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

Protocol dated 26SEP2019

AMERICAN REGENT, INC.

PROTOCOL

No. 1VIT17044

IND #: 63,243

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

SPONSOR

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SIGNATURES OF AGREEMENT FOR PROTOCOL

26 SEP 2019

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Date

26 SEP 2019

Mark Falone, MD
Medical Director, Clinical Research and Development
American Regent, Inc.

Date

Study Synopsis

Protocol No. 1VIT17044

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

Study Drug: Ferric carboxymaltose (Injectafer®)
Oral Iron (Ferrous sulfate)

Objective: 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).

Design: 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 randomization.

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. Randomization will occur via the Interactive Response Technology (IRT) system in a 1:1 ratio to either Group A, participants receiving FCM, or Group B, participants receiving oral iron (oral solution drops, elixir or oral tablets). Randomization will be stratified by baseline Hgb (<10, ≥10 g/dL) and age (1 to <12 years 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. Participants who experience adverse clinical symptoms due to the oral iron during the treatment phase may have a weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. If the participant is receiving 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.

Inclusion Criteria:

1. Male or female participants 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening Hgb <11 g/dL.
3. Screening ferritin ≤300 ng/mL and transferrin saturation (TSAT) <30%.
4. Participants must have a documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to randomization.
5. For participants who are receiving an erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for at least 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial.
6. Participants undergoing treatment for inflammatory bowel disease (IBD) must be on stable therapy for at least 8 weeks prior to consent.

Exclusion Criteria:

1. Known history of hypersensitivity reaction to any component of FCM.
2. Previous randomization and treatment in this study or any other clinical study of FCM.
3. History of acquired iron overload, hemochromatosis, or other iron accumulation disorders.
4. History of significant diseases of the liver, hematopoietic system, cardiovascular system, psychiatric disorder, or other conditions which, on the opinion of the investigator, may place a subject at added risk for participation in the study.
5. Any existing non-viral infection.
6. Known history of positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
7. Known history of positive HIV-1/HIV-2 antibodies (anti-HIV).
8. Anemia due to reasons other than iron deficiency (e.g., hemoglobinopathy and vitamin B12 or folic acid deficiency) that has not been corrected.
9. Intravenous iron and /or blood transfusion in the 4 weeks prior to consent.
10. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
11. Alcohol or drug abuse within the past six months.
12. Female participant who is pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
13. Unable to comply with study procedures and assessments.

Study Drug Administration	**Group A (FCM)** will receive 2 doses (Day 0 and Day 7) of FCM at 15 mg/kg to a maximum single dose of 750 mg (whichever is smaller) up to a maximum total dose of 1500 mg. FCM will be administered as either an undiluted IV push at a rate of 100 mg (2 mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes.

Group B (Oral ferrous sulfate) will receive an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age will receive 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 will receive 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) will receive oral ferrous sulfate drops, while children (ages ≥4 to <12 years) will have the option to receive oral ferrous sulfate elixir or oral ferrous sulfate tablets. Adolescents (ages ≥12 to 17 years) will receive an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants is 130 mg of elemental iron.

Patient Assessments

All participants who provide informed consent/assent, meet inclusion criteria, and do not meet exclusion criteria will be randomized. Starting on Day 0 (the time of study drug dosing) through Day 35, all randomized participants will be subject to safety assessments including vital signs (including sitting heart rate and blood pressure), laboratory samples include hematology, chemistries and iron indices, and adverse event queries. Participants receiving oral iron treatment will be assessed for degree of compliance.

Primary Endpoint:

Change in hemoglobin from baseline to Day 35.

Secondary Endpoints:

Change in ferritin from baseline to Day 35
Change in TSAT from baseline to Day 35
Changes from baseline in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin content throughout the study.
Pharmacokinetic assessments, including C_{max}, T_{max}, $AUC_{0\text{-time last measured concentration}}$, $AUC_{0\text{-infinity}}$, $T_{1/2}$, MRT, Cl, V_D, V_{Dc}, V_{Dss}, and V_{Darea}.

Study duration per participant:

Approximately 6 weeks

Study Sites:

Approximately 30

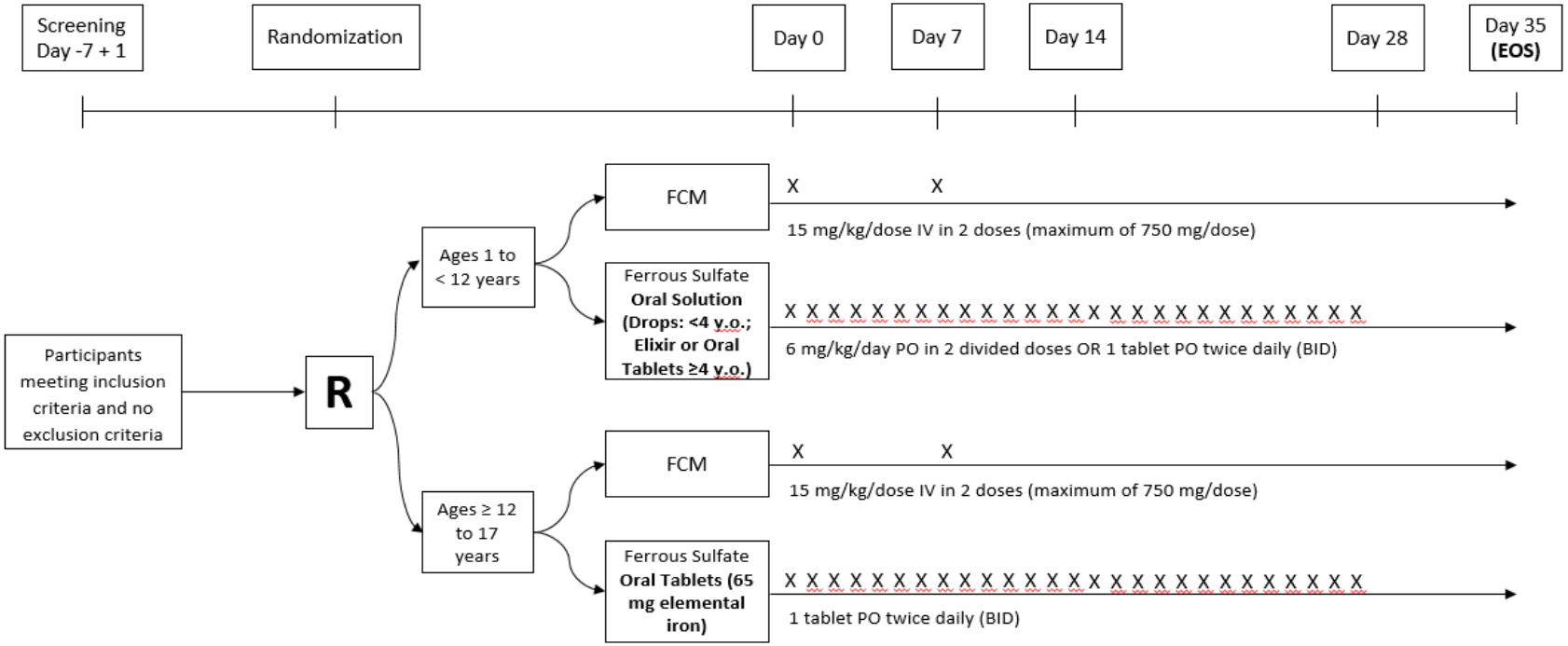
Participant Number: Approximately 72 randomized (N=36 FCM / N=36 Oral Iron)

Sample Size Rationale:

A total of 60 participants (30 per treatment group) are required to detect an expected difference in Hgb of 1.0 g/dL (common standard deviation = 1.16 g/dL) at two-sided alpha = 0.05 with 90% power.

Assuming 20% attrition of subjects not meeting the definition of modified intention to treat (mITT), approximately 72 participants will be randomized.

