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1VIT17044 Multicenter Randomized Active-controlled Study to Investigate Efficacy & Safety of IV FCM in Pediatric Patients With IDA

State Plan dated 26SEP2019

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Statistical Analysis Plan

Protocol No.: 1VIT17044

A Multicenter, Multinational, Randomized, Active-Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia

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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS

AST	Aspartate Aminotransferase Test
ALT	Alanine Transaminase Test
ATC	Anatomical Therapeutic Chemical
ANCOVA	Analysis of Covariance
$AUC_{0-infinity}$	Extrapolated Area Under the Serum Concentration- time Curve from Time Zero to Infinity
$AUC_{0-time\ last\ measured\ concentration}$	Area Under the Serum Concentration-time Curve from Time Zero to the Last Sampling Time with a Quantifiable Concentration
BP	Blood Pressure
BUN	Blood Urea Nitrogen
eCRF	Electronic Case Report Form
C_{max}	Maximum Serum Concentration
CHr	Reticulocyte Hemoglobin Content
Cl	Apparent Serum Clearance
CI	Confidence Interval
DSMB	Data and Safety Monitoring Board
ESA	Erythropoietin Stimulating Agent
FCM	Ferric Carboxymaltose
GGT	Gamma-Glutamyl Transferase
Hct	Hematocrit Test
Hgb	Hemoglobin
IDA	Iron-deficiency Anemia
IBD	Inflammatory Bowel Disease
IRT	Interactive Response Technology
IV	Intravenous
LDH	Lactate Dehydrogenase
MCH	Mean Cell Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
mg	Milligrams
PCS	Potentially Clinically Significant
PE	Physical Examination
PT	Preferred Term
RBC	Red Blood Cells
RDW	Red Cell Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SD	Standard Deviation

T_{max}	Time at Which C_{max} Occurs
$T_{1/2}$	Half-life
TEAE	Treament Emergent Adverse Event
TIBC	Total Iron Binding Capcacity
TSAT	% Transferrin Saturation
V_D	Apparent Volume of Distribution
V_{Dc}	Apparent Volume of Distribution Includes the Initial Volume of Distribution Following the Injection
V_{Dss}	Volume of Distribution at the Steady State
V_{Darea}	Volume of Distribution at the Final Elimination
WBC	White Blood Cells
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol 1VIT17044 (Administrative Change 1 Protocol Date: 26 SEP 2019). This SAP pertains to clinical safety and efficacy analysis and should be read in conjunction with the study protocol and electronic case report forms (eCRFs). Pharmacokinetic analyses are out of scope for this SAP.

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective(s)

The primary objective of this study is to demonstrate the efficacy and safety of intravenous (IV) ferric carboxymaltose (FCM), compared to oral iron, in pediatric participants who have iron deficiency anemia (IDA).

1.2 STUDY ENDPOINTS

1.2.1 Primary Efficacy Endpoint

Change in hemoglobin from baseline to Day 35.

1.2.2 Secondary Efficacy Endpoint(s)

- Change in ferritin from baseline to Day 35
- Change in transferrin saturation (TSAT) from baseline to Day 35
- Changes from baseline in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin content (CHr) throughout the study.
- Pharmacokinetic assessments, including C_{max}, T_{max}, $T_{1/2}$, MRT, Cl, V_D, V_{Dc}, V_{Dss}, V_{Darea}, $AUC_{0-infinity}$ and $AUC_{0-\text{time last measured concentration}}$. These assessments will be based on a population pharmacokinetic analysis using data from this study and the 1VIT13036 study.

The analysis of PK assessments is not addressed in this SAP.

1.2.3 Safety Endpoints

Safety endpoints include:

- Extent of exposure
- Adverse events
- Laboratory assessments
- Vital signs

1.3 SUMMARY OF THE STUDY DESIGN

1.3.1 General Study Design and Plan

This is a Phase III, multicenter, multinational, randomized, active-controlled study that compares the efficacy and safety of FCM to oral iron in pediatric participants with IDA and a documented history of an inadequate response to oral iron therapy at least 8 weeks (56 days) prior to screening.

FCM injection is a stable, non-dextran, Type I polynuclear iron (III) -hydroxide carbohydrate complex developed as an intravenous (IV) iron replacement therapy for the treatment of IDA. The duration of this study is approximately 6 weeks and the number of sites is approximately 30. Participants who satisfy the inclusion requirements and no exclusion criteria will be eligible to participate in this study and enter into a screening phase to confirm eligibility. All eligible participants will be randomized in a 1:1 ratio to receive either FCM at 15 mg/kg to a maximum single dose of 750 mg on Days 0 and 7 for a maximum total dose of 1500 mg in Group A or oral iron (oral solution drops, elixir or oral tablets) twice daily for 28 days in Group B. Randomization will be stratified by baseline hemoglobin (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years). The oral ferrous sulfate formulation received will be based on the participant's age, such that infants and children (1 to <4 years of age) will receive ferrous sulfate drops, children (≥4 to <12 years of age) will have the option to receive ferrous sulfate elixir or ferrous sulfate tablets, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. If the participants experience adverse clinical symptoms due to the oral iron during the treatment phase, the weight-based dose of ferrous sulfate will be reduced from 6 mg/kg to 3 mg/kg. As for the participants who receive tablets, the dose will be reduced from one tablet taken twice daily to one tablet per day.

