms of the Disease Under Study

Signs or symptoms of IDA and the underlying disease (e.g., heavy uterine bleeding (HUB), CKD) should not be classed as AEs as long as they are within the normal day-to-day fluctuation of the disease. If a sign or symptom of the disease has unexpectedly worsened in severity or frequency or changed in nature at any time during the study, the symptoms and signs should be recorded as AEs, and clearly marked as worsening of the signs or symptoms in the CRF.

10.2.6 Clinical Laboratory Evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically significant and clinically relevant or if, during treatment with the

investigational product, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are pathological laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter is clinically significant and clinically relevant and therefore represents an AE. If the Investigator considers such an AE as serious (e.g., medically significant event fulfilling criteria as per Section 10.1.5, Serious Adverse Event) it must be reported as an SAE.

Iron parameters such as serum iron, TSAT, UIBC, serum ferritin, serum transferrin, Hb, and reticulocytes are expected to be out of range after administration of IV iron products, and will therefore not be considered as AEs. They can be classed as clinically significant but are usually not clinically relevant and therefore are not reported as AEs.

If a laboratory abnormality meeting the above criteria is a sign of a disease or syndrome only the diagnosis should be recorded in the CRF.

If a laboratory abnormality meeting the above criteria is not a sign of a disease or syndrome, the abnormality itself should be recorded in the CRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., “elevated potassium,” as opposed to “abnormal potassium”).

If the laboratory abnormality can be characterised by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, hyperkalaemia or hypoglycaemia. Observations of the same laboratory abnormality from visit to visit should not be repeatedly recorded in the CRF, unless the aetiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

At the end of the study period all pathological laboratory findings/values diagnosed throughout the treatment period should be reviewed by the Investigator to provide a final clinical assessment in view of the dynamic of laboratory changes/abnormalities.

10.2.7 Special Situations

All special situations (Section 10.1.7) have to be documented in the subject's CRF as well as on the form "Documentation of Special Situations". If any overdose, and medication errors leads to any event that fulfils any seriousness criteria (see Section 10.1.5, Serious Adverse Event), the event has to be reported as an SAE.

10.3 Reporting Procedure for AEs, SAEs, Special Situations and Pregnancy

10.3.1 Adverse Events

All AEs either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to a direct question, will be noted in the AE section of the subject's CRF and source document. This applies to all AEs regardless of presumed relationship to the study treatment, and to the investigational product as well as AEs that occurred before randomisation. Adverse events leading to discontinuation of study treatment should also be collected.

If any AE is reported, the date of onset and time (only for AEs that start on dosing days), relationship to study medication or treatment, any action taken, date of resolution (or the fact that it is still continuing or has become chronic), outcome, intensity (worst at any point during the event) and whether the AE is serious or not at any time during the event will be recorded. In order to establish the duration of any SAE, the dates of hospitalisation and discharge or dates of meeting other SAE criteria will be recorded.

Where possible, the Investigator should report a diagnosis rather than signs and symptoms or abnormal laboratory values. However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis. The Investigator should use standard medical terminology/concepts; avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in each event field in the CRF.

The AE reporting period begins at the time the ICF is signed by the subject. The AE reporting period ends at the End of Study visit (Week 8 \pm 4 days). Adverse events that extend continuously, without resolution, between trial assessments should only be recorded once in the CRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens.

Adverse events that resolve and subsequently recur should have each recurrence recorded separately in the CRF.

Adverse events persisting at the time of study completion will be followed by the Investigator through contact with the subject until resolution or stabilisation or the subject is lost to follow-up and cannot be contacted. The outcome must be documented in the subject's source documents.

If the subject reports an AE, it is the Investigator's responsibility to acquire sufficient information in order to assess causality. This may require additional laboratory testing, physical examinations, telephone contacts, etc.

In order to avoid bias in eliciting AEs, subjects should be asked a non-leading question, such as "How are you feeling?" It is also important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. This information should be collected prior to completion of assessments at all study visits. In addition, any symptoms/conditions reported during assessments and deemed to be clinically significant by the Investigator will be assessed as AEs.

10.3.2 Serious Adverse Events and Special Situations

The occurrence of any SAE must be reported immediately (i.e., within 24 hours of awareness) to Vifor Pharma (or its delegate; e.g., contract research organisation (CRO)) by email, facsimile (fax) or telephone. In addition, SAEs must also be reported to CFDA, ECs, Province and Municipality.