Figure 1. Study Diagram



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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-infinity}}$	Extrapolated Area Under the Serum Concentration-Time Curve from Time Zero to Infinity
$AUC_{0\text{-time last measured concentration}}$	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
CFR	Code of Federal Regulations
CHr	reticulocyte hemoglobin content
CI	Confidence interval
Cl	Apparent Serum Clearance
C_{max}	Maximum Serum Concentration
CKD	Chronic Kidney Disease
cm	Centimeter
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DSMB	Data and Safety Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
e.g.	For exampleEOS End of Study
ESA	Erythropoiesis-Stimulating Agent
FCM	Ferric carboxymaltose
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
Hct	Hematocrit
Hgb	Hemoglobin
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation
IDA	Iron deficiency anemia
i.e.	that is
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
IRT	Interactive Response Technology
ITT	Intent-to-Treat

kg	Kilogram
L	Liter
LDH	Lactic dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mITT	Modified Intent-to-Treat
MRT	Mean Residence Time
m	Meter
mg	Milligram
mL	Milliliter
ng	Nanogram
NS	Normal saline
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
RBC	Red Blood Cell
RDW	Red (cell) Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
$T_{1/2}$	Half-Life
T_{max}	The time at maximum serum concentration
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
TSI	Total Serum Iron
US	United States
USP	United States Pharmacopeia
WBC	White Blood Cell
w/v	weight / volume
V_D	Apparent Volume of Distribution
V_{Dc}	Initial Volume of Distribution following injection
V_{Dss}	Volume of distribtion at the steady state
V_{Darea}	Volume of distribution at the final elimination

1.0 Introduction

1.1 Treatment of Iron Deficiency Anemia

Iron deficiency anemia (IDA) remains the most common nutritional deficiency in children in the United States (US).[1] Rapid growth, insufficient dietary intake, and limited absorption of dietary iron combine to place children at increased risk for iron deficiency. Iron malabsorption, gastrointestinal blood loss, or iatrogenesis due to repeated blood sampling all represent common clinical mechanisms that can result in IDA. Even when recognized, some children are unable to tolerate prescribed oral iron supplementation or are unresponsive to it.[2] Anemia may also decrease survival rates in adults and children with chronic renal impairment where it is a commonly encountered problem.[3,4] In addition, under-recognized or inadequately treated anemia is likely the most common extra-intestinal manifestation of IBD in children, and it can result in a decrease in quality of life and increased morbidity, inclusive of hospitalization, in affected patients.[2]

Non-hematologic consequences of iron deficiency in children include poor weight gain, anorexia, irritability, decreased attention span, exercise intolerance, and decreased physical activity.[5] Existing data suggests that chronic IDA in infants and toddlers is associated with long-term diminished mental, motor, and behavioral functioning. Although the exact relationship between iron deficiency and its detrimental effects on growth and development is not well-understood, it appears that these effects do not occur until iron deficiency becomes severe and chronic enough to produce anemia.[6]

Options for correcting iron deficiency include both oral and parenteral formulations. As previously described, some children are unable to tolerate or are non-responsive to oral iron. Blood transfusion is an option to treat anemia and replete iron stores, but often scarce supply, as well as the potential risk of blood-borne pathogens, limits its use to severely ill or clinically unstable patients.[2] In view of the limitations associated with oral iron administration or blood transfusions, IV iron administration is an important therapeutic option for use in patients with IDA.[10]

Multiple parenteral iron products are available. These products vary in the way that iron is complexed, which influences the total amount of iron that may be administered during a single administration. Numerous other differences differentiate the products. However, all appear to effectively release iron post administration and can restore iron deficit in the patient. Previous studies with parenteral iron sucrose (Venofer®) have been performed in the pediatric population.[7-9] Iron doses have varied in these studies, and the data demonstrates the efficacy and safety of Venofer® in doses up to 7 mg iron/kg (or 200 mg) administered over 3 minutes, which was shown to be beneficial to both the child and health care facility.[7]

FCM has been characterized as an iron complex (Type 1) with a molecular mass of about 150,000 Daltons (Da). The solution is a dark brown color with a near neutral pH (5.0 to 7.0) and a physiological osmolarity permitting administration of higher single doses in short time periods. Although no randomized interventional studies have been conducted with FCM in the pediatric population to date, the product has been used successfully to address iron deficiency in pediatric patients with ulcerative colitis and Crohn's disease. A non-

interventional, retrospective observational data collection reported FCM exposure in 79 patients aged 2 to 18 years with a mean age of 12.7 years. In these patients, FCM was found to be safe, well-tolerated, and effective in increasing hemoglobin, ferritin, and TSAT.[18]

The proposed study will provide safety and efficacy data on the use of FCM in pediatric patients (aged between 1 and 17 years) with IDA. FCM will be administered in 2 doses at 15 mg/kg maximum single dose of 750 mg with a total maximum cumulative dose of 1500 mg. The ability to infuse higher doses of elemental iron should permit repletion in fewer overall infusions, and in doing so may ultimately permit fewer visits to the treating facilities.

1.2 Ferric Carboxymaltose

1.2.1 Key features of Ferric Carboxymaltose

FCM injection is a stable, non-dextran, Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as an IV iron replacement therapy for the treatment of IDA. After IV administration, FCM is mainly found in the liver, spleen, and bone marrow. The iron slowly dissociates from the complex and can be efficiently used in the bone marrow for hemoglobin synthesis. The carbohydrate moiety of FCM is metabolized by the glycolytic pathway.

1.2.2 Ferric Carboxymaltose versus Other Parenteral Iron Agents

There is considerable efficacy and safety data in the literature with respect to existing parenteral iron formulations.[4] However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted their use. FCM offers significant advantages compared to other available IV iron preparations.

Iron dextran, the first parenteral iron product available in the US, has been associated with an incidence of anaphylaxis/anaphylactoid reactions (i.e., dyspnea, wheezing, hypotension, urticaria, angioedema) as high as 1.7%.[7] Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran.[17] The high incidence of anaphylaxis/anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Although some have suggested that high molecular weight (HMW) iron dextran is associated with a higher rate of life threatening adverse events and anaphylactic reactions in comparison to low molecular weight (LMW) iron dextran, the US Food and Drug Administration was unable to find a clear difference after an examination of post-marketing data, clinical trial data, death certificates, and emergency room diagnoses.[8] Iron dextran is limited to second line therapy for treatment of iron deficiency.

More recently approved intravenous iron formulations, including iron sucrose and iron gluconate, do not contain the dextran moiety. However, they too have significant dosage and administration rate limitations. If the body's ability to sequester, store, and transport infused iron is overwhelmed, a reaction to excess free iron in circulation, referred to as a bioactive iron reaction, may occur. Iron sucrose and iron gluconate preparations carry a significant risk of inducing a bioactive iron reaction when delivered at higher doses. These reactions are characterized by hypotension (without allergic signs) accompanied by pain in the chest, abdomen, flank and/or nausea, vomiting, and diarrhea.[19]

Due to its structure, FCM is more stable than iron gluconate and iron sucrose, and this results in a slower delivery of the complexed iron to endogenous iron binding sites. FCM has an acute toxicity in animals approximately 1/5 that of iron sucrose.[16] These characteristics of FCM make it possible to administer much higher single doses over shorter periods of time than iron gluconate or iron sucrose, resulting in the need for fewer administrations to replete iron stores.

2.0 TRIAL OBJECTIVE

2.1 Primary Objective

The primary objective of this study is to demonstrate the efficacy and safety of IV FCM compared to oral iron in pediatric participants who have IDA.

3.0 OVERALL STUDY DESIGN AND RATIONALE

3.1 Overall Study Design

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 at least 8 weeks (56 days) prior to randomization.

Participants who satisfy the inclusion requirements and no exclusionary criteria will be eligible to participate in this study and enter into a screening phase to confirm eligibility. Randomization will occur via the IRT system in a 1:1 ratio to either Group A, participants receiving FCM, or Group B, participants receiving oral iron (oral solution drops, elixir or oral tablets) up to Day 28. 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. Participants who experience adverse clinical symptoms due to the oral iron during the treatment phase may have the weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. If the participant is receiving 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.

3.2 Rationale of Study Design and Choice of Control Groups

Oral ferrous sulfate was selected as the active comparator because in addition to tablets, liquid formulations suitable for administration to pediatric participants in different age

groups are available. This iron salt is the most widely prescribed oral iron preparation for use in the treatment of pediatric IDA, relative to other preparations, according to a survey of pediatric hematology/oncology specialists.[11] Ferrous sulfate drops, (15 mg elemental iron/mL), may be used as an iron supplement for infants and children up to 4 years of age, per manufacturer labeling.[15] Oral ferrous sulfate elixir will be provided as an alternative preparation to oral tablets in order to ameliorate the difficulty of swallowing tablets with children. Per the recommended total daily dose of oral elemental iron for the treatment of IDA in pediatric patients ranges between 3-6 mg/kg/day divided into one to three doses, a total daily dose of 6 mg/kg/day divided into 2 doses (maximum daily dose of 130 mg of elemental iron) was selected for all ages based on the most common practice of pediatric hematology physicians in the United States.[11] Additionally, the simplified regimen may minimize adverse effects associated with high-dose oral iron therapy and thus improve medication adherence.[13]

With respect to FCM, doses of 15 mg/kg with a maximum of 750 mg per dose have been selected based off evidence generated from American Regent's Phase II dose-finding PK/PD study in which cohorts received single, weight-based doses of FCM at either 7.5 mg/kg or 15 mg/kg.[16] Results from this study demonstrate that the higher weight-based dose is both efficacious and safe. The mean increase from baseline to Day 35 was larger for participants in Cohort 2 receiving 15 mg/kg (2.8 ± 1.15 g/dL) than those in Cohort 1 receiving 7.5 mg/kg (1.9 ± 1.38 g/dL). The mean increase in ferritin and TSAT at Day 35 was 35.1 ± 98.22 ng/mL and 9.9 ± 11.54%, respectively, for Cohort 1 (N=16) and 52.4 ± 31.7 ng/mL and 13.5 ± 6.88%, respectively, for Cohort 2 (N=18), respectively. (Table 1)

Table 1. Mean Change from Screening in Hemoglobin, Ferritin, and TSAT (Safety Population) in 1VIT13036

Parameter	Cohort 1 (N=16)	Cohort 2 (N=19)
Hemoglobin, g/dL		
Screening mean (SD)	9.2 (1.20)	9.5 (0.81)
Mean change at Day 35 (SD)	1.9 (1.38)	2.8 (1.15)
Ferritin, ng/mL		
Screening mean (SD)	8.9 (9.94)	20.2 (67.37)
		N=18
Mean change at Day 35 (SD)	35.1 (98.22)	52.4 (31.70)
TSAT, %		
Screening mean (SD)	7.5 (4.64)	3.4 (1.61)
		N=18
Mean change at Day 35 (SD)	9.9 (11.54)	13.5 (6.88)

SD = standard deviation.

