STATISTICAL ANALYSIS PLAN (SAP)

Treatment: Ferric Carboxymaltose in Iron Deficiency Anaemia

Study Phase: Phase III

Study 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

Protocol Number:	**VIT-IRON-2011-004**
SAP Final Version:	**1.0**
Date:	**19 July 2019**
Author:	**[[redacted], Statistician/Stat]**

APPROVAL SIGNATURES FOR SAP

Study 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

Protocol Number: VIT-IRON-2011-004
Protocol Version: 5.0
Date: 14 August 2017
SAP Final Version: 1.0
Date: 19 July 2019

This Statistical Analysis Plan was subjected to critical review and complies with the statistical principles set out in the ICH E9 and E3, and the guidelines on Good Clinical Practice.

Prepared by:

[redacted] Date

[redacted]
Stat/Statistician
Tigermed Consulting Ltd.

Reviewed by:

[redacted] Date

[redacted]
Stat/Senior Research Statistician
[redacted]

[redacted] Date

[redacted]
Senior Clinical Research Manager
Vifor Pharma – Vifor Pharma Group.

[redacted] Date

[redacted]
Head of Clinical Drug Safety
Vifor Pharma – Vifor Pharma Group.

[redacted] Date

[redacted]
Principal Statistician
Vifor Pharma – Vifor Pharma Group.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

%	Percentage
AE	Adverse event
CI	Confidence interval
CRF	Case report form
ECG	Electrocardiogram
FAS	Full analysis set
FCM	Ferric carboxymaltose
GCP	Good clinical practice
GI	Gastro Intestinal
Hb	Haemoglobin
HUB	Heavy uterine bleeding
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International conference on harmonization
IDA	Iron deficiency anemia
IRT	Interactive response technology
IS	Iron Sucrose
MedDRA	Medical dictionary for regulatory activities
N	Number
PP	Per protocol
PPS	Per protocol set
PV	Protocol violation
SAE	Serious adverse event
SS	Safety set
TEAE	Treatment emergent adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
TFL	Tables, figures and listings
TOC	Table of content

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under protocol VIT-IRON-2011-004 version 5.0 dated 14 August 2017.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using protocol version 5.0 dated 14 August 2017 and CRF version 5.0 dated 17 January 2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

1.1 Study Rationale

Ferric carboxymaltose (FCM) has been developed by Vifor Pharma – Vifor International Inc. as a formulation enabling the application of high iron doses up to 1000 mg in a single dose with a maximum of 20 mg/kg body weight. FCM 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 (as for Venofer) 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. 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.

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 Council 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.

FCM 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.

2 STUDY SUMMARY

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to demonstrate the efficacy of FCM given in a simple dosing regimen in correcting Iron deficiency anaemia (IDA), by demonstrating non-inferiority to treatment with the currently approved intravenous (IV) iron therapy of iron sucrose (IS, Venofer) in the Chinese population.

2.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- 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

2.2 Study Design

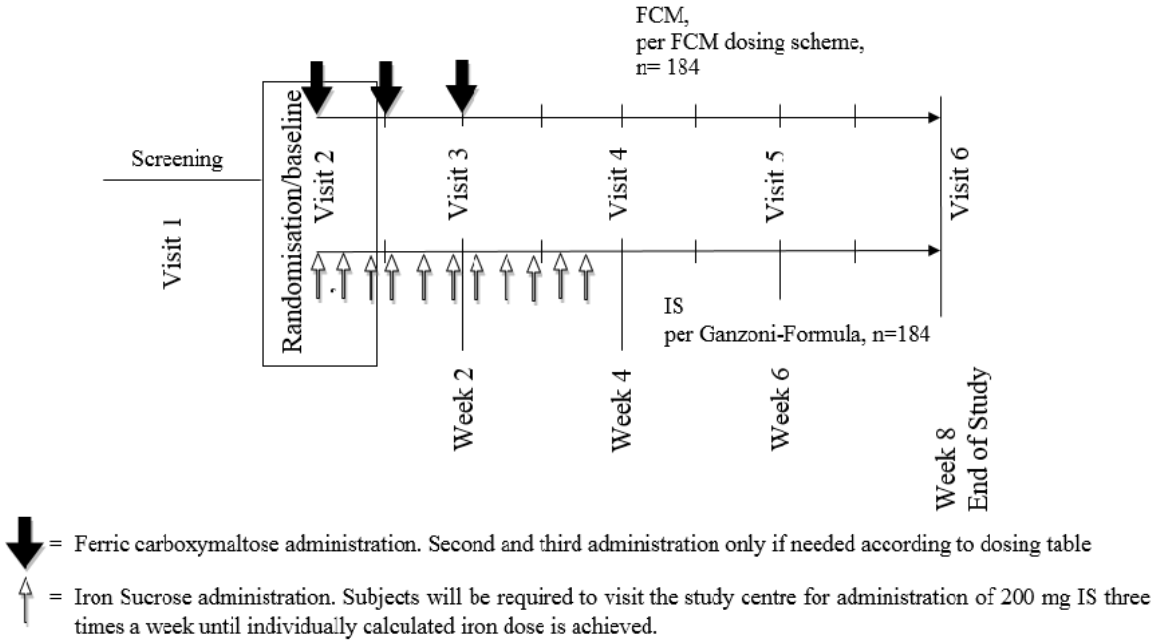
This is an open-label, randomised controlled study to assess the impact of FCM in correcting IDA compared to Venofer (IS) in Chinese subjects. The study will randomise approximately 368 subjects (184 per group) suffering from different underlying diseases leading to IDA. It is expected that approximately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

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.

2.3 Schedule of Events

	Visit			
Procedures	**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	✓	✓	✓	✓

	Visit			
Procedures	**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**
(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), C-reactive protein (CRP).
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; CRP = 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.

2.4 Sample Size Determination

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 ≥ 2g/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 Gastro Intestinal (GI) disorders and women with heavy uterine bleeding (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 inflammatory bowel disease (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 ≥ 2g/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 ≥ 2g/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 ≥ 2g/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 subjects are treated with Venofer, it has been assumed that Venofer would have the same response rate as FCM in this subject 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 an 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 ≥ 2g/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.

2.5 Randomisation and Blinding

This study is an open-label, randomised controlled study to assess the impact of FCM in correcting IDA compared with Venofer.

Subjects will be allocated one of the following treatments: FCM or IS. The randomisation allocation ratio will be 1:1 and the randomisation will be blocked by centre. They will be assigned to site via Interactive Response Technology system during study. Totally, there will be 600 blocks with 4 as block size (15 block per centre). The randomisation schedule was generated and maintained by Tigermed according to Tigermed SOPs.

Table 1 presents the treatment group labels and Table 2 presents the visit labels that will be used in all output.

Table 1: Study Treatments

Studied Treatment	Treatment Label
FCM	FCM
Venofer	IS

Table 2: Study Visits

Visit Number (title)	Visit Label
Visit 1 (Screening)	Screening
Visit 2 (Day 1)	Baseline
Visit 3 (Week 2)	Week 2
Visit 4 (Week 4)	Week 4
Visit 5 (Week 6)	Week 6
Visit 6 (Follow-Up, Week 8)	End of study

2.5.1 Interim Analysis

No interim analyses are planned.

2.6 Study endpoints

2.6.1 Primary endpoint for efficacy

Percentage of subjects achieving an increase in Hb of ≥ 2 g/dL (responders) from baseline at any time up to Week 8.