Once randomized, all participants will return for efficacy and safety evaluations, including adverse events and laboratory assessments, on Days 7, 14, 28, and 35. Additional pharmacokinetic sampling and analyses will be performed for participants receiving FCM on Days 0 and 7.

The Schedule of Events is presented by Table 1.

Table 1 Schedule of Events

Visit Day	Screening (Day -7 + 1)	Day 0	Day 7	Day 14	Day 28	DAY 35
Informed Consent / Assent	X					
Medical History	X					
Physical Exam		X				X
Inclusion/Exclusion Criteria	X	X				
IRT	X	X				X
Vital Signs	X	X	X	X	X	X
Weight	X	X				
Height	X					
Temperature		X	X			
Hematology, Chemistry and Iron Indices[1]	X	X	X	X	X	X
Serum Pregnancy Test	X					X
Concomitant Medications	X	X	X	X	X	X
IBD Treatment / ESA Stability (if applicable)	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X
Randomization		X				
Injectafer® Dosing		X	X			
Pharmacokinetic Sampling[2]		X	X			
Oral Iron Dosing		X	X	X	X	
Oral Iron Dispensing		X	X	X		
Oral Iron Compliance Assessment			X	X	X	

[1]For a full description of central laboratory assessments, refer to Protocol Section 6.4.
[2]Blood samples for pharmacokinetic analysis will be collected pre-dose, immediately (within 5 minutes) post-dose, and 60 minutes post-dose for participants receiving FCM. For a full description of the pharmacokinetic parameters, refer to Protocol section 6.3.6.

1.3.2 Stratification/Randomization

On Day 0, participants who meet the inclusion/exclusion criteria will be randomized via IRT system in a 1:1 ratio to receive either FCM in Group A or oral iron (oral solution drops, elixir or oral tablets) in Group B. Randomization will be stratified by baseline hemoglobin (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years).

1.3.3 Blinding

The randomization schedule is generated by an independent randomization statistician. Although the study is open-label, other than designated randomization personnel, the study statisticians and the ARI statistician are blinded to study drug assignment prior to database lock.

1.3.4 Sample Size and Statistical Power Considerations

A total of 60 participants (30 per treatment group) are required to detect an expected difference in hemoglobin of 1.0 g/dL (common standard deviation = 1.16 g/dL) at two-sided alpha=0.05 with 90% power. Assuming attrition of subjects not being evaluable for efficacy analysis, approximately 72 participants will be randomized.

2. STATISTICAL METHODS

2.1 GENERAL CONSIDERATIONS

Analysis datasets will be produced according to CDISC standards. All study-collected data will be summarized in tables or graphs. Listing will be produced when appropriate and all ICH-required listings will be produced.

Continuous variables will be summarized by number of observations (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min), and maximum (max) values. Other descriptive statistics (e.g., coefficient of variation) may be reported when appropriate. Analysis of categorical variables will include frequency counts and percentages. Unknown and missing data may be presented as a separate category and the denominator will include unknown or missing values as appropriate.

If applicable, hypothesis testing will be carried out at the two-sided α=0.05 level unless otherwise specified; 2-sided 95% confidence intervals (CIs) will be presented, where specified.

2.1.1 Reporting Precision

Summary statistics will be presented to the following degree of precision, unless otherwise specified:

Statistics	Degree of Precision

Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries	One decimal place more than the raw data.
Standard deviation, Standard error	Two decimal places more than the raw data.
Minimum, Maximum	The same as the raw data.
p-value	Rounded to 4 decimal places and therefore presented as 0. xxxx; p-values smaller than 0.0001 as '<0.0001'; p-values greater than 0.9999 as '>0.9999'.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

For weight and height, one decimal place will be used for summary statistics. Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30).

2.2 DEFINITIONS OF ANALYSIS POPULATIONS (ANALYSIS SETS)

2.2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will comprise all randomized participants. Participants will be evaluated according to the treatment to which they were randomized. Any participant who receives a treatment randomization number will be considered to have been randomized. Unless otherwise stated, disposition and baseline data will be summarized in ITT population. The primary population for assessing efficacy will be the ITT population.

2.2.2 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will comprise all participants in the ITT population who receive at least one dose of study drug, have a baseline hemoglobin measurement, and at least one corresponding post-baseline measurement. Participants will be evaluated according to the treatment to which they were randomized. The mITT population may be used for *post hoc* sensitivity analyses.