Similar percentages of participants in Cohort 1 (56.3%) and Cohort 2 (63.2%) reported at least 1 treatment-emergent adverse event (TEAE). At least 1 drug-related treatment-emergent adverse event was reported by 3 of 16 (18.8%) participants in Cohort 1 and 6 of 19 (31.6%) participants in Cohort 2. Specifically, the only TEAE considered related to study drug that was experienced by >1 participant was urticaria (3 participants in Cohort 2). Other TEAEs considered related to study drug and experienced by 1 participant each included infusion site pruritus, thirst, and hot flush in Cohort 1 and abdominal pain upper, gastroduodenitis, hyperthermia, injection site pain, alanine aminotransferase increased, headache, pruritus, rash, and hypertension in Cohort 2. Two participants in Cohort 1 experienced a serious adverse event. (Table 2)

Table 2. Overview of Treatment-Emergent Adverse Events (Safety Population) in 35 Study Subjects

Type of Treatment-Emergent Adverse Event	Cohort 1 (N=16) No. (%)	Cohort 2 (N=19) No (%)
Any[a]	9 (56.3)	12 (63.2)
At least 1 serious event	2 (12.5)	0
At least 1 severe event[b]	1 (6.3)	0
At least 1 related to study drug[c]	3 (18.8)	6 (31.6)

CTCAE = Common Terminology Criteria for Adverse Event
a If a subject experienced the same event more than once, the first occurrence was tabulated.
b CTCAE Grade 3, 4, or 5.
c Possibly or probably related to study drug.

Further justification for the 15 mg/kg dose is provided by internal modeling data, which demonstrated comparable total serum iron clearance profiles between pediatric and adult populations.[14] Lastly, a retrospective cohort study of 72 pediatric patients with IDA refractory to oral iron treatment ranging in age from 9 months to 18 years treated with 15 mg/kg of FCM (maximum single dose of 750 mg; median dose 750 mg) supports this dosing.[12]

3.3 Rationale for Sparse Pharmacokinetic Sampling:

Population-based PK/PD modelling describing the time course of total serum iron (TSI) concentrations and the relationship between TSI and changes of hemoglobin following a single dose of intravenous FCM in pediatric subjects with IDA has been performed using intensively sampled data from Study 1VIT13036.[16] It is proposed to supplement this initial modelling with additional sparsely sampled PK data from this study. Based on the anticipated visit duration on the 2 FCM administration days in this study, the following sparse PK sampling scheme is proposed: pre-dose, immediately (within 5 minutes) post-infusion and 60 minutes post-dose on Days 0 and 7, on which subjects will receive 15 mg/kg (up to a maximum dose of 750 mg). This pragmatic approach, which minimizes the number of blood draws compared to a full PK profile, is expected to facilitate exposure-response analysis for the proposed FCM regimen.

3.4 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 Assessments		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.

4.0 PARTICIPANT SELECTION

4.1 Number and Type of Participants

Approximately 72 participants who have given written informed consent/assent with a diagnosis of IDA who fulfill the inclusion criteria and do not meet any of the exclusion criteria will be randomized to receive either FCM or Oral Iron.

4.2 Screening Phase

A subject who enters the screening phase will be assigned, via the IRT system, a unique screening number. From the time of consent until the start of treatment with study drug, the participant will not receive any form of supplemental iron outside of the study (intravenous or blood transfusion iron from 4 weeks prior to consent or oral iron including multivitamins with iron from time of consent). Dietary iron intake will not be restricted during participation in the study.

If the participant does not qualify for study entry, the participant should be entered into the IRT system as a screen failure. Participants can be re-screened once (**See section 6.2**).

4.2.1 Inclusion Criteria

1. Male or female participants 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening hemoglobin <11 g/dL.
3. Screening ferritin ≤ 300 ng/mL and TSAT <30%.
4. Documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to randomization.
5. If receiving an ESA: stable ESA therapy (+/- 20% of current dose) for at least 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial.
6. If undergoing treatment for IBD must be on stable therapy for at least 8 weeks prior to consent.

4.2.2 Exclusion Criteria

1. Known history of hypersensitivity reaction to any component of FCM.
2. Previous randomization and treatment in this study or any other clinical study of FCM.
3. History of acquired iron overload, hemochromatosis, or other iron accumulation disorders.
4. Significant severe diseases of the liver, hematopoietic system, cardiovascular system, psychiatric disorder, or other conditions which on the opinion of the investigator may place a subject at added risk.
5. Any existing non-viral infection.
6. Known history of positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.

7. Known history of positive HIV-1/HIV-2 antibodies (anti-HIV).
8. Anemia due to reasons other than iron deficiency (e.g., hemoglobinopathy and vitamin B12 or folic acid deficiency) that have not been corrected.
9. Intravenous iron and /or blood transfusion in the 4 weeks prior to consent.
10. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
11. Alcohol or drug abuse within the past six months.
12. Female participant who is pregnant or lactating, or sexually active female of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
13. Unable to comply with study procedures and assessments.

4.3 Participant Assignment and Randomization Process

Participants who satisfy the inclusion requirements and no exclusionary criteria will be eligible to participate in this study and entered into the IRT system. Randomization will occur in a 1:1 ratio to either Group A, participants receiving FCM, or Group B, participants receiving oral iron (oral solution drops, elixir or oral tablets). 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 receive ferrous sulfate elixir or ferrous sulfate tablets, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. Participants who experience adverse clinical symptoms due to the oral iron during the treatment phase may have their weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. If the participant is receiving tablets, the dose will be reduced from one tablet taken twice daily to one tablet per day.

4.4 Withdrawal from Study

Any participant who wishes to withdraw from the study may do so at any time without the need to justify their decision. The investigator may withdraw a participant from active study treatment at any time if it is felt to be in the best interest of the participant.

4.5 Discontinuation from Study Drug

Participants may elect to discontinue study drug, but wish to remain in the study for follow-up. In those situations, patients will be asked to continue the normal clinical trial schedule for ascertainment of safety events.

4.6 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

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.

5.0 STUDY DRUG

5.1 Formulation, Packaging and Storage

All investigational medication to be used in this study [supplied by American Regent, Inc.] will have been prepared according to Good Manufacturing Practices (GMP).

FCM (trade name, Injectafer®) will be supplied as 15 ml vials, containing 750 mg of iron as 5% w/v iron containing a polynuclear iron(III)-hydroxide 4(R)–(poly-(1→4)-*O* α -D-glucopyranosyl)-oxy-2 (R), 3(S), 5(R), 6-tetrahydroxy-hexonate complex in a solution of water for injection [50 mg/ml] and will be labeled according to FDA investigational regulatory requirements.

Oral iron will be provided depending on participant's age as either blister packs of oral iron tablets or oral liquid formulation (drops or elixir) in pre-filled syringes.

All study drugs (FCM and ferrous sulfate) must be kept in a secure place at the investigational site, and stored at room temperature (See USP). The study medication should not be frozen. Vials of FCM may not be used for more than 1 dose, or for more than 1 participant. All FCM vials, oral iron blister packs and syringes (used and unused) should be kept by the study staff for reconciliation by the monitor. Following reconciliation, sites may destroy used and unused study drug on site using local procedures, provided a drug destruction policy is in place, or it may be returned to American Regent, Inc.

5.2 Drug Administration/Regimen

The Principal Investigator or designee will supervise administration of the study drug to participants. Group B (Ferrous sulfate) the first dose of will be administered before the end of the Day 0 visit.

Group A: Group A (FCM) will receive a dose of FCM at 15 mg/kg to a maximum single dose of 750 mg (whichever is smaller) on Days 0 and 7 for a maximum total dose of 1500 mg. FCM will be administered as either an undiluted IV push at a rate of 100 mgs (2 mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes.

Group B: Group B (Oral Ferrous sulfate) will receive an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age will receive 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 will receive 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) will receive oral ferrous sulfate drops, while children (ages ≥4 to <12 years)

will have the option to receive oral ferrous sulfate elixir or oral ferrous sulfate tablets. Adolescents (ages ≥12 to 17 years) will receive an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants is 130 mg of elemental iron.