2.6.2 Secondary endpoints for efficacy

- 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 ≥ 16% and serum ferritin ≥100 ng/mL (for subjects with underlying inflammatory disease as determined by hsCRP levels above the normal range) or > 14ng/mL (in subjects with no apparent underlying inflammatory disease as determined by hsCRP levels within normal range) 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**.**

2.6.3 Endpoint for safety

- 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.
- Summary of changes in electrocardiogram (ECG) and physical examination (including body weight) from baseline to Week 4 (for ECG only) and Week 8.

3 ANALYSIS SETS

3.1 Safety Set

All randomised subjects who have received at least one dose of study medication will be in the Safety Set (SS). The subjects in the SS will be analysed based on the treatment that they received.

3.2 Full Analysis Set

The Full Analysis Set (FAS) consists of those subjects who satisfy the following criteria:

- Randomised to treatment
- Received at least one dose of study treatment
- Had at least 1 baseline and post-baseline efficacy parameter (Hb, Ferritin or TSAT) value

The FAS will be created in accordance with the Intent-To-Treat principles.

The subjects in the FAS will be analysed based on the treatment that they were randomised to.

3.3 Per Protocol Set

The Per-Protocol Set (PPS) is defined as all subjects in the FAS with a study drug compliance between 80 and 120% and do not have any major protocol violations (appendix 1).

The subjects in the PPS will be analysed based on the treatment that they were randomised to.

As per protocol, blood samples had to be drawn before study drug administration (when planned). All laboratory efficacy assessments (Hb, Ferritin, and TSAT) that are measured from a blood sample

taken after the study drug administration will not be considered for any efficacy analysis for both PPS and FAS. The subjects will still be in the PPS if they do not have a major protocol deviation.

For subjects who took prohibited concomitant medication, all laboratory efficacy assessments (Hb, Ferritin, and TSAT) will be censored after the prohibited medication start date for both PPS and FAS. The subjects will still be in the PPS if they do not have a major protocol deviation.

4 DESCRIPTION OF THE STATISTICAL ANALYSIS

This section describes the statistical analyses, presentation of the results, and the study endpoints/measures that will be collected and/or derived during the study at the time points specified in the Schedule of Events (see Section 2.3).

4.1 General Considerations

All confidence intervals (CI) and statistical tests will be 2-sided unless otherwise specified. P-values which are greater than or equal to 0.001, and less than or equal to 0.999, will be presented to 3 decimal places. All other p-values which are less than 0.001 will be presented as <0.001, while p-values greater than 0.999 will be presented as >0.999. Confidence intervals will be presented to 1 more decimal place than the raw data. In general, the maximum number of decimal places reported shall be four.

The software used for all summary statistics and statistical analyses will be SAS® Version 9.2 or later (SAS Institute, Inc.).

4.1.1 Standard descriptive statistics

Continuous variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be obtained for continuous variables: number, mean, standard deviation, median, quartiles (Q1, Q3), minimum, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The Q1, Q3, mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be presented for categorical values: total number, number of values in each class of the variable and the corresponding percentage of the total number of values available will be calculated.

4.1.2 Definition of baseline, visits and visit windows

The baseline will be defined as the last available (non-missing) value before or on the day of the first administration of study drug. Study day 1 is defined as the day of the first study drug administration. For analysis relative day, if considered date less than first study drug administration date, then analysis relative day will be considered date minus first study drug administration date, otherwise, it will be considered date minus first study drug administration date + 1.

4.1.3 Planned Assessment Windows

Table 3 describes the Planned Assessment Windows that will be used in all analyses.

Table 3: Planned Assessment Windows

Visit Label	Planned Visits (Protocol Specified)	Analysis Assessment Window	Target Day
Baseline (Day 1)	--	<=1 Day	1
Week 2	± 3 days	from Day 2 to Day 21	14
Week 4	± 3 days	from Day 22 to Day 35	28
Week 6	± 3 days	from Day 36 to day 49	42
Week 8	± 4 days	>= Day 50	56

All assessments will be re-mapped into the analysis windows. For a parameter, if several assessments fall into the same analysis window, the closest to the target day will be considered for the analysis. When there are 2 assessments closest to the target day, the latest one will be considered for the analysis.

4.1.4 Treatment start/stop dates

If there are no treatment dates available in the administration page of the CRF, date of randomisation will be imputed as the start of treatment date, if it is known that the subject received study drug (information recorded in the administration page of the CRF or any information from monitoring).

If the end of treatment date is missing in the administration page of the CRF, it will be imputed with the start date + administration duration of the same administration record.

If the end of treatment date is missing in the treatment termination page of the CRF, the latest stop date from administration page (including imputed ones) would be imputed.

4.1.5 Tables and listings presentation

The treatment groups will be displayed as in table 1.

Listings will display all data contained in the CRF, excluding collected information on the screen failure subjects and subjects randomised and not treated. Screen failure and not treated subjects will be displayed in a separate listing. Listings will be ordered by treatment, centre, subject ID, and visit date or event/medication start date.

4.1.6 Analysis Sets

The analysis of the primary endpoint 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). All secondary endpoints will be analysed on the FAS and the PPS. All statistical tests will be performed at a 5% level (2-sided).

All safety analyses will be performed on the Safety Set.

4.1.7 Analysis of Subgroups

[redacted]

4.1.8 Methods for Handling and imputation of Missing Data

Incomplete or missing data will not be imputed unless otherwise specified (Treatment start date (see 4.1.4.), medical history and concomitant medications (see 4.4), adverse events (see 4.7.1)).

4.2 Subject Disposition, Randomisation Assignment and Subject Populations

Subject disposition data will be collected on the study termination CRF page when a subject complete or discontinue from the study. The subject disposition data will be summarised. The following data will also be presented in the listings:

- Date of randomisation, randomisation number, planned treatment group, actual treatment received, and first administration date and time in the randomisation listing.
- Data of subjects included and excluded in FAS, PPS, and Safety Set with the reason of exclusion of any analysis set in the analysis population listing.

4.3 Demographics and Baseline Subject Characteristics

Subject demographic and baseline characteristics data (sex, race, age, weight, and height) will be collected on the demographics CRF. The following baseline laboratory parameters Hb, TSAT, Serum ferritin, hsCRP will be collected on the laboratory CRF.

The demographics will be summarised and listed (demographic listing includes dates of informed consent).

Body mass index (BMI) will be calculated from weight and height as below

$$BMI = weight(kg)/[height(m)]^2$$

4.4 Medical History and Concurrent Medical Conditions

All medical history (stopped prior to study drug administration) and concurrent medical conditions (started before dosing and ongoing or started after dosing) will be coded using the MedDRA (version 19.1).

Medical history identified as cause of IDA will be summarised separately by system organ class and preferred term.

All medical history and concurrent medical conditions (including the ones identified as cause of IDA) will be summarised by system organ class and preferred term. Also all medical history and concurrent medical conditions will be listed separately (Medical history identified as cause of IDA will be flagged). Prior and Concomitant Procedures will be listed separately.

Missing dates/partial dates will be handled per below.

Imputation of Start Dates:

- If only the month and year are specified, 1st of the month will be used.

- If only the year is specified, January 01 will be used.
- If the start date is completely unknown, no imputation will be performed.

Imputation of Stop Dates:

- If only the month and year are specified, then use the last day of the month.
- If only the year is specified, then use December 31 of that year.
- If the stop date is completely unknown, no imputation will be performed.

4.5 Study Drug Exposure and Compliance

All individual dosing information will be listed and will include planned dose, dose form, Planned /Actual kit No., the start/end date and time of study drug administration, duration of administration, arm used for injection/infusion and actual volume administered. Any reasons for incomplete dose will be listed if applicable. A subject is defined as treatment compliant if he or she has taken at least 80% and not more than 120% of the investigational product dosage planned for that interval. The dose of study drug information (cumulative planned dose, cumulative actual dose, days on treatment, duration of study participation, Total no. of injections/infusions received, treatment compliance rate, and compliance rate category (<80%, 80 to <120 %, >=120 %)) will also be summarised by treatment group.