2.2.3 Safety Population

The safety population will consist of all participants in the ITT population who received at least one dose of study drug. Participants will be evaluated according to treatment received. This population will be used for assessing safety.

2.3 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

2.3.1 Baseline Definition

For evaluations collected at multiple time points, the baseline will be defined as the last value obtained before randomization.

2.3.2 Study Day

Study Day will be calculated relative to the day of first dose (defined as Day 1).

If the assessment (or event) date falls on or after the date of first dose then

Study Day = Assessment Date – Date of First Dose + 1

If assessment date falls before the date of first dose then

Study Day = Assessment Date – Date of First Dose

In the case of adverse events or concomitant medications where the assessment date is partially or completely missing, Study Day and any corresponding durations will follow the conventions given in Section 2.3.4.

2.3.3 Time Windows for Analysis

Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times for safety and efficacy analyses. The summary by visit will be based on the observations at scheduled visits only. Shift tables will be based on the observations at all visits including both scheduled and unscheduled visits.

2.3.4 Handling of Missing Data

A participant who withdraws from the study for any reason will be included in the analyses regardless of time on study. Methods for handling withdrawals and missing data will be specific to each endpoint to be analyzed. Missing data will not be imputed for descriptive statistical summaries in safety or efficacy.

For statistical inferential (models) analyses, missing data will be imputed using last observation carried forward (LOCF) method for hemoglobin and other efficacy endpoints. e.g. for primary endpoint, hemoglobin, when Day 35 data is missing (subject has discontinued before Day 35, or measurement not taken at Day 35 though subject was not discontinued), Day 28 result will be carried forward. If the post-baseline value of the first scheduled visit is missing, the worst value obtained from the same time point of all subjects in ITT population will be used for both treatment groups. The worst value is defined as the lowest value for hemoglobin, ferritin, TSAT and reticulocyte hemoglobin content.

Supportive analyses will assess the impact of missing values on inferences based on primary efficacy endpoints and missing data will be handled by using missing at random (MAR) in

mixed effect model repeat measurement (MMRM) model. The observed case will also be applied for primary analysis.

Dates missing the day or both day and month of the year will adhere to the following conventions to classify TEAE and to classify prior/concomitant medications.

- A medication with a completely missing start date will be considered a prior medication. A medication with a completely missing stop date will be considered a concomitant medication.

- If complete AE onset date is missing and AE end date is on or after the first dose date then it will be counted as a treatment emergent AE (TEAE) for the study. If complete AE onset date is missing and AE end date is before the first dose date then it will be counted as a not treatment emergent AE (TEAE) for the study.

- If an AE or a medication has a partial missing start or stop date, the following rules will be used for imputation:

    - If year is present but month and day are missing, impute start date as January 1 of that year or first dose date if the year is the same as the year of first dose date and impute stop date as December 31 of that year.

    - If year and day are present but month is missing, impute start month as January or the month of the first dose date if the year and day is the same as the year and day of first dose date and impute stop month as December.

    - If year and month are present but day is missing, impute start date as first day of that month or first dose date if the year and month are the same as the year and month of first dose date and impute stop date as last day of that month.

2.4 POOLING OF CENTERS

The study centers are not planned to be used as a stratification factor nor a covariate in the statistical modeling and testing, therefore it is not necessary to pool small centers together.

2.5 ANALYSIS SOFTWARE

All summaries and statistical analyses will be generated using SAS® version 9.4 or higher.

3. STUDY SUBJECTS

3.1 DISPOSITION OF SUBJECTS

Disposition will be summarized by treatment group and overall for all enrolled subjects and also summarized in each investigative site.

The disposition will include the following:

- Participants who are randomized (= ITT population)
- Participants who are in Safety Population
- Participants who complete the study
- Participants who discontinue the study

The number and percent of subjects will be summarized for each reason for premature discontinuation based on the ITT population.

A listing of dispositions will be provided for all randomized subjects. In addition, a listing of randomization will also be provided.

3.2 PROTOCOL DEVIATIONS

The clinical team will identify deviations and the deviations will be identified in the database prior to database lock. The number and percent of participants with clinically important protocol deviations will be summarized for each type of deviation by treatment group and overall based on the ITT population.

A listing of inclusion/exclusion criteria violations and a listing of all protocol deviations will be provided.

3.3 CONCOMITANT INTERVENTION

Concomitant intervention is defined as follows:

- Blood transfusion.
- Use of IV or oral iron outside of protocol.
- Increase in erythropoietin for any reason (Day 0 thru Day 35).
- Change in IBD treatment

The interventions mentioned above are non-study interventions. When concomitant intervention occurs, the date of the intervening event should be recorded in the source documents, and the electronic Case Report Form (eCRF). The participant should continue in the study as scheduled. The number (percentage) of subjects who have concomitant intervention will be summarized by treatment group and overall for ITT population.