5.3 IV Medication Precautions

When administering FCM, the following precautions will be taken:

- The participant will be evaluated clinically prior to drug administration to assess the development of clinically-significant conditions.
- The vials will be visually inspected for particulate matter and discoloration before use. If noted, the vial will not be used, and the Investigator or his designee will notify the sponsor or sponsor's designee for replacement of the study drug, and for direction on the return of the unused vial.
- Heart rate and blood pressure will be assessed pre-, immediately (within 5 minutes) post, and 30 minutes post administration. Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.
- The participant will be monitored for at least 30 minutes for serious acute reactions as hypersensitivity or bioactive (labile) iron reactions to non-dextran IV iron products have rarely been reported. The reactions include: hypotension, loss of consciousness, bronchospasm with dyspnea, shortness of breath, and seizures.
    - In the event a serious acute reaction is seen, the site must have the capability to provide appropriate resuscitation measures. These may include IV NS, IV epinephrine, steroids, and/or antihistamines.

5.4 Drug Accountability

Investigators will keep records of the receipt, administration and return of the study drug (FCM and ferrous sulfate). They will not allow the study drug to be used for purposes other than as directed by this protocol. The investigator agrees that he/she will not supply study medication to any persons other than those enrolled in the study, or to investigators not listed on the FDA 1572. When the study is completed, or if it is prematurely terminated, a final inventory of all clinical supplies must be compiled and the remainder of the unused study drug will be returned to American Regent, Inc., or destroyed on site, per the site's documented locally accepted policies. All data regarding the study drug must be recorded as per the Monitoring Plan.

5.5 Concomitant Medication

All concomitant medications will be recorded in the eCRF from 30 days prior to consent. **No additional iron preparations (IV iron from 4 weeks prior to consent or oral iron**

including multivitamins with iron, from time of consent) will be allowed. No prophylactic medications may be administered prior to FCM administration without prior approval from American Regent, Inc.

If receiving an ESA, a stable (± 20%) dose is required for at least 8 weeks prior to consent. The ESA type, route, frequency and dose will remain unchanged throughout the study unless the dose should be decreased or held per the package label. Once decreased or held, it may not be increased or restarted unless thought necessary by the subject's physician. If the latter event occurs, these data points will be collected and the subject will continue for safety analysis.

If receiving treatment for IBD, therapy must be stable for at least 8 weeks prior to consent and remain stable through the duration of the study.

6.0 STUDY PROCEDURES

6.1 Informed Consent

Prior to any study specific procedures, the investigator must explain to each participant the nature of the study, its purpose, procedures to be performed, expected duration, and the benefits and risks of study participation. After this explanation, the participant (who for this trial is 1 -17 years old) must assent, if appropriate, and his/her legal guardian (who is above age of legal consent) voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The Code of Federal Regulations (CFR) is a codification of rules and regulations of the US government. Subjects who are too young to sign an ICF, but mature enough to understand the study, will provide informed assent per local law. The subject must be able to understand that he or she can withdraw from the trial at any time and for any reason. The participant's legal guardian will be given a copy of the signed consent form.

6.2 Screening Phase

6.2.1 Screening Visit 1 (Day -7 ± 1)

Each participant who qualifies for inclusion will undergo the following clinical evaluations to confirm their eligibility for the study:

- Obtain screening number from IRT
- Medical history, including documented history of an inadequate response after at least 8 weeks of prior oral iron therapy use
- Hematology, chemistries and iron indices
- Serum pregnancy test for female participants of child bearing potential (negative results must be obtained prior to randomizing the participant for study drug dosing).
- Height and weight
- Vitals signs (including sitting heart rate and blood pressure)

- Concomitant medications assessment
- ESA and IBD therapy stability (if applicable)

** Participants who do not meet the entry criteria should be entered into the IRT system as a screen failure. A participant may be re-screened, only one time, once it is believed that they would qualify for study entry. The participant will need to re-sign a new consent form and all screening procedures in section 6.2 will need to be repeated.

6.3 Treatment Phase (Day 0 to Day 35)

6.3.1 Day 0 Visit

The following will be obtained and/or completed before contacting IRT for randomization:

For all participants:

- Verify all inclusion and exclusion criteria (**See section 4.2.1 and 4.2.2**)
- Physical exam
- Review concomitant medications (to include ESA and IBD stability, if applicable).

A participant who develops a bacterial infection during the screening phase should be discontinued and treated appropriately. These participants may be re-screened, one time, once the enrolling physician deems the participant would qualify for study entry. The participant will need to re-sign a new consent / assent form and all screening procedures in section 6.2 will need to be repeated.

After verifying the eligibility of the participant, the IRT system will then be contacted by a study team member. Randomization will be stratified by hemoglobin (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years), and randomized in a 1:1 ratio to either Group A (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) or Group B (Ferrous sulfate, dose and regimen dependent upon age and weight, twice daily for 28 days.

After a randomization number has been obtained, the **first dose** of oral ferrous sulfate will be administered in the clinic according to the following: infants and children (1 to <4 years of age) will receive ferrous sulfate drops; children (≥4 to <12 years of age) will receive ferrous sulfate elixir or ferrous sulfate tablets; and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets.

A sufficient quantity of doses for a 7-day period will be dispensed to the parent or guardian of the participant. The parent or guardian of the participant will be responsible for the administration of two daily doses of oral ferrous sulfate to the participant.

After assignment of the treatment group, the following will occur:

All participant's (prior to study drug administration/dispensing, if applicable) on Day 0:

- Blood samples for central lab hematology, chemistries, and iron indices (Group

A participants will have an additional blood sample for PK prior to dosing)
- Vital signs: temperature, sitting heart rate and blood pressure
- Weight

Group A:

- Blood samples for PK immediately (within 5 minutes) post-dose and 60 minutes post dose.
- Verify amount of single FCM dose (15mg/kg up to a maximum single dose of 750 mg).
- Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute or in no more than 250 mL of normal saline and infused over 15 minutes.
- Document start and stop time of FCM administration and the total dose administered and if diluted.
- Post-administration evaluation to include measurement of sitting heart rate and blood pressure immediately (within 5 minutes) after and 30 minutes after FCM administration.
- Adverse event / serious adverse event assessment (starting at beginning of FCM injection).

Group B:

- Oral ferrous sulfate dispensing:
    - The first dose of ferrous sulfate will be administered before the end of the Day 0 visit.
    - Parents or guardians of participants will be responsible for the administration of twice daily dosing of oral ferrous sulfate. Participants that experience adverse events may continue with a dose-reduced regimen [3 mg/kg twice daily] of oral ferrous sulfate after a consult with the investigator. (**See Section 6.3.5 for oral iron dose reduction)**
    - Parents or guardians of participants will be dispensed oral iron on Days 0, 7, and 14. Used dispensing packs/blisters/syringes will be returned and are to include both the empty containers and any unused medication.
    - A record of compliance will be maintained for each participant and reviewed at each study visit. (**See Section 6.3.2 for compliance assessment**).
    - If the participant took less than the amount of oral iron expected, document the reason(s) for missed doses and counsel the participant/parents/guardians about the importance of taking the study drug as prescribed.
- Adverse event assessment (starting once the participant takes the first in-clinic dose).

6.3.2 Day 7 and Day 14 Visit

All participants will return to the clinic on Day 7 and 14. Prior to the administration of the study drug (if applicable), the participant will be evaluated clinically to assess for the development of clinically significant conditions that may contraindicate dosing.

- Vital signs (including sitting heart rate and blood pressure)
- Blood samples for central lab hematology, chemistries and iron indices (Group A participants will have an additional blood sample for PK prior to dosing).
- Concomitant medications assessment
- Adverse events assessment
- ESA and IBD stability (if applicable)

For Group A participants the following will be performed on **Day 7 only**:

- Blood samples for PK immediately (within 5 minutes) post-dose and 60 minutes post dose.
- Verify amount of single FCM dose (15mg/kg up to a maximum dose of 750 mg).
- Pre-administration evaluation to include measurement of heart rate, blood pressure, and body temperature.
- Administer FCM as a slow IV injection at the rate of approximately 2 mL /minute or in no more than 250 mL of normal saline and infused over 15 minutes.
- Document start and stop time of FCM administration and the total dose administered and if diluted.
- Post-administration, obtain sitting heart rate and blood pressure immediately (within 5 minutes) after and 30 minutes after FCM administration.

For Group B participants the following will be performed:

- Oral iron dispensing **(Day 7 and Day 14).**

- Compliance will be assessed according to the following:

For ferrous sulfate tablets:

  - Used blister packs will be returned and are to include both the empty containers and any unused medication.
  - The blister packs will be examined to assess compliance (the number taken divided by the number of pills expected to be taken). A record of compliance will be maintained for each participant and reviewed.
  - If the participant took less than the number of tablets expected, document the reason(s) for missed doses and counsel the participant/parent/guardian about the importance of taking the study drug as prescribed.

For ferrous sulfate drops and elixir:

  - Used oral syringes will be returned which will include any unused medication.

- The oral syringes will be examined to assess compliance (the volume remaining in the oral syringes divided by the expected amount to be taken). A record of compliance will be maintained for each participant and reviewed.
- If the participant took less than the volume expected, document the reason(s) for missed doses and counsel the participant/parent/guardian about the importance of taking the study drug as prescribed.