Cumulative treatment compliance percentage will be calculated as:

$$\text{Cumulative treatment compliance} = 100 \times \frac{\text{Total Iron administered (mg)}}{\text{Total Iron planned (mg) (1)}}$$

(1) For subjects who withdraw the study the Total planned Iron is the Iron they should receive up to their discontinuation day.

For subjects in FCM arm with a body weight <50kg and who withdrew on Day 8 or Day 15, they may have withdrawn the study before or after drug administration and therefore, will be considered compliant in either case unless consideration is required for under or over dosing (if they received the dose planned that day, the dose of the day should be added to the Total planned Dose, If they did not received it, the dose of the day should not be added to the Total planned dose.)

For subjects in the IS arm, drug administrations could happen on any day within each week windows. The following table shows the total doses a subject could have received by day of withdrawal. If a subject has a Total Iron received equal to any possible total dose or equal to the calculated Total planned Iron (by Ganzoni formula) if he/she withdrew after day 28, he should be considered as compliant. Otherwise, if the total received dose is different to all possible doses at the time of withdrawal, the possible dose which is the closest to the received dose should be considered as the total planned dose.

Day of study withdrawal	Possible Total doses*			
1	200			
2	200	400		
3 to 6	200	400	600	
7	400	600		
8	600	800		
9	600	800	1000	
10 to 12	600	800	1000	1200
13	800	1000	1200	
14	1000	1200		
15	1200	1400		

16	1200	1400	1600	
17 to 19	1200	1400	1600	1800
20	1400	1600	1800	
21	1600	1800		
22	1800	2000		
23	1800	2000	2200	
24 to 26	1800	2000	2200	2400
27	2000	2200	2400	
28	2200	2400		

*: If the minimal possible dose is greater than the planned dose calculated by Ganzoni formula, the planned dose by Ganzoni formula should be consider as the total planned dose.

4.6 Efficacy Analysis

4.6.1 Primary Efficacy Analysis

The primary endpoint is the percentage of subjects achieving an increase in Hb of ≥ 2g/dL (responders) from baseline at any time up to Week 8. The non-inferiority test will be applied to the difference (FCM - IS) between the proportions of subjects meeting the primary endpoint using the PPS and FAS. Non-inferiority will be determined if the lower bound of the 95% CI of this difference is above the non-inferiority margin as defined -15%. The difference in proportions between the FCM and Venofer groups from baseline at any time up to Week 8 and its one‑sided 97.5% confidence intervals (CIs) will be computed using the Wilson score method with continuity correction described by Newcombe (1998).

4.6.2 Secondary Efficacy Analysis

All secondary endpoints will be analysed on the FAS and the PPS. All statistical tests will be performed at a 5% level (2-sided).

Percentage of subjects achieving an increase in Hb ≥ 2 g/dL from baseline at Weeks 2, 4, 6 and 8. The difference in proportions between the FCM and Venofer groups from baseline at Weeks 2, 4, 6 and 8 and its two‑sided 95% confidence intervals (CIs) will be computed using the Wilson score method with continuity correction described by Newcombe (1998).

Change in Hb from baseline to Weeks 2, 4, 6 and 8. Summary statistics will be presented at baseline, Weeks 2, 4, 6 and 8. Treatment comparisons for change in Hb from baseline will also be assessed using an analysis of MMRM model including treatment, haemoglobin baseline, site and visit as factors. Interaction between visit and treatment is also included in the model. The covariance structure to model the within-subject errors will be unstructured. The REML will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons at each visits will be reported. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure.

The percentage of subjects with ID correction defined as TSAT ≥ 16% and serum ferritin ≥ 100 ng/mL (for subjects with underlying inflammatory disease as determined by hsCRP levels above the normal range) or > 14ng/mL (in subjects with no apparent underlying inflammatory disease as determined by hsCRP levels within normal range) at Weeks 2, 4, 6 and 8. The difference in proportions between the FCM and Venofer groups at Weeks 2, 4, 6 and 8 and its two‑sided 95% confidence intervals (CIs) will be computed using the Wilson score method with continuity correction described by Newcombe

(1998). Treatment comparisons of subjects with ID correction variable will be assessed using a logistic regression analysis with treatment, baseline serum ferritin, baseline TSAT, and site in the model.

Change in TSAT from baseline to Weeks 2, 4, 6 and 8. Summary statistics will be presented at baseline, Weeks 2, 4, 6 and 8. Treatment comparisons for Change in TSAT from baseline will also be assessed using an analysis of MMRM model including treatment, haemoglobin baseline, site and visit as factors. Interaction between visit and treatment is also included in the model. The covariance structure to model the within-subject errors will be unstructured. The REML will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons at each visits will be reported. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure.

Change in serum ferritin from baseline to Weeks 2, 4, 6 and 8. Summary statistics will be presented at baseline, Weeks 2, 4, 6 and 8. Treatment comparisons for Change in serum ferritin from baseline will also be assessed using an analysis of MMRM model including treatment, haemoglobin baseline, site and visit as factors. Interaction between visit and treatment is also included in the model. The covariance structure to model the within-subject errors will be unstructured. The REML will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparison; the 95% CI will also be reported. Treatment group comparisons at each visits will be reported. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by the compound symmetry will be used. This order is specified according to a decreasing number of covariance parameters in the structure.

4.7 Safety Analyses

Safety evaluations will be performed using the safety set. Missing values will not be imputed unless otherwise decided and specified before database locked.

4.7.1 Adverse Events

Adverse events data was collected from the time informed consent was obtained until the end of last study visit. Missing AE data will be handled according to the rules specified in below.

Adverse Event Definitions

Adverse events reported after the time the ICF is signed until the end of study visit (Week 8 ± 4 days). A treatment-emergent adverse event (TEAE) is defined as an AE that occurred or increased in severity after the first dose of study medication was taken.

A serious treatment-emergent adverse event (TEAE) is defined as a SAE occurring or increasing in severity after the first dose of study medication was taken, including SAEs occurring up to 30 days after the End of study/Early Withdrawal visit. An AE will be classified as related to study medication if the relationship to study medication was recorded as “certain”, “probable/likely”, “possible”. An AE will be classified as unrelated to study medication if the relationship to study medication was recorded as “unrelated”.

An AE leading to study discontinuation will be defined as an AE where the reason for study withdrawal was recorded as being due to an AE on the Study Termination CRF page and the response to “Action taken with study drug” on the “Adverse Events” CRF page, was recorded as “Drug withdrawn”.

An AE leading to treatment discontinuation is defined as an AE where the outcome of the event was recorded as 'Drug withdrawn' on the 'Adverse Events' CRF page.

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.

All special situations have to be documented in the subject's CRF as well as on the form "Documentation of Special Situations". If any overdose, or medication error leads to any event that fulfils any seriousness criteria, the event has to be reported as an SAE.

Coding of Adverse Event Terms

The AE term (Investigator term) will be assigned to the lowest level term (LLT), and a preferred term (PT) will be classified by a high level term (HLT), a high level group term (HLGT) and a system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, the MedDRA version to be used will be the latest version available at the time of study initiation.

Although there can be multiple SOCs for a PT, each PT will be linked with one SOC, namely the primary SOC which is automatically assigned by MedDRA via one HLT, HLGT route.

The following coding data will be presented:

- PT.
- primary SOC.