4. DEMOGRAPHY AND BASELINE CHARACTERISTICS

4.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS

Demography data such as sex, age, age group (1 to <12 and ≥12 to 17 years), race, ethnicity, body height, body weight, BMI and BMI group (underweight ≤18.5, 18.5 < normal weight≤ 24.9, 25 < overweight ≤ 29.9, obesity = BMI of 30 or greater) will be summarized with descriptive statistics or frequency counts by treatment group and overall for all patients in ITT and Safety populations..

The following disease-specific baseline characteristics will also be summarized with descriptive statistics or frequency counts by treatment and overall for ITT and Safety populations,

- Cause of IDA
- Baseline hemoglobin and the categories (baseline hemoglobin <10 g/dL, baseline hemoglobin≥10 g/dL).
- Status of IV iron intolerance
- Status of oral iron tolerance response
- Status of drug allergy/intolerance (other than iron)

A subject data listing of demographics and baseline characteristics will be provided.

4.2 MEDICAL HISTORY

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. Events will be coded to System Organ Class (SOC) and preferred term (PT) using MedDRA Version 22.0 or higher. The number and percent of subjects with clinically significant medical history at screening will be summarized by SOC and PT by treatment group and overall for the ITT and Safety Populations. Documented history of an inadequate response after at least 8 weeks of prior oral iron therapy use will be included in medical history.

5. STUDY DRUG

5.1 TREATMENT COMPLIANCE

As for each subject, the individual compliance rate will be summarized by descriptive statistics for ITT population.

FCM Compliance = (total dose of iron administered/target dose) ×100

Oral iron compliance = (total dose of iron taken/total dose prescribed) ×100

5.2 PRIOR AND CONCOMITANT MEDICATION

Prior medications are defined as medications that started prior to the first dose of study drug. Concomitant medications are defined as medications (other than the study drug) taken on or after the first dose of the study drug during the entire study. Medications started before the first dose of study drug and continuing at the time of the first dose of study drug are considered both prior medication and concomitant medication. As for the medications that stopped with end date prior to study drug start date will be considered as prior medications. Partial dates for prior/concomitant medication will be classified based on rules in Section 2.3.4.

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) drug dictionary (WHODrug, March 2019 B3). Summaries of prior and concomitant medications will be provided by level 3 ATC classification and preferred term using frequency and percentages by treatment

group and overall for safety population. If ATC level 3 is not applicable, then the level 2 ATC will be used.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT Population. Missing data will be imputed per Section 2.3.4 for statistical inference analysis (no imputation for descriptive statistical summaries).

6.1 PRIMARY EFFICACY ANALYSIS

6.1.1 Change in hemoglobin from baseline to Day 35

The actual value of hemoglobin on baseline, Day 35, and change from baseline to Day 35 will be summarized via descriptive statistics by treatment group.

Treatment group difference for change in hemoglobin will be assessed with the analysis of covariance (ANCOVA), with treatment and randomization strata (hemoglobin and age categories) as fixed factors and baseline value of hemoglobin as a covariate. Baseline hemoglobin will be defined as the last hemoglobin obtained before randomization. Missing value will be imputed using LOCF as specified in Section 2.3.4. P-values to test treatment effect will be determined. Point estimates, associated 95% confidence interval and p-values will be reported.

Supportive analysis
To assess the robustness of this primary efficacy analysis, supportive analyses will be performed using the MMRM model described in the following for this primary endpoint:

MMRM Analysis of Change in hemoglobin from baseline to Day 35:

A mixed model repeated measures (MMRM) model will be conducted to provide an analysis under the assumption that data are missing at random (MAR). The MMRM model will include changes in hemoglobin from baseline to each post-baseline visit as the dependent variables; and treatment group, visit and treatment group by visit interaction as fixed effects; and subjects within treatment group as random effects; and baseline hemoglobin (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years) as covariate. An unstructured covariance matrix will be used to allow for unequal variances between visits. If the model does not converge with unstructured variance – covariance matrix, then the Toeplitz, first-order autoregressive, compound symmetric, variance components structures will be tried and the covariance structure will be decided based on model convergence status and the AKaike information criterion. The Kenward-Roger approximation will be used to calculate the denominator of degrees of freedom for the fixed effect. If the interaction term is not significant, it will be dropped from the model. No imputation of missing data other than that inherent in the MMRM model will be performed. P-values to test treatment effect on Day 35 will be reported. Point estimates and associated 95% confidence interval will be reported.

6.1.2 Examination of Subgroups

The following subgroups using LOCF will be examined for the primary efficacy endpoint (i.e., change in hemoglobin from baseline to Day 35):

- Baseline hemoglobin (<10, ≥10 g/dL)
- Age (1 to <12, ≥12 to 17 years)

The actual value of hemoglobin on baseline, Day 35, and change from baseline to Day 35 will be summarized via descriptive statistics by treatment group and subgroups.