A safety contact sheet will be provided by the Sponsor to the Investigator (prior to first subject providing informed consent) detailing all applicable contact information. This will be kept up to date with any changes being provided to the Investigator immediately.

Full contact details to report SAEs will be provided in the study-specific documents (SAE Processing and Reporting Plan). The SAE must be reported to Vifor Pharma (or Tigermed) using the Vifor Pharma SAE reporting form provided by Vifor Pharma and at the same time the CFDA form for SAE reporting to the concerned authorities. The Investigator must complete, sign and date the SAE pages, and verify the accuracy of the information recorded on the SAE pages with the corresponding source documents. The Vifor Pharma SAE reporting form must be completed in capital letters, in medical terms, in English and to the best extent possible given the time constraints.

Where possible, the Investigator should report a diagnosis rather than signs and symptoms. Death should be considered an outcome and not a distinct event. In case of a fatal outcome, the Investigator should provide a working diagnosis (event which caused outcome, e.g., death due to fatal myocardial infarction) instead of reporting only death; and an autopsy report should be provided where possible. If the cause of death later becomes available (e.g., after autopsy), this working diagnosis should be replaced by the established cause of death.

Where the SAE reporting form cannot be transmitted due to technical problems, the Investigator must inform the CRO/Vifor Pharma about the SAE by phone. As soon as technical problems are resolved, the Investigator will send a copy of the SAE reporting form to the CRO/Vifor Pharma.

All SAEs (regardless of the causal relationship), from the time the informed consent is signed until 30 days following the End of study/Early Withdrawal visit, as well as any medication given/taken for these events, must be reported in the CRF.

No formal study visit is required but the Investigator must report any SAEs that occur during this period using the SAE form. SAEs starting before first administration of study drug must be identified as such on the CRF and source documentation. The onset date of the AE is defined as the onset of signs and symptoms or a change in baseline. The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious, i.e., met at least 1 of the ICH criteria for serious (see section 10.1.5). The resolution date of the SAE is defined as when the symptoms resolve, or the event is considered chronic (e.g., sequelae) or stable, and/or if the seriousness criteria are no longer applicable. Serious adverse events that are ongoing events at the time of death are considered unresolved. All recorded SAEs, regardless of relationship to investigational product, will be followed up until resolution, stabilisation, or the subject is lost to follow-up and cannot be contacted. No further updates should be entered into the CRF after the completion of the final follow-up visit, but should be notified to the CRO/Vifor Pharma using the Vifor Pharma SAE form. In circumstances where the Investigator is unable to make contact with the subject, the Investigator must provide a written statement (recorded in the subject's source documents) to the CRO/Vifor Pharma, confirming that the subject is lost to follow-up.

Any SAE considered to have a causal relationship (i.e., “certainly, probably/likely, possibly” related) to the investigational product and discovered by the Investigator at any time after the study should be reported. A rationale for the assessment of a causal relationship must be provided by the Investigator together with the Vifor Pharma SAE reporting form. Any safety information that is obtained after clinical database lock will be documented only in the safety database and implications for handling the data in the clinical database assessed on an individual basis.

A death occurring during the study or which comes to the attention of the Investigator within 30 days after the End of Study visit/Early Withdrawal visit, whether considered treatment-related or not, must be reported to the CRO/Vifor Pharma using the Vifor Pharma and the CFDA SAE reporting forms. Preliminary reports will be followed by detailed descriptions which will include copies of hospital case reports, autopsy reports/certificates and other documents when requested and applicable.

The occurrence of any special situation (see Section 10.2.7) at the investigational site must be documented by completing the form “Documentation of Special Situations”.

This must be reported by the investigator to the CRO/Vifor Pharma within 5 working days after awareness, if the special situation does not fulfil a SAE criterion, and within 24 hours if after awareness if it does fulfil a SAE criterion.

NOTE: Drug exposure during pregnancy always has to be reported within 24 hours after awareness (Section 10.3.3).

Contact information for reporting of SAEs/Special Situation Reports:

Pharmacovigilance Officer
Hangzhou Tigermed Consulting Co. Ltd.
Room 813, 999 West Zhongshan Road,
Shanghai, 200051
P.R. China

24-hour SAE reporting fax: +86-21-33275864
Email: PV@tigermed.net

The detailed SAE reporting procedures will be provided to the investigators in the study documentation (SAE Processing and Reporting Plan).