Adverse events will be reported on a per-subject basis and per-event. On a per-subject basis this means that even if a subject reported the same event repeatedly (i.e., events mapped to the same PT) during the study period, the event will be counted only once. In the latter case the event will be assigned the worst severity and the strongest relationship to the study medication when summarised. The earliest date will be regarded as start date of the event and the latest date/time will be regarded as stop date of the event within the assigned study period.

Missing and/or incomplete dates/times for AEs are imputed in a manner resulting in the earliest onset or the longest duration during the treatment period, taking additionally into account that the start date/time should not be after the stop date/time. Stop dates/times will not be imputed if the AE is ongoing. This will be done as follows:

For a missing/incomplete start date/time the minimum of the following will be imputed:

- The maximum of the earliest possible start date/time and the date/time of first study medication administration.
- The latest possible start date/time.
- The latest possible stop date/time.

For a missing/incomplete stop date/time the maximum of the following will be imputed:

- The minimum of the latest possible stop date/time and the date/time of last study medication administration.
- The earliest possible stop date/time.
- The earliest possible start date/time.

The earliest (latest) possible date is defined as:

- The date itself if it is complete.
- The date of the first (last) day of the month, if month and year are available but day is missing.
- The date of the first (last) day of the year, if year is available but day and month are missing.
- A very early (late) date, e.g., 01JAN2000 (01JAN2100), if the date is completely missing.

The imputation method will only be used to determine treatment emergence and to determine the time of the event relative to the first administration of study medication. A worst-case approach will be followed in the event of missing severity or causality data. If the severity is missing, 'Severe' will be imputed. If causality data is missing, 'Certain' will be imputed. In the event that no coding information is available for a specific AE, the AE will be presented as an 'Uncoded' in summary tables.

The following listings will also be generated:

- Treatment Emergent Adverse Events Listing
- Non-Treatment Emergent Adverse Events
- Adverse Events (Screened Only/Not Treated)
- Treatment Emergent Treatment Related Adverse Events
- Treatment Emergent Serious Adverse Events
- Treatment Emergent Adverse Events Leading to Premature Study Withdrawal
- Treatment Emergent Adverse Event Leading to Death
- Special Situations

The following summary tables will be provided:

- Overall Summary of Treatment Emergent Adverse Events
- Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term
- Treatment Emergent Treatment Related Adverse Events by Primary System Organ Class and Preferred Term
- Treatment Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term
- Treatment Emergent Treatment Related Serious Adverse Events by Primary System Organ Class and Preferred Term
- Treatment Emergent Adverse Events Leading to Premature Study Withdrawal by Primary System Organ Class and Preferred Term
- Treatment Emergent Adverse Events Leading to Death by Primary System Organ Class and Preferred Term
- Treatment Emergent Adverse Events Leading to Study Drug Interruption by Primary System Organ Class and Preferred Term
- Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Medication
- Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity
- Treatment Emergent Adverse Events by Preferred Term

Each summary table will include incidences of adverse events.

4.7.2 Clinical Laboratory Evaluations

Descriptive statistics will be performed for laboratory parameters on a continuous scale for the absolute and change from baseline for each visit split by treatment group. Subjects with Potential clinical significance will be summarised by treatment group.

If multiple tests were performed at baseline, the latest non-missing measurement prior to the first administration of study treatment will be used for the baseline value. For multiple tests at post-baseline visits occurring during the same visit window, the closest measurement will be used for the

analyses and summary tables. When two measurements are exactly equidistant to the exact visit date, the later will be used for the analyses and summary tables. Laboratory values expressed as 'less than" or "greater than" will be imputed using the next numerical value (i.e. '<2.00' imputed as 1.99, ">0.3" imputed as 0.4).

Shift tables for the hematology and biochemistry laboratory parameters comparing values low, normal and high using the standard reference ranges will be presented for the baseline laboratory measurement versus the endpoint measurement for each subject. The number and percentage of subjects with abnormal values for each analyte will be summarised at each analysis visit. Abnormal values for each analyte will be determined using normal ranges provided by the central laboratory.

All laboratory results will be listed, including all unscheduled visits. Decimal place for each parameter is described in appendix 2.

4.7.3 Electrocardiogram (ECG) Evaluations

A summary of abnormal clinically significant and abnormal not clinically significant electrocardiogram (ECG) results will be presented by treatment and visit. Absolute and change from baseline ECG results will be tabulated (Heart Rate, PR interval, QRS interval, RR interval, QT interval, QTcF interval) by treatment group and overall. QT and QTc will be analyzed in accordance with ICH E14 guidance. All ECG tests and results will be listed. A summary of Electrocardiogram Abnormal Results (QT and QTcF) will be presented by treatment and visit. Also a shift table for QT and QTcF for interval class will be presented for the baseline measurement versus the endpoint measurement by treatment and visit.

If multiple ECG evaluations were performed at baseline, the latest non-missing measurement prior to the first administration of study treatment will be used for the baseline value. For multiple ECG evaluations at post-baseline visits occurring during the same visit window, the closest measurement to the actual visit date will be used for the analyses and summary tables. When two measurements are exactly equidistant to the exact visit date, the later will be used for the analyses and summary tables.

All ECG tests and results will be listed.

4.7.4 Vital Signs Evaluations

The raw scores and change from baseline results of blood pressure, heart rate, temperature, body weight and BMI will be summarised by treatment and visit.

For each vital signs variable, the Baseline value is defined as the last non-missing measurement collected/derived prior to the first study medication administration at Baseline visit.

Vital signs will be presented for individual subjects in data listings.

If multiple Vital signs evaluations were performed at baseline, the latest non-missing measurement prior to the first administration of study treatment will be used for the baseline value. For multiple Vital signs evaluations at post-baseline visits occurring during the same visit window, the closets measurement to the actual visit date will be used for the analyses and summary tables. When two measurements are exactly equidistant to the exact visit date, the later will be used for the analyses and summary tables.

4.7.5 Other measures

4.7.5.1 Concomitant Medications and procedures and medication history

Medication history refers to the medications that the study subjects stopped taking before or at baseline. Concomitant medications are defined as medications taken from baseline through the end of the study. Counts and percentages of subject used for each medication will be computed and

summarised by ATC level 2, level 4 and preferred term for each treatment and overall. If coding levels are empty, text “Uncoded” will be displayed.

All procedures will be listed.

4.8 Physical Examinations

Data has been documented into AE or medical history. No separate analysis will be performed.

4.9 Other Analyses

Not applicable.

REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95- adopted December 1995).

2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

3. Guidance on Statistical Principles for Clinical Trials in Pharmaceutical Development. China Food and Drug Administration, P. R. China; Jun 2016.

4. Newcombe, R. G. (1998), Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods, Statistics in Medicine. 1998: 17, 873–890.