Treatment group difference for change in hemoglobin by subgroup will be assessed with the analysis of covariance (ANCOVA), with treatment and randomization strata (hemoglobin and age categories) as fixed factors and baseline value of hemoglobin as a covariate. Missing value will be imputed using LOCF as specified in Section 2.3.4. Point estimates and associated 95% confidence interval will be reported.

6.2 SECONDARY EFFICACY ANALYSES

6.2.1 Change in ferritin from baseline to Day 35

The actual value of ferritin on baseline, Day 35, and change from baseline to Day 35 will be summarized via descriptive statistics by treatment group.

Treatment group difference for change in ferritin will be assessed with the analysis of covariance (ANCOVA), with treatment and randomization strata (hemoglobin and age categories) as fixed factors and baseline value of ferritin as a covariate. Missing value will be imputed using LOCF as specified in Section 2.3.4. P-values to test treatment effect will be determined. Point estimates, associated 95% confidence interval and p-values will be reported.

Supportive analysis
To assess the robustness of this secondary efficacy analysis, supportive analyses will be performed using the following approach.

MMRM Analysis of Change in ferritin from baseline to Day 35:

A mixed model repeated measures (MMRM) model will be conducted to provide an analysis under the assumption that data are missing at random (MAR). The MMRM model will include changes in ferritin from baseline to each post-baseline visit as the dependent variables; and treatment group, visit and treatment group by visit interaction as fixed effects; and subjects within treatment group as random effects; and baseline ferritin and randomization strata (hemoglobin and age categories) as covariate. An unstructured covariance matrix will be used to allow for unequal variances between visits. If the model does not converge with unstructured variance – covariance matrix, then the Toeplitz, first-order autoregressive, compound symmetric,

variance components structures will be tried and the covariance structure will be decided based on model convergence status and the AKaike information criterion. The Kenward-Roger approximation will be used to calculate the denominator of degrees of freedom for the fixed effect. If the interaction term is not significant, it will be dropped from the model. No imputation of missing data other than that inherent in the MMRM model will be performed. P-values to test treatment effect on Day 35 will be reported. Point estimates and associated 95% confidence interval will be reported.

6.2.2 Change in TSAT from baseline to Day 35

The actual value of TSAT on baseline, Day 35, and change from baseline to Day 35 will be summarized via descriptive statistics by treatment group.

Treatment group difference for change in TSAT will be assessed with the analysis of covariance (ANCOVA), with treatment and randomization strata (hemoglobin and age categories) as fixed factors and baseline value of TSAT as a covariate. Missing value will be imputed using LOCF as specified in Section 2.3.4. P-values to test treatment effect will be determined. Point estimates, associated 95% confidence interval and p-values will be reported.

To assess the robustness of this secondary efficacy analysis, supportive analyses will be performed using the following approach:

MMRM Analysis of Change in TSAT from baseline to Day 35:

A mixed model repeated measures (MMRM) model will be conducted to provide an analysis under the assumption that data are missing at random (MAR). The MMRM model will include changes in TSAT from baseline to each post-baseline visit as the dependent variables; and treatment group, visit and treatment group by visit interaction as fixed effects; and subjects within treatment group as random effects; and baseline TSAT and randomization strata (hemoglobin and age categories) as covariate. An unstructured covariance matrix will be used to allow for unequal variances between visits. If the model does not converge with unstructured variance – covariance matrix, then the Toeplitz, first-order autoregressive, compound symmetric, variance components structures will be tried and the covariance structure will be decided based on model convergence status and the AKaike information criterion. The Kenward-Roger approximation will be used to calculate the denominator of degrees of freedom for the fixed effect. If the interaction term is not significant, it will be dropped from the model. No imputation of missing data other than that inherent in the MMRM model will be performed. P-values to test treatment effect on Day 35 will be reported. Point estimates and associated 95% confidence interval will be reported.

6.2.3 Change in hemoglobin from baseline to each visit

The actual value of hemoglobin on baseline, each post-baseline visit, and change from baseline to each post-baseline visit will be summarized via descriptive statistics by treatment group.

6.2.4 Change in ferritin from baseline to each visit

The actual value of ferritin on baseline, each post-baseline visit, and change from baseline to each post-baseline visit will be summarized via descriptive statistics by treatment group.

6.2.5 Change in TSAT from baseline to each visit

The actual value of TSAT on baseline, each post-baseline visit, and change from baseline to each post-baseline visit will be summarized via descriptive statistics by treatment group.

6.2.6 Change in Reticulocyte Hemoglobin Content from baseline to each visit

The actual value of reticulocyte hemoglobin content (CHr) on baseline, each post-baseline visit, and change from baseline to each post-baseline visit will be summarized via descriptive statistics by treatment group.