6.3.3 Day 28

- Vitals signs
- Hematology, chemistries and iron indices
- Concomitant medications assessment
- ESA and IBD stability (if applicable)
- Adverse events assessment
- For Group B participants, oral iron compliance assessment

6.3.4 Day 35 (End of Study / Early Termination)

- Physical exam
- Vitals signs
- Hematology, chemistries, and iron indices
- Serum pregnancy test for female participants of child bearing potential
- Concomitant medications assessment
- ESA and IBD stability (if applicable)
- Adverse events assessment
- Log into IRT and enter participant as complete

The participant has completed the study after the Day 35 visit is complete. If for any reason the participant does not complete the study the Day 35 procedures should be completed prior to the participant exiting from the trial.

6.3.5 Oral Iron Dose Reduction during the Treatment Phase

Participants who experience adverse events possibly or probably due to the oral iron during the treatment phase will have their dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg while maintaining the same frequency of twice per day. If the participant is receiving tablets, the dose will be reduced from one tablet taken twice daily to one tablet per day.

6.3.6 Pharmacokinetic Sampling

Blood samples will be collected for PK assessment pre-dose, immediately (within 5 minutes) post-dose, and 60 minutes post-dose for participants receiving FCM on Days 0 and 7. Blood samples should be taken at approximately the same time of day (within 1 hour) on Day 7 as Day 0.

The pharmacokinetic parameters to be analyzed in this study are as follows: the maximum serum concentration (C_{max}) and the time at which C_{max} occurs (T_{max}), the area under the

serum concentration-time curve from time zero to the last sampling time with a quantifiable concentration ($AUC_{0\text{-time last measured concentration}}$), the extrapolated area under the serum concentration- time curve from time zero to infinity ($AUC_{0\text{-infinity}}$), and the half-life ($T_{1/2}$). The secondary parameters were the mean residence time (MRT), the apparent serum clearance (Cl), and the apparent volume of distribution (V_D), which includes the initial volume of distribution following the injection (V_{Dc}), the volume of distribution at the steady state (V_{Dss}), and the volume of distribution at the final elimination (V_{Darea}).

6.4 Central Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. All serum laboratory testing will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 35 laboratory, this laboratory may be obtained after notification of the Sponsor. The laboratory assessments will be determined as listed in Section 3.4.

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

7.0 ASSESSMENT OF SAFETY

7.1 Adverse Events

Any untoward medical event experienced by a participant during the course of this clinical trial, whether or not it is related to the investigational product, at any dose, is considered an adverse event (AE).

For any laboratory abnormality, the investigator will make a judgment as to its clinical significance. If the laboratory value is outside the normal limits and is felt to represent a clinically significant worsening from the baseline value, it should be considered an adverse event and should be recorded on the Adverse Events page of the eCRF. If the laboratory value is outside the normal range, but not an adverse event, the investigator should comment on the findings (i.e., “not clinically significant” or “unchanged from baseline”) in the source documentation [laboratory report]. All laboratory values at the end of study/Day 35 that have been deemed clinical significant by the Investigator should be followed until they are back into normal range.

For the purposes of this study, non-serious anemia (Hgb or Hct 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.

To quantify the severity of adverse events, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version 5 or higher should be used to grade all events. These criteria are provided in the procedure manual.

If a CTCAE criterion does not exist, the investigator should use Table 7.1.1 to assign the adverse event grade.

Table 7.1.1 Grading of Adverse Event Severity

Grade	Adjective	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (i.e., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (i.e., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Results in death due to the AE

Timing: Non-serious AE will be reported from the initial treatment with *Study Drug through the completion of the study Day 35. Adverse events will be captured 28 days post the last dose of study drug for participants who receive study drug and terminate early from the trial. This can be completed via a phone call. All ongoing AE's related to study drug (FCM or ferrous sulfate) should be followed until they are no longer related, have taken a confounding medication or return to baseline grade

Relationship (Causality): The Investigator will be asked to document his/her opinion of the relationship of the event to the study drug* as follows:

- NONE There is *no* evidence of any causal relationship.

- UNLIKELY There is *little* evidence to suggest there is a causal relationship. There is *another reasonable explanation* for the event (e.g., the participant's clinical condition, other concomitant treatments).
- POSSIBLE There is some evidence to suggest a causal relationship (i.e., there is a reasonable possibility that the adverse experience may have been caused by the agent). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- PROBABLE There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

* For the purposes of this trial, "study drug" is defined as:

FCM

OR

Ferrous Sulfate

7.2 Reporting of Adverse Events

Adverse experiences will be elicited by nonspecific questions such as "Have you noticed any problems?" Participants will be encouraged to report adverse events at their onset. Any adverse experience spontaneously reported by, elicited from the participant, or observed by the physician or study staff, shall be recorded on the appropriate Adverse Event page of the eCRF. The investigator will record the date and time of onset, severity, the relationship to study medication, the date and time of resolution (or the fact that the event is still continuing), the action taken, and the outcome of the adverse experience on the Adverse Event page of the eCRF. Whenever possible, the investigator should group together, into a single term, signs and symptoms which constitute a single diagnosis. For example, cough, rhinitis and sneezing might be grouped together as "upper respiratory infection."

7.3 Serious Adverse Events

Definition: An adverse event is classified as SERIOUS if it meets any one of the following criteria:

- **Death**
- **Life-Threatening:** The participant was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the participant's death.
- **Hospitalization (initial or prolonged):** Required admission to the hospital or prolongation of a hospital stay.

- **Disability:** Resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function/structure, physical activities or quality of life.
- **Congenital Anomaly/Birth Defect.**
- **Important medical events:** Other medically important events that, in the opinion of the investigator, may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

A distinction should be drawn between SAE and severe AE. A SAE is a major experience of its type. A SAE is not necessarily serious: e.g. nausea, which persists for several hours, may be considered severe nausea, but it is not an SAE. On the other hand a stroke, which results in only a limited degree of disability may be considered a mild stroke, but would be a SAE.

Timing: All SAEs will be reported from the day of initial treatment with *study drug through the completion of the study Day 35. Serious adverse events will be captured 28 days post the last dose of study drug for participants who are randomized and terminate early from the trial. This can be completed via a phone call. Hospitalization resulting from a historical condition (present prior to initial treatment with study drug or prescheduled prior to treatment with study drug) that has not increased in severity or led to prolongation of hospital stay should not be considered a SAE. All reported SAE should be followed until they are no longer serious or return to baseline grade.

Reporting: Any SAE, starting with the first dose of study drug, that is to be reported (as outlined in Timing section above) must be reported immediately (**within 24 hours of learning of the event**) to American Regent, Inc. by telephone, email and/or fax of the written SAE report form to the contacts listed below:

American Regent, Inc.

Tel: 800-734-9236

Email: pv@americanregent.com

The local investigator is responsible for reporting SAEs to their local IRB/ Ethics Committee based on local reporting guidelines (which may be different than those specified in this protocol). The responsible investigator should institute appropriate diagnostic and therapeutic measures and keep the participant under observation for as long as is medically indicated.

8.0 STATISTICS

All hypothesis tests and confidence intervals will be two-sided. No correction for multiple testing will be applied amongst the secondary endpoints. Except where otherwise noted, the statistical model on which inference is based will include terms for randomization strata.

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, Q1, Q3, minimum and maximum. Other descriptive statistics (e.g., coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages.

Generally, data will be summarized by nominal visit. However, data from both unscheduled and scheduled will be used for determination of last observed value, and in worst- or best-case changes and/or shifts from baseline. Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

A complete description of the statistical analyses and methods will be available in a Statistical Analysis Plan (SAP), which will be finalized before the database is locked.

8.1 Stratification/Randomization

Participants who meet the inclusion/exclusion criteria will be randomized on Day 0 to FCM or oral iron in a 1:1 ratio. The randomization will be stratified by hemoglobin (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years).

8.2 Analysis Populations

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.

Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will comprise all participated 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 primary population for the assessing efficacy will be the mITT population.

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.

Pharmacokinetics Population

The Pharmacokinetics (PK) population will consist of all participants in the Safety population with at least one measurable concentration of FCM.

8.3 Disposition and Baseline Characteristics

The number of participants in each investigative site will be summarized. The number of participants who are screened, randomized, treated, prematurely discontinue, and complete the study will be summarized.

The clinical team will identify deviations and the deviations will be identified in the database. Participants with clinically important protocol deviations will be summarized.

Demographics and baseline characteristics will be summarized using descriptive statistics or frequency counts.

8.4 Endpoints and Definitions

8.4.1 Primary Endpoint

The primary endpoint is the change in hemoglobin from baseline to day 35. The change in hemoglobin from baseline to day 35 will be analyzed using parametric analysis of covariance (ANCOVA). The model will include terms for the randomization strata (hemoglobin and age categories), baseline hemoglobin, as well as treatment group. Baseline hemoglobin will be defined as the last hemoglobin obtained before randomization.

The primary endpoint will be analyzed for the mITT population.

Subgroup analyses

The change in hemoglobin from baseline to day 35 will be summarized separately for the following subgroups:

- Cause of IDA: IBD, not IBD
- CKD, not CKD
- Baseline hemoglobin : <10, ≥10 g/dL
- Age: 1 to <12, ≥12 to 17 years

Estimates of treatment effect together with 95% confidence intervals will be displayed graphically.

Subgroup analyses will be conducted for the mITT population.