APPENDICES

Appendix 1: Major or Minor PDs

Vifor DVSCAT (Categories of PDs)	Vifor DVDECOD (Sub-Categories of PDs)	Details	Major or Minor
ICF PROCEDURE ERROR	**ICF PROCEDURE ERROR**	Written informed consent obtained after study specific procedure conducted	**Major**
	PRE-ICF PROCEDURE	Written informed consent not obtained and study specific procedure conducted	**Major**
INCLUSION CRITERIA	**INCLUSION CRITERION # 1**	At least 18 years of age **Deviation: <18 years**	**Major**
	INCLUSION CRITERION # 2	Hb <11 g/dL (females) or Hb <12 g/dL (males) at the screening visit **Deviation: Hb >=11 g/dL (females) or Hb >=12 g/dL (males) at screening visit**	**Major**
	INCLUSION CRITERION # 3	Serum ferritin <100 ng/mL for subjects with underlying inflammatory disease (e.g., inflammatory bowel disease (IBD), chronic kidney disease (CKD) or chronic heart failure (CHF), as determined by C-reactive protein [CRP] levels above the normal range) otherwise ⩽14 ng/mL in subjects with no apparent underlying inflammatory disease (as determined by CRP levels within normal range) at the screening visit **Deviation:** **Serum ferritin >=100 ng/mL for subjects with underlying inflammatory disease (CRP level above NR) at screening visit** **Serum ferritin >14 ng/mL for subjects without underlying inflammatory disease (CRP level within NR) at screening visit**	**Major**
	INCLUSION CRITERION # 4	TSAT <16% (any subject) at the screening visit **Deviation: TSAT >=16 % at screening visit**	**Major**
	INCLUSION CRITERION # 5	Microcytic, hypochromic anaemia defined as: a. Mean corpuscular Hb concentration (MCHC) <32% b. Mean corpuscular volume (MCV) < 80 fL c. Mean corpuscular Hb (MCH) <27 pg **Deviation: MCHC >=32% or MCV >= 80fL or MCH >=27 pg at screening**	**Major**
EXCLUSION CRITERIA	**EXCLUSION CRITERION # 1**	Subject has known hypersensitivity to any of the products to be administered during dosing	**Major**
	EXCLUSION CRITERION # 2	Any history of iron storage diseases such as haemochromatosis	**Major**
	EXCLUSION CRITERION # 3	Any history or clinical findings of iron utilisation disorders such as sideroachrestic anaemia	**Major**
	EXCLUSION CRITERION # 4	Known haemoglobinopathy (e.g. thalassaemia)	**Major**
	EXCLUSION CRITERION # 5	Any history or clinical findings of an anaemia associated with: a. Haematuria b. Vitamin B12 or folic acid deficiency that requires treatment (subjects can be included after deficiency	**Major**

Vifor DVSCAT (Categories of PDs)	Vifor DVDECOD (Sub-Categories of PDs)	Details	Major or Minor
		is corrected)	
	EXCLUSION CRITERION # 6	Any allergic predisposition, ie any history of asthma or atopic allergy. This includes drug allergies.	**Major**
	EXCLUSION CRITERION # 7	Planned surgery with anticipated blood loss (defined as Hb drop >2 g/dL) in the 3 months post randomisation	**Major**
	EXCLUSION CRITERION # 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	**Major**
	EXCLUSION CRITERION # 9	Haemodialysis (current or planned within the next 3 months)	**Major**
	EXCLUSION CRITERION # 10	History of IV iron therapy, erythropoiesis stimulating agent (ESA) therapy and/or blood transfusion in previous 4 weeks prior to screening, and oral iron or oral iron-containing products including Chinese herbal medicines (>75mg iron/day) in the 7 days prior to screening	**Major**
	EXCLUSION CRITERION # 11	Body weight <35 kg	**Major**
	EXCLUSION CRITERION # 12	Chronic liver disease and/or screening alanine transaminase (ALT) or aspartate transaminase (AST) above 3 times the upper limit of the normal range	**Major**
	EXCLUSION CRITERION # 13	Known human immunodeficiency virus infection, acquired immunedeficiency syndrome, tuberculosis	**Major**
	EXCLUSION CRITERION # 14	Known active hepatitis B or C or other active infection (acute or chronic)	**Major**
	EXCLUSION CRITERION # 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)	**Major**
	EXCLUSION CRITERION # 16	Subject is pregnant or is breast feeding	**Major**
	EXCLUSION CRITERION # 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.	**Major**
	EXCLUSION CRITERION # 18	Male subjects fathering a child within 7 days from the last study drug administration	**Major**
	EXCLUSION CRITERION # 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	**TBD***
NON-COMPLIANCE WITH STUDY	**NON-COMPLIANCE WITH STUDY DRUG # 1**	Incomplete FCM dose administered on Day 1, Day 8 or Day 15	**TBD***

Vifor DVSCAT (Categories of PDs)	Vifor DVDECOD (Sub-Categories of PDs)	Details	Major or Minor
DRUG			
	NON-COMPLIANCE WITH STUDY DRUG # 2	Incomplete IS dose administered	**TBD***
STUDY DRUG ADMINISTRATION/TECHNICAL ERROR	**STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 1**	FCM Dose not administered according to visit schedule (as per table 2 in protocol)	**TBD***
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 2	Total daily FCM Dose not administered according to body weight and Hb	**TBD***
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 3	Incorrect FCM administration times (infusion of 500 mg < 5 min OR infusion of 1000mg < 15 min AND for both doses >30 min) Major for rapid administration (< 5min for 500 mg dose or <15 min for1000mg dose); Minor for longer administration (>30 min)	**Major/Minor**
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 4	FCM diluted with the incorrect volume (infusion of 500 mg NOT diluted in 100mL OR infusion of 1000mg NOT diluted in 250mL) For over dilution in larger volume: Major For dilution in smaller volume(<100ml for 500mg dose or <250ml for 1000mg dose: Minor	**Major/Minor**
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 5	IS Dose not administered according to Ganzoni formula	**TBD***
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 6	IS Dose not administered according to visit schedule Major for overdose (> 3 doses per week) Minor for dose omission	**Major/Minor**
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 7	Maximum daily IS dose exceeded(> 200mg)	**Major**
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 8	IS diluted with the incorrect volume (Dilution of 10 ml of the product intended for slow IV push injection OR drip infusion of 10 ml diluted in > 200ml)	**Major**
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 9	Incorrect IS administration time (infusion >60 mins)	**Minor**
	STUDY DRUG ADMINISTRATION/TECHNICAL ERROR # 10	Incorrect IS administration time (for undiluted injection< 10 mins OR for diluted drip infusion < 30 mins)	**Major**
STUDY DRUG DEVIATION	**STUDY DRUG DEVIATION # 1**	Incorrect IMPs storage condition (FCM store > 30°C or freeze / IS store < 4°C or > 25°C or freeze)	**TBD***
	STUDY DRUG DEVIATION # 2	Incorrect treatment administration vs randomization	**Major**
	STUDY DRUG DEVIATION # 3	Study drug not stopped when subject experienced any kind of hypersensitivity reaction related to the study drug during administration	**Major**