At a minimum the following should be provided at the time of the initial SAE report:

- Study name and/or number
- Subject number, year of birth and gender/sex
- Event description (including onset date of the event, outcome and reason for it being considered serious)
- Relationship to investigational product (i.e., causality)
- Name of the investigational product (including drug dose and administration dates)
- Investigator name and address
- Name of the reporter (including site name or number and country), and
- Dated signature of the Investigator or Sub-/Co-investigator.

Additional follow-up information, if required or available, must be faxed immediately (within 24 hours of awareness) following Investigator (or site) awareness of the information. The follow-up information must be completed on a Vifor Pharma SAE reporting form (marked follow-up) and placed with the original in the appropriate section of the study file.

The Investigator is encouraged to discuss with CRO/Sponsor any AEs for which the issue of seriousness is unclear or questionable.

Vifor Pharma, or its delegate, is responsible for expedited reporting to the relevant Regulatory Authorities, to Investigators and to local and central Institutional Review Board (IRB)/Ethics Committee (EC)/Independent Ethics Committee (IEC) as per local regulations.

Additional details regarding SAE reporting is available in the document “SAE Processing and Reporting Plan.

10.3.2.1 Elective Surgery/Routine Examination

Elective surgery (a planned, non-emergency medical procedure) and in-patient routine examination for a pre-existing condition (i.e., recorded in the medical history) do not qualify as SAEs as long as the procedure was not performed as a result of a worsening of the condition. In addition, hospitalisation for the purpose of study drug administration should not be recorded as an SAE. However, AEs which occur during the (elective) hospitalisation will need to be collected and reported.

10.3.3 Pregnancy

The safety of study treatment in pregnant women needs to be monitored once study treatment has been administered to them (as per protocol, pregnancy is an exclusion criteria). Therefore, the outcome of all such pregnancies (including normal births) must be followed up and documented, even if the subject was withdrawn from the study.

Women of childbearing potential should have a negative serum pregnancy test at screening and at the End of Study Visit. 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 before beginning study medication, during study dosing, and for 1 month following discontinuation of study medication.

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

The Investigator/Sponsor is responsible for monitoring the subject and pregnancy outcome. Every effort should be made to gather information regarding the pregnancy outcome until 90 days postpartum (or otherwise as appropriate). It will be the responsibility of the Sponsor, together with the appropriate support of the Investigator, to obtain this information.

A male subject must immediately inform the Investigator if his female partner becomes pregnant during the study. The female partner of a male subject should also be counselled and followed-up as described above.

Any report of pregnancy recorded for any female subject or for a female partner of a male subject should be reported to the CRO/Vifor Pharma within the same timelines as a SAE, i.e., immediately (within 24 hours of awareness). The Investigator should complete a Vifor Pharma Report on Exposure to Medicines During Pregnancy form and forward to the CRO/Vifor Pharma. Complications of pregnancy such as abortion (spontaneous or induced), premature birth or congenital abnormality are considered SAEs and should be reported using the Vifor Pharma SAE form.

All pregnancies occurring in a female subject or the female partner of a male subject within 90 days after discontinuation of investigational product should be reported as though they were an SAE to the CRO/Vifor Pharma.

11. STATISTICAL ANALYSIS

11.1 Statistical Methods

All statistical analyses will be performed using SAS Version 9.0 or later (SAS Institute Inc. SAS/STAT, Cary, NC). Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a statistical analysis plan (SAP), which will be finalised prior to database lock. Any deviation from the SAP will be noted and explained in the final study report. All individual data will be listed as measured.

11.2 Sample Size and Power Calculations

To assess the non-inferiority of FCM compared to IS in the proportion of subjects who will have an increase from baseline in Hb of $\geq 2\text{g/dL}$ at any time up to Week 8 (responders), the following assumptions have been made:

- Subjects that will be included in the study will be mainly subjects with GI disorders and women with HUB. The responder rate after IS treatment is expected to be 70%. This is based on the mean of the proportion of responders in the 2 studies described below in IDA subjects with IBD and IDA subjects with HUB respectively.