8.4.2 Secondary Endpoints

Secondary efficacy endpoints include:

- Change in ferritin from baseline to Day 35
- Change in TSAT from baseline to Day 35
- Changes from baseline to in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin content.
- Pharmacokinetic assessments, including C_{max}, T_{max}, $AUC_{0\text{-time last measured concentration}}$, $AUC_{0\text{-infinity}}$, $T_{1/2}$, MRT, Cl, V_D, V_{Dc}, V_{Dss}, and V_{Darea}. These assessments will be

based on a population pharmacokinetic analysis using data from this study and 1VIT13036.

Continuous efficacy endpoints will be analyzed using ANCOVA as described for the primary endpoint. Binary efficacy variables will be analyzed using stratified Cochran-Mantel-Haenszel chi-square tests.

All secondary efficacy endpoints will be analyzed for the mITT population.

Details of analyses for these endpoints will be outlined in the SAP.

Pharmacokinetics and Pharmacodynamics (PK/PD) Endpoints

The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin®. All calculations of non-compartmental parameters will be based on actual sampling times. The actual sampling times and doses will be used for the analysis. The PK parameters will be calculated with and without adjustment for baseline. All derived PK parameters will be listed. The following summary statistics will be calculated: n, mean, standard deviation [SD], coefficient of variation (CV) , median, minimum, and maximum, along with geometric mean, geometric mean SD, geometric percent coefficient of variation [%CV], and 95% CIs around the geometric mean. For T_{max}, only n, median, minimum and maximum will be presented.

In addition, nonlinear mixed effects modelling will be used derive population PK parameters and/or models. The influence of various covariates (e.g., age, weight, sex, race) on the variability will be examined. Further details will be provided in the SAP.

The relationship between FCM exposure and clinical outcome may be explored graphically. If appropriate, a relationship may be established between FCM exposure and effect or any special interest adverse events. Further details will be provided in the SAP.

8.4.3 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. Details will be provided in the SAP.

8.5 Analyses of Safety

8.5.1 Study Drug Exposure

For FCM, the number of infusions and total administered amount of iron will be summarized descriptively. For oral iron, the total amount of iron will be summarized descriptively.

8.5.2 Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The number and percent of participants who report TEAE will be summarized for each treatment group. A TEAE is an event with onset date on or after the study drug start date.

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.

The adverse event profile will be characterized with severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) and relationship (unrelated and related) to study drug. Related adverse events will be events that are possibly or probably related to treatment in the investigator's judgment.

Participants who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study drug when summarized by relationship. If a participant reports multiple preferred terms for a SOC, the subject will be counted only once for that SOC.

The number and percent of participants who report treatment-emergent serious adverse events will be similarly summarized for each treatment group. The number and percent of participants who report treatment-emergent adverse events resulting in discontinuation of study drug will be similarly summarized for each treatment group.

8.5.3 Adverse Events of Special Interest

Adverse events (AEs) of special interest include hypersensitivity, hypersensitivity-like reactions, and cardiovascular events. Hypersensitivity and hypersensitivity-like reactions will be identified using standardized MedDRA queries. Cardiovascular events will be identified using the SOCs for cardiac disorders and vascular disorders.

The overviews and summaries that are provided for all TEAEs will also be provided for the AEs of special interest. In addition, the time to onset and time to recovery will be summarized.

8.5.4 Clinical Laboratory Findings

Clinical laboratory variables will be presented in two ways. First, the mean change from baseline to each scheduled visit will be summarized. Second, the number and percent of participants with treatment-emergent PCS laboratory values will be tabulated. Treatment-emergent PCS laboratory tests are those in which the baseline value is normal and post-baseline value is abnormal (i.e., meets Grade III or Grade IV toxicity criteria from the NCI-CTC Version 5 or higher). Baseline will be defined as the last value obtained before randomization.

No formal statistical tests will be performed.

8.5.5 Vital Signs

For the FCM group, 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.

8.6 Sample Size Rationale

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 20% attrition of subjects not meeting the definition of mITT, approximately 72 participants will be randomized.

9.0 ADMINISTRATIVE CONSIDERATIONS

9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including a copy of the eCRFs, Informed Consent documents, and adequate records for the receipt and disposition of study medications, for a period of two years following a supplemental application for the drug for the indication being investigated, or until two years after the drug investigational program is discontinued.

The Investigator must make study data accessible to the monitor, Sponsors, or other authorized representatives of the Sponsor and Regulatory Agency (i.e., FDA inspectors.) A case history for each participant must be maintained, and this should include the signed Informed Consent form and copies of all study documentation related to that participant. The investigator must ensure the availability of source documents including the electronic health record, if applicable, from which the information on the eCRF was derived.

9.2 Investigator Responsibilities

By signing the Form FDA 1572 the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor, except when necessary to protect the safety, rights or welfare of participants.
2. Personally conduct or supervise the study (or investigation).
3. Inform any participants that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator's Brochure, including potential risks and side effects of the drug.

7. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62, and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to participants or others (including amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the participant/participants.
12. To comply with all other requirements regarding the obligations of the clinical investigators and all other pertinent requirements listed in 21 CFR Part 312.

9.3 Financial Disclosure

All principal investigators and co-investigators will be required to complete FDA-required financial forms provided by American Regent, Inc. All signed financial disclosure forms must be submitted to the Sponsor prior to the site enrolling participants into the study.

9.4 Advertisement for Participant Recruitment

All advertisement for participant recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisement may include but is not limited to: newspaper, fliers, radio, and television. Any compensation to the participant included in the advertisement must be identical to the compensation stated in the IRB-approved informed consent.

9.5 Documents Required for Study Initiation

Prior to study initiation, the investigator must provide American Regent, Inc. or its designee with the following documentation:

- Curriculum Vitae and medical licenses for Principal Investigators and co-investigators.
- Form FDA 1572
- Financial disclosure form(s)
- IRB approval of protocol and informed consent
- Copy of IRB approved informed consent
- IRB membership list or assurance number
- Protocol signature page
- IRB approval of any advertising for participant recruitment [if applicable]
- Copy of advertising [if applicable]

- IRB approval of translation of informed consent [if applicable]

9.6 Quality Control and Quality Assurance

9.6.1 Investigator Selection Criteria

Each investigator participating in this study will meet the following criteria:

- Accessible, interested, and available support staff.
- Availability of adequate facilities to support study requirements.
- Availability of physician emergency response at all times.
- Adequate time to conduct study.
- Adequate training and experience of personnel to conduct study.
- Ability to recruit enough participants to conduct study.

Prior to investigator selection, each site will be evaluated to ensure they meet the criteria noted above.

American Regent, Inc. and/or their designee will insure that no investigator is on FDA's Debarment List or Disqualified Investigator List.

9.6.2 Clinical Monitoring

This study will be monitored by the Sponsor (or its designee) in accordance with FDA and International Conference on Harmonisation Good Clinical Practices (GCPs), 21CFR Part 312. As part of a concerted effort to follow the study in a detailed and orderly manner, and in accordance with established principles of GCP and applicable regulations, a Monitor will visit the site according to the monitoring plan and will maintain telephone and written communication throughout the duration of the study.

9.6.3 Quality Assurance Audit

For the purpose of data validation, the principal investigators will permit a member of the quality assurance unit of American Regent, Inc. or its designee to inspect the source data and compare them with the eCRFs. Pre-study audits, interim audits, and post-study audits may be performed and these may include a review of facilities, equipment, pertinent site documentation, and personnel qualifications. Notification of these audits will be sent to investigators in advance.

9.7 Ethics

9.7.1 Ethical and Legal Issues

This study will be performed in accordance with the U.S. Code of Federal Regulations on Protection of Human Participants (21 CFR 50), IRB regulations (21 CFR 56), the most recent revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312, and applicable ICH guidelines.

9.7.2 Institutional Review Board

The Protocol and the Informed Consent must be approved by an appropriate Institutional Review Board (IRB) before the study is initiated. Documentation of this approval must be provided to the Sponsor or designee. The IRB must comply with current U.S. Regulations (21 CFR 56) for the protection of Human Subjects in Research. Investigators are responsible for the following:

- Obtain IRB approval of the protocol, Informed Consent, and any advertisements to recruit participants; obtain IRB approval for any protocol amendments and Informed Consent revisions before implementing the changes.
- Provide the IRB with any information it requests before or during the study.
- Submit progress reports and a final report to the IRB, as required, during the conduct of the study; request re-review and approval of the study as needed; provide copies of all IRB re-approvals and relevant communication with the Sponsor.
- Notify the IRB of all serious adverse events that occur or are reported to you by the Sponsor as required by the IRB.

9.7.3 Informed Consent

Informed consent / Assent (when appropriate) must be obtained from each participant prior to study participation. The informed consent / assent will be provided to the participant in their native language. The consent/assent form must be signed by the participant and/or the participants legally authorized representative. Each investigational site must provide the Sponsor (or designee) with a copy of the Informed Consent / Assent approved by that site's Institutional Review Board. The original signed consent / assent form will be retained in the participant's study records, and a copy will be provided to the participant. The Clinical Monitor will assure that each Informed Consent / Assent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outlines the basic elements of informed consent and ICH guidelines. Translations of the informed consent / assent must be certified by a qualified translator and their use must be documented.