Vifor DVSCAT (Categories of PDs)	Vifor DVDECOD (Sub-Categories of PDs)	Details	Major or Minor
PROHIBITED MEDICATION	**PROHIBITED MEDICATION**	Prohibited Therapy and Concomitant Treatment (Oral or other IV iron therapy (other than the study medication), multivitamins or nutritional supplements containing iron > 75 mg per day, ESAs, Blood transfusions)	**Major**
PROCEDURE/TEST NOT DONE	**PROCEDURE/TEST NOT DONE # 1**	Vital Signs missing	**Major**
	PROCEDURE/TEST NOT DONE # 2	Physical Examination missing (Fully missing is Major at Screening/Fully missing is Minor at EOS/Partially missing is Minor at Screening and EOS)	**Major/Minor**
	PROCEDURE/TEST NOT DONE # 3	Laboratory tests: Haematology & Iron status missing from Visit 2 to Visit 6(Missing assessment is major/Missing parameter is minor	**Major/Minor**
	PROCEDURE/TEST NOT DONE # 4	Laboratory tests: Haematology & Iron status missing at Visit 1(Missing assessment is major/Parameters Hb, MCH, MCV, MCHC, Serum Ferritin, TSAT missing is major/Other parameters missing is minor)	**Major/Minor**
	PROCEDURE/TEST NOT DONE # 5	Laboratory tests : Chemistry missing from Visit 2 to Visit 6 (Missing assessment is major/Missing parameter is minor)	**Major/Minor**
	PROCEDURE/TEST NOT DONE # 6	Laboratory tests: Chemistry missing at Visit 1(Missing assessment is major/Parameters CRP, ALT, AST missing is major /Other parameters missing is minor)	**Major/Minor**
	PROCEDURE/TEST NOT DONE # 7	Laboratory tests at planned visits: Urinalysis missing (Missing assessment is major/Missing parameter is minor)	**Major/Minor**
	PROCEDURE/TEST NOT DONE # 8	Laboratory tests: Hepatitis B and C missing at Visit 1 (Any parameters missing is major)	**Major**
	PROCEDURE/TEST NOT DONE # 9	ECG missing	**Minor**
	PROCEDURE/TEST NOT DONE # 10	Laboratory tests: Pregnancy Test at Screening **missing**	**Major**
	PROCEDURE/TEST NOT DONE # 11	Laboratory tests: Pregnancy Test at Visit 6 **missing**	**Major**
PROCEDURE OUTSIDE WINDOW	**PROCEDURE OUTSIDE WINDOW # 1**	Laboratory tests Out Of planned Window	**Minor**
	PROCEDURE OUTSIDE WINDOW # 2	Vital Signs out of planned window	**Minor**
	PROCEDURE OUTSIDE WINDOW # 3	ECG Out Of planned Window (Not done at Screening & Week 4 & EOS)	**Minor**
NON-COMPLIANCE WITH PROCEDURE	**NON-COMPLIANCE WITH PROCEDURE #1**	Dosing NOT performed after all study assessments for the visit(Out of chronological order is minor)	**Minor**
	NON-COMPLIANCE WITH PROCEDURE #2	Missing reporting of SAEs to sponsor within the agreed timeframe "within 24 hours of awareness"	**Major**
VISIT OUTSIDE WINDOW	**VISIT OUTSIDE WINDOW # 1**	Screening duration > 7 days	**Minor**
	VISIT OUTSIDE WINDOW # 2	visits out of window (Planned chronological visits schedule not respected is major)	**Major**
VIST NOT DONE	**VISIT NOT DONE**	Visits NOT done	**Major**

Vifor DVSCAT (Categories of PDs)	Vifor DVDECOD (Sub-Categories of PDs)	Details	Major or Minor
SUBJECT NOT WITHDRAWN AS PER PROTOCOL	**SUBJECT NOT WITHDRAWN AS PER PROTOCOL**	Site satff failed to take the appropriate action in response to protocol-specific discontinuation/withdraw criteria such as:severe anaemia (Hb <6 g/dL) and the subject continued the study	**Major**
OTHER	**NON-COMPLIANCE WITH PROCEDURE # 1**	Rescreening within 4 weeks of original screening visit(minor)	**Minor**
	NON-COMPLIANCE WITH PROCEDURE # 2	Race is not Chinese and subject randomized (minor)	**Minor**
	OTHER	Any other protocol deviation (e.g., as outlined in the monitoring plan):	**TBD***
NOTE		***TBD**(to be discussed): PDs will be determined of major or minor by TMM and consult with Sponsor if necessary CRA will submit the signed and dated major protocol deviation to local EC within 15 working days.	

Appendix 2: Decimal place

Category for Lab	Lab Test Short Name	Lab Test Name	Original Units	Standard Units	Conversion Factor	Decimal Place
CHEMISTRY	ALP	Alkaline Phosphatase	U/L	U/L	1	0
CHEMISTRY	ALT	Alanine Aminotransferase	U/L	U/L	1	0
CHEMISTRY	AST	Aspartate Aminotransferase	U/L	U/L	1	0
CHEMISTRY	CA	Calcium	mmol/L	mmol/L	1	2
CHEMISTRY	CL	Chloride	mmol/L	mmol/L	1	1
CHEMISTRY	CRP	C Reactive Protein	mg/L	mg/L	1	2
CHEMISTRY	GGT	Gamma Glutamyl Transferase	U/L	U/L	1	0
CHEMISTRY	GLUC	Glucose	mmol/L	mmol/L	1	2
CHEMISTRY	K	Potassium	mmol/L	mmol/L	1	2
CHEMISTRY	LDH	Lactate Dehydrogenase	U/L	U/L	1	0
CHEMISTRY	MG	Magnesium	mmol/L	mmol/L	1	2
CHEMISTRY	PHOS	Phosphate	mmol/L	mmol/L	1	2
CHEMISTRY	SODIUM	Sodium	mmol/L	mmol/L	1	0
HEMATOLOGY	BASO	Basophils	10^9/L	10^9/L	1	2
HEMATOLOGY	BASOLE	Basophils/Leukocytes	%	%	1	1
HEMATOLOGY	EOS	Eosinophils	10^9/L	10^9/L	1	2
HEMATOLOGY	EOSLE	Eosinophils/Leukocytes	%	%	1	1
HEMATOLOGY	HBDNA	Hepatitis B DNA	IU/mL	IU/mL	1	0
HEMATOLOGY	HBSAG	Hepatitis B Virus Surface Antigen	IU/mL	IU/mL	1	3
HEMATOLOGY	HCT	Hematocrit	%	%	1	1
HEMATOLOGY	HGB	Hemoglobin	g/L	g/dL	0.1	1
HEMATOLOGY	LYM	Lymphocytes	10^9/L	10^9/L	1	2
HEMATOLOGY	LYMLE	Lymphocytes/Leukocytes	%	%	1	1
HEMATOLOGY	MCH	Ery. Mean Corpuscular Hemoglobin	pg	pg	1	1
HEMATOLOGY	MCHC	Ery. Mean Corpuscular HGB Concentration	g/L	g/L	1	0
HEMATOLOGY	MCV	Ery. Mean Corpuscular Volume	fL	fL	1	1

Category for Lab	Lab Test Short Name	Lab Test Name	Original Units	Standard Units	Conversion Factor	Decimal Place
HEMATOLOGY	MONO	Monocytes	10^9/L	10^9/L	1	2
HEMATOLOGY	MONOLE	Monocytes/Leukocytes	%	%	1	1
HEMATOLOGY	NEUT	Neutrophils	10^9/L	10^9/L	1	2
HEMATOLOGY	NEUTLE	Neutrophils/Leukocytes	%	%	1	1
HEMATOLOGY	PLAT	Platelets	10^9/L	10^9/L	1	0
HEMATOLOGY	RBC	Erythrocytes	10^12/L	10^12/L	1	2
HEMATOLOGY	RETI	Reticulocytes	10^9/L	10^9/L	1	1
HEMATOLOGY	RETICH	Ret. Corpuscular Hemoglobin Content	pg	pg	1	1
HEMATOLOGY	WBC	Leukocytes	10^9/L	10^9/L	1	2
IRON INDICES	FERRITIN	Ferritin	ug/L	ng/mL	1	1
IRON INDICES	IBCU	Unsaturated Iron Binding Capacity	umol/L	umol/L	1	1
IRON INDICES	IRON	Iron	umol/L	umol/L	1	1
IRON INDICES	TFERRIN	Transferrin	g/L	g/L	1	2
IRON INDICES	TFRRNSAT	Transferrin Saturation	%	%	1	1
URINALYSIS	PH	pH				0
URINALYSIS	PHOS	Phosphate	mmol/L	mmol/L	1	2

Appendix 3: List of TFLs

Table 14.1.1 Subject Enrollment

Table 14.1.2 Number of Subjects Randomised by Site and Treatment Group

Table 14.1.3 Subject Disposition

Table 14.1.4 Subject Populations

Table 14.1.5.1 Demographic and Baseline Characteristics (SS)

Table 14.1.5.2 Demographic and Baseline Characteristics (FAS)