In study FER-IBD-07-COR, which compared FCM to IS in IDA subjects with IBD, the proportion of subjects who had an increase from baseline in Hb $\geq 2\text{g/dL}$ at Week 8 was 72% in FCM group and 55% in IS group (Per Protocol Set (PPS)). Seventy three percent in the FCM group and 58% in the IS group had an increase of at least $\geq 2\text{g/dL}$ at any time up to Week 8.

In study 1VIT04002/1VIT04003, which compared FCM to oral iron in IDA subjects with HUB, 82% of subjects in the FCM group had an increase from baseline in Hb $\geq 2\text{g/dL}$ at any time up to Week 6. Although no subjects in this study were treated with Venofer, and no other data are available from studies in which HUB patients are treated with Venofer, it has been assumed that Venofer would have the same response rate as FCM in this patient population.

- The non-inferiority margin for the difference in the proportion of responders between FCM and IS was set to -15%. This margin will ensure a treatment effect for FCM ($70 - 15 = 55$) greater than 33%, the upper bound of the 95% confidence interval (CI) of the proportion of responder of an estimated placebo effect, by more than half the effect itself ($33 + 16.5 = 49.5$). The placebo effect was estimated as follows:

In study 1VIT07017 which compared FCM to Standard Medical Care (SMC) in IDA subjects with HUB or post-partum, there were 55 subjects in the SMC group who did not receive any Iron treatment. Of these, 50 had a Hb assessment at Day

30. At Day 30 the proportion of non-treated subjects with an Hb increase ≥ 2 g/dL was 22% (11/50) with a 95% CI from 11% to 33%.

The sample size is based on showing non-inferiority in the difference in the proportion of subjects achieving an increase in Hb of ≥ 2 g/dL at any time up to Week 8 between FCM and IS. Applying a test at a one-sided alpha level of 2.5%, and a -15% non-inferiority margin, 147 subjects per group will have 80% power to detect that FCM is non-inferior to IS with an expected IS responder proportion of 70%. The total sample size is 368 (184 per treatment group), taking into account an estimated drop-out rate of 20% of the randomised subjects.

11.3 Analysis Set

11.3.1 Full Analysis Set

The full analysis set (FAS) consists of all subjects who satisfy the following criteria:

- Randomised to treatment
- Received at least 1 dose of study treatment
- Had at least 1 baseline and post-baseline Hb value.

Subjects will be analysed in the treatment group they were randomised to.

11.3.2 Per-Protocol Set

The PPS consists of all subjects who, in addition to the FAS criteria, had no major protocol violations (as defined in the SAP).

11.3.3 Safety Set

The safety set consists of all randomised subjects who have received at least 1 dose of study medication. The subjects in this group will be analysed based on the treatment they received.

11.4 Background and Demographic Characteristics

All background and demographic data will be described by mean tables (continuous variables) or frequency tables (categorical variables). Medical history will be coded according to a standard dictionary (Medical Dictionary for Regulatory Activities (MedDRA)) and tabulated according to system organ class and preferred term. The MedDRA version to be used will be the latest version available at the time of study initiation.

11.5 Study Medication

Doses of study drug are defined in Table 2 Iron dosing Schedule for FCM subjects and by the Ganzoni formula for IS subjects. If an incomplete dose of study drug was given to the subject for any reason (e.g.: due to leakage or AE) or a different dose

from the planned dose was administered, this should be recorded in the CRF together with the reason. The dose of study drug received and the number of injections/infusions received will be tabulated for each subject and summarised by treatment group, by visit and overall. Treatment compliance will be calculated for each subject by the percentage of study drug received compared to the planned dose and summarised by treatment group by visit and overall.

11.6 Concomitant Therapy

At each visit, the Investigator will obtain and record any information about concomitant illnesses and any therapeutic interventions (e.g., drug therapy, surgery, etc.) Concomitant medications will be coded using the World Health Organization Anatomical Therapeutic Chemical Drug Reference List classifications (ATC). Counts and percentages of subject use for each medication by ATC Level 2 and 4 and preferred term will be computed and summarised by treatment group.

11.7 Efficacy Evaluations

11.7.1 Primary

The primary endpoint is the percentage of subjects achieving an increase in Hb of ≥ 2 g/dL (responders) from baseline at any time up to Week 8. The non-inferiority test will be applied to the difference between the proportions of subjects meeting the primary endpoint using the PPS. Non-inferiority will be determined if the lower bound of the 95% CI of this difference is above the non-inferiority margin as defined in Section 11.2. Further details will be specified in the SAP.