The Informed Consent / Assent documents the information that the Investigator provides to the participant and the participants agreement to participate. The Investigator will fully explain the nature of the study, along with the aims, methods, anticipated benefits, potential hazards and discomfort that participation might entail. The Informed Consent / Assent must be signed and dated by each participant and/or legal representative before entering the study and prior to the performance of any study specific procedures.

9.7.4 Good Clinical Practice

The conduct of the study will conform with the recommendations for clinical studies in humans as set out in the most current revision of the “Declaration of Helsinki”, the local

legal requirements and the guidelines on "Good Clinical Practice", [21 CFR Part 312 and ICH guidelines].

9.8 Data Handling and Record Keeping

9.8.1 Case Report Form

The eCRFs will be completed for each participant in this study. The participants in this study will be identified only by a participant number on these forms.

The eCRF used will be 21 CFR 11 compliant. The system used for data collection (eCRF) will meet all applicable regulatory requirements for recordkeeping and record retention as would be provided with a paper system. Security measures will be utilized to prevent unauthorized access to the data and to the computerized system. Changes made to data that are stored on electronic media will always require an audit trail, in accordance with 21 CFR 11.10(e).

The eCRFs must be reviewed and verified for accuracy by the Principal Investigator. An electronic copy of the eCRF will remain at the site at the completion of the study.

9.8.2 Confidentiality

All unpublished information given to the investigator or institution dealing with this study, study drug, or the conduct, financial agreements, or methodologies used in this protocol, as well as information obtained during the course of the study, remains confidential and proprietary to the Sponsor ["Proprietary Information"]. The Investigator shall not disclose any such Proprietary Information to any third party without prior written consent from the sponsor [See also Section 9.9 Publication Policy]. For purposes of this Section, "Investigator" includes, but is not limited to the Principal Investigator and/or his/her agents, designees, sub-investigators or other individuals involved in the running, administration, collection or evaluation of participants or data for this study.

All pharmaceutical formulations supplied for the purpose of the trial shall remain the sole property of American Regent, Inc. They will be used exclusively for the purposes specified in the protocol. Any unused medication will be returned to the sponsor at the conclusion of the study.

No patent application based on the results of this study should be made by the investigator and all such rights assigned to American Regent, Inc., and no assistance should be given to any third party to make such an application without the written authorization of American Regent, Inc.

9.8.3 Termination of the Study

The study may be terminated if the Data Safety Monitoring Board (DSMB), Sponsor, or Steering Committee discovers conditions arising during the course of the study, which indicate that the clinical investigation should be halted. The study may be terminated after appropriate consultation and discussion.

Conditions that may warrant study termination include, but are not limited to, the discovery of a significant, unexpected and unacceptable risk to the participants, failure of the investigator to enroll participants at an acceptable rate, insufficient adherence to the protocol requirements, completion of study objectives, or at the discretion of the sponsor.

9.8.4 Protocol Revisions

Changes in any portion of this protocol that affect participant safety or welfare or which alter the scientific validity of the study must be documented in the form of an amendment. This change must be signed by the appropriate American Regent personnel and the investigator and be approved by the site's IRB, before the revision may be implemented. The protocol revision will be submitted to the FDA.

9.8.5 Protocol Administrative Changes

Clarification or interpretation of the study protocol or changes in the methods of statistical analysis may be documented in the form of a numbered memo or other applicable document (charter, plan, etc.). Numbered memos do not typically require the investigator's signature or IRB approval.

9.9 Publication Policy

All information resulting from this study is the Proprietary Information of American Regent Inc., as per the Confidentiality Section of this protocol. The Steering Committee will be responsible for the manuscript describing the main study results, and oversee publications requiring trial data. A separate publication charter will govern the process of publications.

American Regent, Inc., and the Steering Committee shall have final and sole control over the content of any publication. The Principal Investigator and any sub-investigators may make presentations on the study, or may publish results of the study at their site, but only after the results of the study have been published, or with the prior approval of American Regent, Inc.

The Investigator will provide to the Sponsor any announcement, publication, or presentation of data from this study for the Sponsor's review and comments at least 10 days in advance of such disclosure. Sponsor may, at its sole discretion, require the removal of any proprietary information from the disclosure. The Investigator agrees to provide the Sponsor, at the Sponsor's discretion, with any byline credit in any publication proposed by the Investigator. This is in order to enable American Regent, Inc., to make constructive comments about the manuscript or text and to give the opportunity of assessing whether patent protection should be sought by American Regenton any results or ideas connected with the study.

10.0 GOVERNANCE COMMITTEES

10.1 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.

INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 312 and all applicable local, state, and federal regulations and International Conference on Harmonisation guidelines.

_____

Investigator's signature

_____

Date

_____

Investigator's Name (Please print)

References

1. WHO Micronutrient deficiencies. Iron deficiency anemia. http://www.who.int/nutrition/topics/ida/en/
2. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther.* 2006; 24: 1507-1523
3. Foley RN, Parfrey PS, Harnett JD *et al*. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int.* 1996; 49: 1379-1385
4. Staples AO, Greenbaum LA, Smith JM *et al*. Association between clinical risk factors and progression of chronic kidney disease in children. *Clin J Am Soc Nephrol.* 2010; 5: 2172-2179
5. Wharton BA. Iron deficiency in children: detection and prevention. *Br J Haematol.* 1999; 106: 270-280
6. Kazal LA, Jr. Prevention of iron deficiency in infants and toddlers. *Am Fam Physician* 2002; 66: 1217-1224
7. Michaud L, Guimber D, Mention K *et al*. Tolerance and efficacy of intravenous iron saccharate for iron deficiency anemia in children and adolescents receiving long-term parenteral nutrition. *Clin Nutr.* 2002; 21: 403-407
8. Pinsk V, Levy J, Moser A, Yerushalmi B, Kapelushnik J. Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. *Isr Med Assoc J.* 2008; 10: 335-338
9. Surico G, Muggeo P, Muggeo V *et al*. Parenteral iron supplementation for the treatment of iron deficiency anemia in children. *Ann Hematol.* 2002; 81: 154-157
10. Powers JM, Buchanan GR. Diagnosis and management of iron deficiency anemia. *Hematol Oncol Clin North Am*. 2014;28(4):729-45.
11. Powers JM, McCavit TL, Buchanan GR. Management of iron deficiency anemia: a survey of pediatric hematology/oncology specialists. *Pediatr Blood Cancer*. 2015;62(5):842-6.
12. Powers JM, Shamoun M, McCavit TL, Adix L, Buchanan GR. Intravenous ferric carboxymaltose in children with iron deficiency anemia who respond poorly to oral iron. *J Pediatr*. 2017;180:212-16.
13. Recommendations to prevent and control iron deficiency in the United States: centers for disease control and prevention. *MMWR Recomm Rep*. 1998;47:1-29.
14. Data on File
15. Ferrous Sulfate Drops PI.
16. Data on File.
17. Fishbane S. Safety in iron management. Am J Kidney Dis 2003;41(5Suppl):18-26.
18. Safety and Efficacy of Ferric Carboxymaltose In Pediatric Inflammatory Bowel Disease Poster: Alexander Favreau, Annette Langseder, Ruth Irizarry, Stephanie Schuckalo, Michelle Neier, Joel Rosh. Inflammatory Bowel Diseases: February 2017 doi: 10.1097/01.MIB.0000512714.16903.dc
19. Van Wyck D, Anderson J, Johnson K. Labile iron in parenteral iron formulations: a quantitative and comparative study. 2004;19(3):561-565.

APPENDIX 1: AMENDMENT CHANGES

AMENDMENT 1 CHANGES

Affected Section(s)	Summary of Revisions Made	Rationale
HEADER	Right upper corner of the heading was changed to reflect the current protocol version number and date of version. **Original Wording**: Luitpold Pharmaceuticals, Inc. Protocol No.: 1VIT17044 CONFIDENTIAL version: 1.0, 06 March 2017 **New Wording:** Luitpold Pharmaceuticals, Inc. Protocol No.: 1VIT17044 CONFIDENTIAL Amendment I Date: 14 September 2017	To reflect the updated version of the protocol.
TITLE PAGE	Protocol Date was changed. **Original Wording**: Protocol Date: 20 April 2017 **New Wording:** Protocol Date: 20 April 2017 Amendment I Protocol Date: 14 September 2017	To reflect the date of the current protocol version.