Table 14.1.6.1 Underlying Cause for IDA

Table 14.1.6.2 Medical History

Table 14.1.7.1 Medication History

Table 14.1.7.2 Concomitant Medication

Table 14.1.8.1 Study Drug Exposure

Table 14.1.8.2 Study Drug Compliance

Table 14.2.1.1 Analysis of Percentage of Subjects Achieving an Increase in Hb $\geqslant$ 2g/dL (Responders) - Baseline to any Time up to Week 8 (PPS)

Table 14.2.1.2 Analysis of Percentage of Subjects Achieving an Increase in Hb $\geqslant$ 2g/dL (Responders) - Baseline to any Time up to Week 8 (FAS)

Table 14.2.2.1 Summary of Subjects Achieving an Increase of Hb⩾2 g/dL from Baseline to Weeks 2, 4, 6, and 8 (PPS)

Table 14.2.2.3 Summary of Subjects Achieving an Increase in Hb⩾2 g/dL from Baseline at Weeks 2, 4, 6, and 8 (FAS)

Table 14.2.2.2 Analysis of Percentage of Subjects Achieving an Increase in Hb⩾2 g/dL from Baseline to Weeks 2, 4, 6, and 8 (PPS)

Table 14.2.2.4 Analysis of Percentage of Subjects Achieving an Increase in Hb⩾2 g/dL from Baseline at Weeks 2, 4, 6, and 8 (FAS)

Table 14.2.3.1 Summary of Haemoglobin (g/dL) Data (Absolute and Change from Baseline) Over Time (PPS)

Table 14.2.3.3 Summary of Haemoglobin (g/dL) Data (Absolute and Change from Baseline) Over Time (FAS)

Table 14.2.5.1 Summary of Transferrin Saturation (%) Data (Absolute and Change from Baseline) Over Time (PPS)

Table 14.2.5.3 Summary of Transferrin Saturation (%) Data (Absolute and Change from Baseline) Over Time (FAS)

Table 14.2.6.1 Summary of Serum Ferritin (ng/mL) Data (Absolute and Change from Baseline) Over Time (PPS)

Table 14.2.6.3 Summary of Serum Ferritin (ng/mL) Data (Absolute and Change from Baseline) Over Time (FAS)

Table 14.2.3.2 Analysis of Change in Haemoglobin (g/dL) Over Time (Observed Values, Repeated Measures Model) (PPS)

Table 14.2.3.4 Analysis of Change in Haemoglobin (g/dL) Over Time (Observed Values, Repeated Measures Model) (FAS)

Table 14.2.5.2 Analysis of Change in Transferrin Saturation (%) Over Time (Observed Values, Repeated Measures Model) (PPS)

Table 14.2.5.4 Analysis of Change in Transferrin Saturation (%) Over Time (Observed Values, Repeated Measures Model) (FAS)

Table 14.2.6.2 Analysis of Change in Serum Ferritin (ng/mL) Over Time (Observed Values, Repeated Measures Model) (PPS)

Table 14.2.6.4 Analysis of Change in Serum Ferritin (ng/mL) Over Time (Observed Values, Repeated Measures Model) (FAS)

Table 14.2.4.1 Summary of Subjects with Iron Deficiency Correction Over Time by Treatment (PPS)

Table 14.2.4.3 Summary of Subjects with Iron Deficiency Correction Over Time by Treatment (FAS)

Table 14.2.4.2 Analysis of Iron Deficiency Correction Over Time (Observed Values, logistic Model) (PPS)

Table 14.2.4.4 Analysis of Iron Deficiency Correction Over Time (Observed Values, Repeated Measures Model) (FAS)

Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events

Table 14.3.1.2 Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term

Table 14.3.1.3 Treatment Emergent Treatment Related Adverse Events by Primary System Organ Class and Preferred Term

Table 14.3.1.4 Treatment Emergent Serious Adverse Events by Primary System Organ Class and Preferred Term

Table 14.3.1.5 Treatment Emergent Treatment Related Serious Adverse Events by Primary System Organ Class and Preferred Term

Table 14.3.1.6 Treatment Emergent Adverse Events Leading to Premature Study Withdrawal by Primary System Organ Class and Preferred Term

Table 14.3.1.7 Treatment Emergent Adverse Events Leading to Death by Primary System Organ Class and Preferred Term

Table 14.3.1.8 Treatment Emergent Adverse Events Leading to Study Drug Interruption by Primary System Organ Class and Preferred Term

Table 14.3.1.9 Treatment Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Relationship to Study Medication

Table 14.3.1.10 Treatment Emergent Adverse Events by Primary System Organ Class, Preferred Term, and Maximum Severity

Table 14.3.1.11 Treatment Emergent Adverse Events by Preferred Term

Table 14.3.2.1.1 Summary of Laboratory Haematology Data (Absolute and Change from Baseline) Over Time

Table 14.3.2.2.1 Summary of Laboratory Biochemistry Data (Absolute and Change from Baseline) Over Time

Table 14.3.2.3 Summary of Laboratory Iron Parameters Data (Absolute and Change from Baseline) Over Time

Table 14.3.2.4.1 Summary of Laboratory Urinalysis Data (Absolute and Change from Baseline) Over Time

Table 14.3.2.1.2 Laboratory Data - Haematology Shift over Time by Treatment

Table 14.3.2.2.2 Laboratory Data - Biochemistry Shift over Time by Treatment

Table 14.3.2.1.3 Potentially Clinically Significant Post-Baseline Haematology Results

Table 14.3.2.2.3 Potentially Clinically Significant Post-Baseline Biochemistry Results

Table 14.3.2.4.2 Potentially Clinically Significant Post-Baseline Urinalysis Results

Table 14.3.3.1 Vital Signs Data (Absolute and Change from Baseline) Over Time

Table 14.3.4.1 12-Lead Electrocardiogram Data (Absolute and Change from Baseline) Over Time

Table 14.3.4.2 12-Lead ECG by Visit and Overall Interpretation

Table 14.3.4.3 Summary of Electrocardiogram Abnormal Results (QT and QTcF) by Treatment Group and Visit

Table 14.3.4.4 Electrocardiogram - QT and QTcF Shift Over Time by Treatment

Listing 16.2.1.1.1 Subjects Disposition (Safety)

Listing 16.2.1.1.2 Subjects Disposition (Screened Only/Not Treated)

Listing 16.2.1.2 Randomisation Assignments

Listing 16.2.2.1 Inclusion/Exclusion Criteria Description

Listing 16.2.2.2.1 Inclusion/Exclusion Criteria Failed (Safety)

Listing 16.2.2.2.2 Inclusion/Exclusion Criteria Failed (Screened Only/Not Treated)

Listing 16.2.3 Protocol Deviations

Listing 16.2.4 Subject Populations

Listing 16.2.5.1 Demographic and Baseline Characteristics (Safety)

Listing 16.2.5.2 Demographic and Baseline Characteristics (Screened Only/Not Treated)

Listing 16.2.6.1 Medical History (Safety)

Listing 16.2.6.2 Medical History (Screened Only/Not Treated)

Listing 16.2.7.1 Prior and Concomitant Medications (Safety)

Listing 16.2.7.2 Prior and Concomitant Medications (Screened Only/Not Treated)

Listing 16.2.8.1 Prior and Concomitant Procedures (Safety)

Listing 16.2.8.2 Prior and Concomitant Procedures (Screened Only/Not Treated)

Listing 16.2.9.1 Study Medication Exposure

Listing 16.2.9.2 Study Medication Compliance

Listing 16.2.10.1 Efficacy Haemoglobin (g/dL)

Listing 16.2.10.2 Efficacy Transferrin Saturation (%)