11.7.2 Secondary

The secondary efficacy endpoints for this study are as follows:

- Percentage of subjects achieving an increase in Hb ≥ 2 g/dL from baseline at Weeks 2, 4, 6 and 8.
- Change in Hb from baseline to Weeks 2, 4, 6 and 8.
- The percentage of subjects with TSAT $\geq 16\%$ and serum ferritin ≥ 100 ng/mL (for subjects with underlying inflammatory disease as determined by hsCRP levels above the normal range) or serum ferritin >14 ng/mL (in subjects with no apparent underlying inflammatory disease as determined by hsCRP levels within normal range at screening) at Weeks 2, 4, 6 and 8.
- Change in TSAT from baseline to Weeks 2, 4, 6 and 8.
- Change in serum ferritin from baseline to Weeks 2, 4, 6 and 8.

Appropriate summary descriptive statistics will be determined for all secondary endpoints at each visit for the FAS population using raw scores. Where appropriate,

methods for imputing missing values for both primary and secondary analyses will be described in the SAP. If any spurious data have been identified during the data review process they will be flagged and considered as missing in the analyses. All spurious and unused data will be included and identified in individual data listings. Missing data will be shown as missing in the listings. For continuous secondary endpoints, either analysis of variance or analysis of covariance models will be used and where necessary, the repeated measures procedure will be implemented. Where appropriate, terms for treatment, gender, age and respective baseline characteristics will be included. For non-continuous endpoints, more non-parametric methods will be used to make treatment comparisons, details of which will be fully specified in the SAP. Significance level is set at an alpha of 0.05 and no adjustment will be made for testing multiple secondary outcomes. Some significant findings are expected to occur by chance so undue consideration will not be given to any particular significant difference. Moreover, interpretation of the results will be based on patterns of differences and in conjunction with the results of the primary analyses.

11.8 Safety Evaluations

The safety analyses will be performed on the safety population.. The following safety evaluations will be performed:

Change in laboratory parameters (haematology, clinical chemistry and iron status) over the study duration. Absolute and change from baseline values will be tabulated with descriptive statistics by treatment group across the course of the study. Clinically significant values outside the laboratory criterion values will be tabulated and/or listed for each treatment group.

- Summary of all TEAEs: type, nature, incidence and outcome overall and by underlying disease aetiology All AEs will be coded using the most current version of MedDRA at study initiation and tabulated according to system organ class, preferred term, severity and relationship to study medication. Serious adverse events and AEs leading to premature study withdrawal will be counted as they occur and listed or summarised.
- Summary of changes in vital signs from baseline to Weeks 2, 4, 6 and 8: Blood pressure, temperature and heart rate will be tabulated by treatment group and visit.

Summary of changes in ECG and physical examination (including BW) from baseline to Week 4 (for ECG only) and Week 8: Abnormal features on ECG will be tabulated and listed by treatment group.

11.9 Interim Analyses

There is no planned interim analysis for this study.

11.10 Other Evaluations

Additional exploratory analyses not described above may be performed if indicated in the medical review(s) of the data. [REDACTED]

11.10.1 Pharmacokinetics

There will be no PK assessments in this study.

12. STUDY ETHICAL CONSIDERATIONS

12.1 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 64th WMA General Assembly, Fortaleza, Brazil, October 2013), and the ICH guidelines for GCP. Vifor Pharma will ensure that the study complies with all local, federal or country regulatory requirements.

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 Sponsor or any party completing testing on behalf of the Sponsor (e.g., blood for central laboratory assessments).

All anonymous data remains the property of Vifor Pharma.

12.2 Informed Consent

The ICF used for the study must comply with the Declaration of Helsinki, Chinese 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.

12.3 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. A copy of the approval letter must be forwarded to Vifor Pharma before the study is implemented.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator must ensure that all trial related site source data, study related documents and reports will be available, and that the provision of direct access for monitoring and auditing by Vifor Pharma or its designees will be permitted. In addition, the Investigator must ensure that all trial related site source data, study related documents, and reports will be made available for inspection by the appropriate Regulatory Authority and review by the IRB/EC/IEC.

Accurate and reliable data collection will be assured by verification and cross-check of the CRFs against the Investigator's records by the Study Monitor (source document verification), and the maintenance of a drug dispensing log by the Investigator. The data collected will be entered (electronic data capture) into the study database once it has been verified by the Monitor. A comprehensive validation check program will verify the data and queries will be generated for resolution by the Investigator. Throughout the study, Vifor Pharma or its designates may review data as deemed necessary.