Supportive analysis
To assess the robustness of this secondary efficacy analysis, supportive analyses will be performed using the following approach:

MMRM Analysis of Change in CHr from baseline to Day 35:

A mixed model repeated measures (MMRM) model will be conducted to provide an analysis under the assumption that data are missing at random (MAR). The MMRM model will include changes in CHr from baseline to each post-baseline visit as the dependent variables; and treatment group, visit and treatment group by visit interaction as fixed effects; and subjects within treatment group as random effects; and baseline CHr and randomization strata (hemoglobin and age categories) as covariate. An unstructured covariance matrix will be used to allow for unequal variances between visits. If the model does not converge with unstructured variance – covariance matrix, then the Toeplitz, first-order autoregressive, compound symmetric, variance components structures will be tried and the covariance structure will be decided based on model convergence status and the AKaike information criterion. The Kenward-Roger approximation will be used to calculate the denominator of degrees of freedom for the fixed effect. If the interaction term is not significant, it will be dropped from the model. No imputation of missing data other than that inherent in the MMRM model will be performed. P-values to test treatment effect on Day 35 will be reported. Point estimates, and associated 95% confidence interval will be reported.

7. SAFETY ANALYSES

All safety analyses will be performed on the Safety Population. Safety assessments include:

- Extent of exposure
- Adverse events
- Laboratory assessments (hematology, iron indices, chemistry, and other)

- Vital signs

Baseline of clinical laboratory findings will be defined as the last value obtained before randomization.

7.1 EXTENT OF EXPOSURE

For each type of IV administration of FCM, total dose of iron administered (mg), total calculated FCM dose to be given (mg), the number of infusions will be summarized descriptively. For oral iron, the total dose of iron taken (mg), daily dose of iron (mg) will be summarized descriptively.

The study drug exposure will be presented in subject data listings.

7.2 ADVERSE EVENTS

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The verbatim term will be included in the AE listings. Adverse event summaries will exclude preferred terms that describe asymptomatic serum ferritin, TSAT, and reticulocyte values (or changes). This approach is justified by the reporting of these values in efficacy summaries and is consistent with the protocol-defined reporting standards for hemoglobin/hematocrit and low iron indices. For the purposes of this study, non-serious anemia (hemoglobin or hematocrit below the normal range or worsened from baseline) or iron deficiency (iron indices below the normal range or worsened from baseline) will not be considered adverse events. Anemia or iron deficiency will be considered end points if an intervention is required.

A treatment-emergent adverse event (TEAE) is defined as an event with onset date on or after the study drug start date. Partial date TEAE classification rules refer to Section 2.3.4. Only TEAEs will be included in summary tables by treatment group.

The incidence of TEAEs will be summarized as the number (percentage) of subjects with TEAEs within SOC and PT by treatment group. Subjects who report the same PT on multiple occasions will be counted once for the PT: under the highest severity (severe > moderate > mild) CTCAE when summarized by severity and under the closest relationship (probably related > possibly related > unlikely related > none) to study drug when summarized by relationship. If a subject reports multiple PT for a SOC, the subject will be counted only once for that SOC. Events with unknown severity or relationship will be counted as unknown.

TEAEs will be summarized as below.

- An overview table, including number of subjects with
    - TEAEs
    - serious TEAEs
    - study drug related TEAEs
    - study drug related Serious TEAEs

  - TEAEs by severity
  - TEAEs leading to study drug discontinuation or withdrawal from study
  - TEAEs leading to death
- TEAE by SOC
- TEAE by PT
- TEAE by SOC and PT
- TEAE by SOC, PT, and Severity(CTCAE)
- Study drug related TEAEs by SOC, PT
- Serious TEAEs by SOC and PT
- Study drug related serious TEAEs by SOC and PT
- TEAEs leading to study drug discontinuation or withdrawal from study by SOC and PT
- TEAEs leading to death by SOP and PT

Unless otherwise stated, all TEAE tables will be sorted by SOC and PT in decreasing frequency of the number and percentage of subjects in the treatment group.

7.2.1 Adverse Events of Special Interest

Adverse events of special interest include hypophosphatemia, hypersensitivity/anaphylactoid reactions, injection/infusdion site reactions, and cardiovascular events. The search strategy will be identified as follows:

- TEAEs of hypophosphatemia:
  - MedDRA PT Blood phosphorus decrease
  - MedDRA PT Blood phosphorus abnormal
  - MedDRA PT Hypophosphataemia
  - MedDRA PT Hypophosphataemic rickets
  - MedDRA PT Rickets familial hypophosphataemic

- TEAEs indicative of hypersensitivity/anaphylactoid reactions:
  - SMQ Anaphylactic reaction
  - SMQ Angioedema
  - PT Hypersensitivity

- TEAEs of injection/infusion site reactions:
  - MedDRA HLT Infusion site reactions
  - MedDRA HLT Injection site reactions
  - MedDRA HLT Administration site reactions NEC
  - MedDRA PT Infusion related reaction

- Cardiovascular TEAEs:
  - Cardiovascular disorders SOC
  - Vascular disorders SOC

The AEs of special interest will be summarized as below:

- Treatment-emergent AESI by SOC and PT
- Serious treatment-emergent AESI by SOC, PT
- Serious or severe treatment-emergent AESI by SOC and PT

7.2.2 Deaths, Serious and Other Significant Adverse Events

The AEs, serious AEs, AE leading to study discontinuation of study drug or withdrawal from study, and subjects who died during the study will be listed.