Listing 16.2.10.3 Efficacy Serum Ferritin (ng/mL)

Listing 16.2.10.4 Listing of Iron Deficiency Correction Data

Listing 16.2.11.1.1 Treatment Emergent Adverse Events

Listing 16.2.11.1.2 Non-Treatment Emergent Adverse Events

Listing 16.2.11.1.3 Adverse Events (Screened Only/Not Treated)

Listing 16.2.11.2 Treatment Emergent Treatment Related Adverse Events

Listing 16.2.11.3 Treatment Emergent Serious Adverse Events

Listing 16.2.11.4 Treatment Emergent Adverse Events Leading to Premature Study Withdrawal

Listing 16.2.11.5 Treatment Emergent Adverse Event Leading to Death

Listing 16.2.11.6 Special Situations

Listing 16.2.12.1 Laboratory Reference Ranges

Listing 16.2.12.2 Haematology Results

Listing 16.2.12.3 Biochemistry Results

Listing 16.2.12.4 Iron Parameters Results

Listing 16.2.12.5 Urinalysis Results

Listing 16.2.12.6 Hepatitis B and C Results

Listing 16.2.12.7 Serum Pregnancy Test

Listing 16.2.12.8 Subjects with Potentially Clinically Significant Assessment

Listing 16.2.12.9 Laboratory Data

Listing 16.2.13.1 Vital Signs (Safety)

Listing 16.2.13.2 Vital Signs (Screened Only/Not Treated)

Listing 16.2.14.1.1 12-Lead Electrocardiogram Results (Safety)

Listing 16.2.14.1.2 12-Lead Electrocardiogram Results (Screened Only/Not Treated)

Listing 16.2.14.2.1 Overall Interpretation of 12-Lead Electrocardiogram Results (Safety)

Listing 16.2.14.2.2 Overall Interpretation of 12-Lead Electrocardiogram Results (Screened Only/Not Treated)

Appendix 4: Laboratory assessments: CTC criteria (CTCAE V4.0)

Note: all laboratory PCS or CTC grading is provided for use in medical monitoring/on site monitoring and will not be used for reporting or severity classification of any adverse events/findings.

			CTC Grade				
Laboratory Sub Category	**Laboratory Parameter**	**PCS Criteria**	**1**	**2**	**3**	**4**	**5**
Haematology	Erythrocytes	Below LLN					
	Mean corpuscular volume	Below LLN>week 4					
	Mean corpuscular haemoglobin	Below LLN>week 4					

			CTC Grade				
Laboratory Sub Category	**Laboratory Parameter**	**PCS Criteria**	**1**	**2**	**3**	**4**	**5**
	Mean corpuscular haemoglobin concentration	Below LLN>week 4					
	Haemoglobin	Increase of two CTC grade or to grade 4	LLN-100.0 g/L LLN-6.2 mmol/L	<100.0-80.0 g/L <6.2-4.9 mmol/L-	<80.0 – 65 g/L <4.9- mmol/L	Life-Threatening consequences, urgent intervention indicated	Death
	Haematocrit	Below LLN>week 4					
	Reticulocyte count	Below LLN>week 4					
	HbA1C	Below LLN>week 4					
	Leukocytes	Increase of two CTC grades or to grade 4	<LLN - 3.0 x 10^9/L	<3.0 - 2.0 x 10^9/L	<2.0 - 1.0 x 10^9/L	<1.0 x 10^9/L	Death
	Neutrophils	Increase of two CTC grades or to grade 4	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	
	Eosinophils	Below LLN					
	Basophils	Below LLN					
	Lymphocytes	Increase of two CTC grades or to grade 4	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
	Lymphocytes	Above ULN		>4000/mm3 - 20,000/mm3	>20,000/mm3		
	Monocytes	Below LLN					
	Platelets	Increase of two CTC grade or to grade 4	<LLN - 75.0 x 10^9/L	<75.0 – 50.0 x 10^9/L	<50.0 – 25.0 x 10^9/L	<25.0 x 10^9/L	Death
Serum Chemistry	Phosphorus - low	Grade 2 or above	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
	Calcium (total, corrected and ionised) -	Grade 2 or above	Corrected serum calcium of >ULN -	Corrected serum calcium of >11.5 -	Corrected serum calcium of >12.5 - 13.5	Corrected serum calcium of >13.5	Death

			CTC Grade				
Laboratory Sub Category	**Laboratory Parameter**	**PCS Criteria**	**1**	**2**	**3**	**4**	**5**
	High		11.5 mg/dL; >ULN - 2.9 mmol/L; Ionised calcium >ULN - 1.5 mmol/L	12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionised calcium >1.5 - 1.6 mmol/L; symptomatic	mg/dL; >3.1 - 3.4 mmol/L; Ionised calcium >1.6 - 1.8 mmol/L; hospitalisation indicated	mg/dL; >3.4 mmol/L; Ionised calcium >1.8 mmol/L; life-threatening consequences	
	Calcium (total, corrected and ionised) - low	Grade 2 or above	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionised calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionised calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionised calcium <0.9 - 0.8 mmol/L; hospitalisation indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionised calcium <0.8 mmol/L; life-threatening consequences	Death
	Glucose	Increase by two CTC grades or to grade 4	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; lifethreatening consequences; seizures	Death
	Hs C-reactive protein	Above ULN and greater than baseline result*					
	Sodium - high	Increase by two CTC grades or to grade 4	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	Death
	Sodium - low	Increase by two CTC grades or to grade 4	<LLN – 130 mmol/L	-	<130 – 120 mmol/L	<120 mmol/L	Death
	Potassium - high	Increase by two CTC grades or to grade 4	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalisation indicated	>7.0 mmol/L; life-threatening consequences	Death
	Potassium - low	Increase by two CTC grades or to grade 4	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalisation indicated	<2.5 mmol/L; life-threatening consequences	Death
	Magnesium - High	Increase by two CTC grades or to	>ULN - 3.0	-	>3.0 - 8.0 mg/dL;	>8.0 mg/dL; >3.30	Death

			CTC Grade				
Laboratory Sub Category	**Laboratory Parameter**	**PCS Criteria**	**1**	**2**	**3**	**4**	**5**
		grade 4	mg/dL; >ULN - 1.23 mmol/L		>1.23 - 3.30 mmol/L	mmol/L;life-threatening consequences	
	Magnesium - low	Increase by two CTC grades or to grade 4	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3mmol/L	<0.7 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
	Chloride	Below LLN or above ULN					
Liver Enzymes (Serum)	Alkaline phosphatase (ALP)	increase of two CTC grade or to grade 4	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
	Aspartate transaminase (AST)	increase of two CTC grade or to grade 4	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
	Alanine transaminase (ALT)	Increase of two CTC grade or to grade 4	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
	Lactate dehydrogenase (LDH)	Above ULN					
	Gamma-glutamyl transpeptidase (GGT)	Increase of one CTC grade or to grade 4	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Iron Status Parameters	Serum Iron	n/a					
	Total Iron	n/a					
	UIBC	n/a					
	Ferritin	Above 800 ng/ml at consecutive visits					
	Transferrin	n/a					
	Transferrin saturation	n/a					
Urinalysis	Urobilinogen	n/a					
	Leucocytes	n/a					
	Protein	Positive					
	Glucose	Positive					
	Bilirubin	Positive					
	Nitrite	Positive					

			CTC Grade				
Laboratory Sub Category	**Laboratory Parameter**	**PCS Criteria**	**1**	**2**	**3**	**4**	**5**
	Ketone	Positive					
	Blood	Trace/positive					
	Phosphorus	n/a					

"*" Subjects are permitted to have a hsCRP above the ULN at baseline per protocol.