14. ADMINISTRATIVE PROCEDURES

14.1 Sponsor's Responsibilities

14.1.1 Study Supplies

Sites will be provisioned with all supplies required to manage this study. This will include but is not be limited to:

- Investigator file(s) (for filing of all study related documentation)
- Contact list of all relevant study personnel, including a 24/7 available Sponsor contact for urgent medical questions
- CRF and completion guidelines
- Study Reference Manuals
- All study forms (e.g., SAE, special situations, pregnancy, drug accountability, etc.)

14.1.2 Insurance

Vifor Pharma 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 Vifor products used in clinical studies. 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). Vifor Pharma 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.

14.1.3 Investigator Training

All Investigators and their study personnel will receive training regarding the study procedures and GCP/regulations specific to the conduct of clinical trials. This training will take place prior to enrolment of the first subject at the study centre.

14.1.4 Study Monitoring

The study will be monitored by representatives of Vifor Pharma (or designee) which may include a CRO and/or partner company.

It is understood that the responsible Vifor Pharma Monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial (CRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements.

It will be the Monitor's responsibility to inspect the CRFs at frequent regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The Monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator (or his/her deputy) agrees to co-operate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

14.2 Investigator's Responsibilities

14.2.1 Reporting and Recording of Data

All required study data must be entered in the electronic CRF (eCRF) created for the study. Training on the system will be provided to all sites, including instructions on how to address missing data, corrections, query procedures and electronic signatures. Only individuals who are identified on the authorised signature page may enter/correct data in the eCRF. For those subjects who withdraw before completion of the study, all available efficacy and safety data must be entered in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries addressed to the Investigator for resolution.

14.2.2 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which case reports for each subject are based. They are to be separate and distinct from CRFs. These records should include detailed notes on:

- The medical history prior to participation in the study.
- The basic identifying information, such as demographics, that link the subject's source documents with the CRFs.
- The results of all diagnostic tests performed, diagnoses made, therapy provided and any other data on the condition of the subject.
- The subject's exposure to study treatment.
- All AEs and documentation on reportable events (see Section 10.2.7) and pregnancies (see Section 10.3.3).
- The subject's exposure to any concomitant therapy (including date and quantity dispensed).
- All relevant observations and data on the condition of the subject throughout the study.

- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.
- For some data elements, direct data entry into specified pages of the subject's CRF is acceptable without other source document (or these data elements, the CRFs will be considered source document).

14.2.3 Records Retention

The Investigator must arrange for the retention of all study documentation (such as CRFs, research files, and Investigator site file) for the duration specified in their respective site contract. The Sponsor will inform the Investigator in writing when files can be destroyed. Archived data may be held on microfiche or electronic record, provided that a back-up copy exists and that a hard copy can be generated if required.

The Investigator must inform Vifor Pharma immediately if any documents are lost, to be transferred to a different facility, or to be transferred to a different owner.

14.2.4 Site Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

15. PROCEDURE FOR MODIFICATION OF PROTOCOL OR PREMATURE TERMINATION OF THE STUDY

15.1 Protocol Waivers, Deviations and Violations

Protocol waivers shall not be permitted except where necessary to eliminate an immediate hazard to subjects.

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as minor or major on a case-by-case basis. The criteria describing the deviation(s) and how they will be handled will be documented in the SAP.

15.2 Protocol Amendments

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, will only be introduced by Vifor Pharma. Each IRB/EC/IEC will review and approve amendments prior to their implementation. Institutional Review Board/EC/IEC approval need not be obtained prior to removal of an immediate hazard to subjects.

15.3 Study Termination

Vifor Pharma reserves the right to terminate the study in its entirety or at a site at any time. The reasons for site termination may include (but are not limited to) unsatisfactory subject enrolment with respect to quality and/or quantity, site is unable to comply with the requirements of the protocol or GCP or data recording is inaccurate and/or incomplete.

In terminating the study, Vifor Pharma and the Investigator will assure that adequate consideration is given to the protection of the subject's interests.

16. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

Vifor Pharma is committed to the timely communication of data from clinical research trials, following the Pharmaceutical Research and Manufacturers of America principles [17]. Where possible, authorship will be agreed at the beginning of the study. The authors 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 Vifor Pharma 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 (ICMJE) criteria for authorship [18]. That is, all authors must meet each of the following 4 criteria:

1. Substantial contribution to the conception and design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approved of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Members of the study steering committee generally fulfil the authorship criteria through their involvement in protocol design and review, monitoring of and sometimes direct involvement with recruitment, and thus they will usually be part of the publication committee. If studies are multicentre, it may be appropriate to assign group authorship.

In addition, certain Vifor Pharma employees involved in the design and conception of the protocol, study management and data analysis and interpretation are qualified authors and will be included in the publication committee e.g., the lead physician, statistician and study project manager or their equivalents.

17. REFERENCES

1. Pantopoulos K (2005) Regulation of Iron Metabolism. In: Weiss G VRG, Hershko C (eds) Anemia of chronic disease, Vol 30. CRC Press, Taylor & Francis Group, Boca Raton, p 1.
2. De Benoist B, Mc Lean E, Egli I, Cogswell M. Worldwide prevalence of anaemia 1993–2005 : WHO global database on anaemia, WHO 2008, ISBN 978 92 4 159665 7.
3. Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C. Laboratory diagnosis of iron deficiency anaemia: an overview. *J Gen Int Med.* 1992;7:145-53.
4. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J.* 2010 Aug;31(15):1872-80.
5. Huch R, Schaefer R. Iron Deficiency and Iron Deficiency Anemia. Thieme 2006, p 5, ISBN 1-58890-578-0.
6. Madore F, White CT, Foley RN, Barrett BJ, Moist LM, Klarenbach SW, Culleton BF, Tonelli M, Manns BJ. Clinical practice guidelines for assessment and management of iron deficiency. Canadian Society of Nephrology. *Kidney Int Suppl.* 2008 Aug;(110):S7-S11.
7. Gasche C, Evstatiev R, Haas T, Kaser A, Knoflach P, Petritsch W, Weiss G, Reinisch W. [Diagnosis and treatment of iron deficiency and anaemia in inflammatory bowel diseases. Consensus of the Austrian IBD Working Party]. *Z Gastroenterol.* 2011 May;49(5):627-32.
8. Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, Cella DF, Djulbegovic B, Goode MJ, Jakubowski AA, Rarick MU, Regan DH, Lichtin AE; American Society of Clinical Oncology; American Society of Hematology. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol.* 2008 Jan 1;26(1):132-49.
9. Ganzoni AM. Eisen-dextran intravenös: therapeutische und experimentelle Möglichkeiten. *Schweiz Med Wochenschr.* 1970;100:301-3.
10. Geisser P, Banké-Bochita J. Pharmacokinetics, safety and tolerability of intravenous ferric carboxymaltose: dose-escalation study in volunteers with mild iron –deficiency anaemia. *Drug Res* 2010; 60 (6a): 362-72.
11. Beshara, S, Sörensen J, Lubberink M, Tolmachev V, Långström 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. *British J Haematol*, 2003; 120: 853–859.

12. Funk F, Ryle P, Canclini C, Neiser S, Geisser P. The new generation of intravenous iron: chemistry, pharmacology, and toxicology of ferric carboxymaltose. *Drug Res* 2010; 60(6a): 345–353
13. Geisser P, Baer M, Schaub E. Structure/Histotoxicity relationship of parenteral iron preparations. *Drug Res* 1992; 42(II); 12: 1439-1452.
14. Kim K, Johnson JA, Derendorf H. Differences in Drug Pharmacokinetics Between East Asians and Caucasians and the Role of Genetic Polymorphisms *J Clin Pharmacol* 2004;44;10:1083-1105.
15. Evstatiev R, Marteau P, Iqbal T, Khalif IL, Stein J, Bokemeyer B, Chopey IV, Gutzwiller FS, Riopel L, Gasche C; FERGI Study Group. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology*. 2011 Sep;141(3):846-853.
16. Guidance for the Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. October 2005. Available from: <http://www.fda.gov>
17. PhRMA principles and guidelines: public disclosure of clinical trial results. Pharmaceutical Research and Manufacturers of America [Internet]. 2009. Available from: http://www.phrma.org/principles_and_guidelines.
18. [International Committee of Medicinal Journal Editors (ICMJE) guidelines]. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, Updated December 2016. Available from: <http://www.icmje.org>.