7.3 CLINICAL LABORATORY PARAMETERS

Laboratory assessments include hematology, clinical chemistry, and iron indices:

- Hematology: Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, reticulocyte count and reticulocyte hemoglobin content (CHr)

- Clinical chemistry: sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate and magnesium.

- Iron indices: serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT).

- Other: Serum pregnancy test

All laboratory parameters will be presented in conventional units. The actual value and mean change from baseline to each scheduled visit will be summarized using descriptive statistics by treatment for each laboratory test group above. All abnormal laboratory values will be presented in listings.

Time course table for serum phosphate will be constructed for FCM subjects in safety population. Descriptive statistics of days to first value of specified CTC grade and days to return to normal will be summarized. Only the subjects that were under FCM treatment and had a normal serum phosphate baseline value will be included in this table.

The number and percent of subjects with treatment-emergent potentially clinically significant (PCS) laboratory values after baseline will be summarized by visit and by treatment. The denominator is all subjects with normal baseline and at least one post baseline assessment in the

safety population and the numerator is the number of subjects with PCS (i.e., meets Grade 3 or Grade 4 AE scale defined in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 from March 2017 (Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services)) at any post-baseline visit.

Shift from baseline AE grade to maximum post-baseline AE grade, and shift from baseline to the last visit in terms of AE grade will be summarized by treatment, separately.

The AE grade for Chemistries and Hematology are defined in Appendix 1.1. BUN, hematocrit, bands and iron indices do not have adverse event scales available and are not evaluated separately as possible AEs.

7.4 VITAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

7.4.1 Vital Signs

Vital signs will be collected including sitting body temperature, blood pressure (BP) and heart rate. On study drug dosing days BP and heart rate will be collected pre-dosing, immediately (within 5 minutes) post, and 30 minutes post dosing, and body temperature will be collected on each dosing day. For the FCM group, the actual value and the change in vital signs (including sitting heart rate and blood pressure) from pre-infusion to each post-infusion time point will be summarized descriptively on each dosing day. Markedly abnormal values should be determined by PALS Guidelines, 2015 in Appendix 1.2. Children >15 years of age will use the criteria for 15 years old children.

7.4.2 Physical Examination

Physical examination (PE) results were collected at Day 0 and Day 35 including six body systems, i.e. skin, cardiovascular, pulmonary/respiration, abdominal, central nervous system and musculoskeletal/extremities. Each component of the baseline physical examination will be recorded as normal or abnormal. Each component of the post baseline physical examinations will be recorded as No Change from Previous PE or Change from Previous PE. The number and percent of subjects who have normal, abnormal and significant changes at each visit will be summarized in table.

8. INTERIM ANALYSES AND DATA AND SAFETY MONITORING BOARD (DSMB)

8.1 INTERIM ANALYSES

The study will have a Data Safety Monitoring Board (DSMB) whose primary remit is safety. No formal interim analyses of efficacy are planned for this study.

8.2 DATA AND SAFETY MONITORING BOARD (DSMB)

The DSMB will be composed of at least four senior academic individuals, including the DSMB Chair. The members will have high-level expertise in pediatric IDA and/or statistics. A senior statistician assigned to the trial from the group performing data management services for this trial will oversee the provision of interim data reports for use by the DSMB. The data management group for this trial will transfer pre-agreed datasets to the DSMB. During the Open Session of the DSMB meetings, the Study Chair or American Regent representatives may present updates on the trial status or the safety profile of FCM, but will not be privy to discussions of the data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the participants and, to this end, will undertake reviews of the safety data. The DSMB will have access to an agreed subset of the study data as listed in the DSMB charter (updated as necessary during the trial) throughout the study duration. The DSMB will determine if it believes the trial should be terminated early because clear evidence of a significant safety concern exists.

If the DSMB finds it necessary to recommend actions regarding interruption of the study or changes to the protocol based on medical rationale that would make it unethical to continue the study in its present form, those recommendations will be forwarded to the Study Chair and Sponsor. The details of the DSMB's functions and the early stopping rules will be delineated in a separate DSMB charter.

9. SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

Compared with the study protocol (26SEP2019 Administrative Change 1), below items are the major changes made in this SAP:

1. The efficacy analyses will be conducted for the ITT population instead of the mITT population to be more in keeping with accepted practice. The mITT population will still be defined and will be used for post-hoc sensitivity analyses.

2. In protocol, the sentence of “Changes from baseline in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin content throughout the study” in section 8.4.2 is not consistent with the sentence in study synopsis. In this SAP, we just keep this endpoint in consistency with descriptions in synopsis.

3. To assess the robustness of primary and secondary efficacy analysis, supportive analyses will be performed using MMRM model.

4. The scale defined in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 from March 2017 (Division of AIDS, National Institute of

Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services) will be used to identify abnormal clinical laboratory values instead of toxicity criteria from the National Cancer Institute Common Terminology Criteria version 5 for Adverse Events specified in the protocol.

5. The subgroups Cause of IDA: IBD, not IBD and CKD, not CKD are not included in this SAP because of insufficient sample size for meaningful estimates.

10. APPENDICES

APPENDIX 1.1 ADVERSE EVENT SCALE

CHEMISTRIES Adverse Event Scale				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65* to < *2.88*	11.5 to < 12.5 *2.88* to < *3.13*	12.5 to < 13.5 *3.13* to < *3.38*	⩾ 13.5 *⩾ 3.38*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 *< 1.53*
Creatinine, High *Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant′s baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant′s baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant′s baseline
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*

ULN and LLN required for the chemistries AE Scale
(based on the high and low range from Covance Central Laboratory Services Manual, American Regent, Inc)

Sex	Age	Alkaline Phosphatase LLN (U/L)	ALT ULN (U/L)	AST ULN (U/L)	Age	Creatinine ULN (mg/dL)	Age	Albumin LLN (g/dL)
Female	1-4 yr	<108	>34	>56	1-4 yr	>0.4	2 m–4 yr	<2.8
	4-7 yr	<96	>34	>48	4-7 yr	>0.5	4-16 yr	<2.9
	7-10 yr	<69	>34	>40	7-10 yr	>0.6	16-18 yr	<3.3
	10-15 yr	<51	>34	>40	10-13 yr	>0.7	18 yr	<3.3
	15-18 yr	<31	>34	>40	13-16 yr	>0.8		
	18 yr	<31	>34	>34	16-18 yr	>0.9		
					18 yr	>1.1		
Male	1-4 yr	<104	>34	>69	1-4 yr	>0.4	2 m–4 yr	<2.8

	4-7 yr	<93	>34	>59	4-7 yr	>0.5	4-16 yr	<2.9
	7-10 yr	<86	>34	>40	7-10 yr	>0.6	16-18 yr	<3.3
	10-15 yr	<95	>43	>40	10-13 yr	>0.7	18 yr	<3.3
	15-18 yr	<50	>43	>40	13-16 yr	>0.9		
	18 yr	<31	>43	>36	16-18 yr	>1.1		
					18 yr	>1.2		

HEMATOLOGY Adverse Event Scale				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute Neutrophil Count (ANC), Low (cells/mm3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
Hemoglobin, Low (g/dL; *mmol/L*) *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
Platelets, Decreased (cells/mm3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
WBC, Decreased (cells/mm3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*

APPENDIX 1.2 PEDIATRIC VITAL SIGNS REFERENCE CHART

Heart Rate		
Normal Heart Rate by Age (beats/minute) **Reference: PALS Guidelines, 2015**		
Age	**Awake Rate**	**Sleeping Rate**
Neonate (<28 d)	100-205	90-160
Infant (1 mo-1 y)	100-190	90-160
Toddler (1-2 y)	98-140	80-120
Preschool (3-5 y)	80-120	65-100
School-age (6-11 y)	75-118	58-90
Adolescent (12-15 y)	60-100	50-90

Blood Pressure			
Normal Blood Pressure by Age (mm Hg) **Reference: PALS Guidelines, 2015**			
Age	**Systolic Pressure**	**Diastolic Pressure**	**Systolic Hypotension**
Birth (12 h, <1000 g)	39-59	16-36	<40-50
Birth (12 h, 3 kg)	60-76	31-45	<50
Neonate (96 h)	67-84	35-53	<60
Infant (1-12 mo)	72-104	37-56	<70
Toddler (1-2 y)	86-106	42-63	<70 + (age in years x 2)
Preschooler (3-5 y)	89-112	46-72	<70 + (age in years x 2)
School-age (6-9 y)	97-115	57-76	<70 + (age in years x 2)
Preadolescent (10-11 y)	102-120	61-80	<90
Adolescent (12-15 y)	110-131	64-83	<90

Temperature	
Normal Temperature Range by Method **Reference: CPS Position Statement on Temperature Measurement in Pediatrics, 2015**	
Method	Normal Range (oC)
Rectal	36.6-38
Ear	35.8-38
Oral	35.5-37.5
Axillary	36.5-37.5