SIGNATURES OF AGREEMENT FOR PROTOCOL	**Removal of:** Sumita Chowdhury, MD, MPH, FACC, MBA Prema Krishnarao, MD **Addition of:** Susan Oskins, RN, BSN, Pharmacovigilance Manager Nicole Blackman, PhD	To reflect current reviewers.
STUDY SYNOPSIS: DESIGN **STUDY SYNOPSIS: DESIGN** **&** **3.1 OVERALL STUDY DESIGN**	• The study design has been modified to eliminate the prospective 14 day oral iron run-in phase and randomization based on response to the run-in phase and replaced with participants requiring a documented history of an insufficient response to oral iron therapy over a longer time period (8 weeks) as suggested. • A reduced regimen for Cohort B was modified from the proposed one dose per day to a dose reduction to 3 mg/kg for participants that experience adverse events. • Cohort B age groups cutoffs were modified to 1 to <4 years of age and ≥4 to <12 years of age for those receiving ferrous sulfate drops and elixir, respectively. • Sparse PK sampling on Day 0 and Day 7 for FCM only participants. **Original Wording**: This is a Phase III, multicenter, randomized, active-controlled study that compares the efficacy and safety of FCM to oral iron in pediatric participants with IDA who have had an inadequate response **after a 14-day oral iron run-in period.** Participants who satisfy the inclusion requirements and no exclusionary criteria will be eligible to participate in this study. **All appropriate participants will enter a 14-day oral iron run-in period.** The oral ferrous sulfate formulation received will be based on the participant's age, such that: infants and toddlers (1 to **<5** years of age) will receive ferrous sulfate drops, children (**≥5** to <12 years of age) will receive ferrous sulfate elixir, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets.	The dose reduction is still within the recommended range of 3-6 mg/kg for iron supplementation and will mitigate expected tolerance and/or adherence issues. The cutoffs reflect the age group specified in the oral iron drops supplement label and traditional age range for infants (1 to 3 years old). Sparse PK sampling included to facilitate exposure-response analysis

STUDY SYNOPSIS: DESIGN **&** **3.1 OVERALL STUDY DESIGN**	**Participants who have an adequate response to oral iron (as defined by an increase in hemoglobin (Hgb) of ≥1 g/dL in 14 days) will be defined as oral iron treatment responders and will not be randomized.** **Participants who have an unsatisfactory response to oral iron (as defined by an increase in Hgb of <1 g/dL from baseline despite ≥ 67% compliance based on tablet/drops/elixir count) will be defined as non-responders to oral iron treatment. Non-responders who continue to meet inclusion criteria (including Hgb <12 g/dL) and no exclusion criteria will be stratified by baseline Hgb (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years).** Randomization will occur in a 1:1 ratio to either Group A, participants receiving FCM (oral iron product from the run in phase will be discontinued), or Group B, participants **continuing** to receive oral iron (oral solution drops, elixir or oral tablets) **up to Day 14.** **Participants who had a Hgb value increase <1 g/dL from baseline in the run-in period BUT less than 67% compliance will not be randomized.** Participants who experience other symptoms due to the oral iron during the **run-in** phase **will** have their **twice-daily dose regimen** of ferrous sulfate **reduced to one dose per day. Participants that demonstrate a ≥1 g/dL increase in Hgb in response to once daily oral iron therapy during the run-in phase, or those that experience ongoing adverse clinical symptoms after a reduction to once daily oral iron therapy will not be randomized. Participants receiving once-daily oral iron that do not experience a ≥1 g/dL increase in Hgb after the 14 day run-in phase (despite ≥67% compliance with the reduced dose schedule) will be stratified by Hgb and age, and then randomized in the same 1:1 ratio to either Group A, participants receiving FCM (oral iron product from the run-in phase will be discontinued), or Group B, participants continuing to receive oral iron (Reduced regimen [one dose per day] oral solution drops, elixir or oral tablets) up to Day 14.** **The response to oral iron will be calculated by subtracting the point-of-care Hgb value determined at the initial screening visit (Day -15) from the point-of-care determinations made on Day 0.**	

STUDY SYNOPSIS: DESIGN **&** **3.1 OVERALL STUDY DESIGN**	**Participants who have a >2 g/dL decrease in Hgb from the initial screening visit (Day -15) after compared to the point-of-care sample at Day 0 will not be randomized. These participants will be discontinued in the interactive response technology (IRT) system and referred to their primary health care provider for further management.** Once randomized, all participants will return for efficacy and safety evaluations, including adverse events and laboratory assessments, on Days 7, 14, 28, and 35. **New Wording:** This is a Phase III, multicenter, 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 in at least 8 weeks (56 days) prior to randomization.** Participants who satisfy the inclusion requirements and no exclusionary criteria will be eligible to participate in this study and enter into a screening phase to confirm eligibility. Randomization will occur via the IRT system in a 1:1 ratio to either Group A, participants receiving FCM, or Group B, participants receiving oral iron (oral solution drops, elixir or oral tablets). **Randomization** will be stratified by baseline Hgb (<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 receive ferrous sulfate elixir, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. Participants who experience adverse clinical symptoms due to the oral iron during the treatment phase may have their weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. **If the participant is receiving 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 analysis will be performed for participants receiving FCM on Days 0 and 7.	
STUDY SYNOPSIS: INCLUSION CRITERIA & SECTION 4.2.1 OF PARTIPANT SELECTION **STUDY SYNOPSIS: INCLUSION CRITERIA & SECTION 4.2.1 OF PARTIPANT SELECTION**	Additional diagnostic parameters were included to support the diagnosis of iron deficiency anemia and the unsatisfactory response was changed from prospective to retrospective. No point of care testing will be performed. **Original Wording**: 2. Screening Transferrin Saturation (TSAT) **<20%.** 4. Randomization Hgb <12 g/dL (based on the average point of care Hgb performed on Screening and Day 0). 5. Participants must demonstrate an unsatisfactory response to oral iron after the 14 days prior to randomization. **New Wording:** 3. Screening ferritin ≤300 ng/mL and Transferrin Saturation (TSAT) **<30%**. 4. Participants must have a documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to randomization.	Because ferritin is an acute-phase reactant, ferritin may be normal or increased in iron-deficient participants with other medical problems. This cutoff would not exclude participants with comorbidities. The increased TSAT in combination with the ferritin measurement should adequately identify participants with iron deficiency anemia.
STUDY SYNOPSIS: EXCLUSION CRITERIA & SECTION 4.2.2 OF PARTICIPANT SELECTION	The following exclusion criterion was removed from the original protocol: 8. Development of a bacterial infection in the run-in phase. 12. Cyclophosphamide therapy In addition, the following exclusion criteria were modified as follows: **Original Wording**: 5. Screening ferritin level > 300 ng/mL	Run-in phase removed. The use of cyclophosphamide therapy may be an independent cause of drug-associated anemia. As there are other such potential concomitant medication exposures associated with drug-associated anemia,

	11. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). **Participants treated for vitamin B12 or folic acid deficiency are permitted.** **New Wording:** 10. Anemia due to reasons other than iron deficiency (**e.g.**, hemoglobinopathy **and vitamin B12 or folic acid deficiency**).	Luitpold has removed this exclusion criterion. Participants with vitamin B12 or folic acid deficiency may be receiving hematinic supplementation that may confound outcome measures and will thus be excluded.
STUDY SYNOPSIS: OTHER	The following changes below have been made to the various sections of the study synopsis. • Additionally, Figure 1 of the Study Diagram has been modified to reflect the proposed change in study design. **<u>Study Drug Administration:</u>** **Original Wording**: Group B (Oral ferrous sulfate) will receive **or continue to receive** an age-dependent formulation of oral ferrous sulfate daily for **14** days as follows: participants <12 years of age will receive **3** mg (elemental iron)/kg/day divided into 2 daily doses of an oral drop or elixir and participants ≥12 will receive 2 daily doses of oral tablets. Infants and toddlers (ages 1 to <**5** years) will receive oral ferrous sulfate drops, while children (ages ≥**5** to <12 years) will receive oral ferrous sulfate elixir. Adolescents (ages ≥12 to 17 years) will receive an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for participants **<12**	The change in reticulocyte hemoglobin content will be analyzed at all time points instead of specifically Day 35 only.

STUDY SYNOPSIS: OTHER	years of age is 130 mg of elemental iron. **The maximum daily dose for participants ≥12 years of age is 130 mg of elemental iron.** **New Wording:** Group B (Oral ferrous sulfate) will receive an age-dependent formulation of oral ferrous sulfate daily for **28** days as follows: participants <12 years of age will receive **6** mg (elemental iron)/kg/day divided into 2 daily doses of an oral **liquid formulation, either** drop**s** or elixir, and participants ≥12 will receive 2 daily doses of oral tablets. Infants and **children** (ages 1 to <**4** years) will receive oral ferrous sulfate drops, while children (ages ≥**4** to <12 years) will receive oral ferrous sulfate elixir. Adolescents (ages ≥12 to 17 years) will receive an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for **all** participants is 130 mg of elemental iron. **<u>Patient Assessments:</u>** **Original Wording**: All participants who provide informed consent / assent **will enter a 14-day run-in phase. Participants will be required to return on day 7 to assess adverse events and their degree of compliance with oral iron therapy. Participants completing the run-in phase and are non-responders (see design section above), continue to meet the inclusion criteria, and do not meet exclusion criteria, will be randomized.** Starting on Day 0, the time of study drug dosing, through Day 35, all randomized participants will be subject to safety assessments including vital signs (including sitting heart rate and blood pressure), laboratory samples include hematology, chemistries and iron indices, and adverse event queries. **New Wording:** All participants who provide informed consent/assent, **meet inclusion criteria, and do not meet exclusion criteria will be randomized.** Starting on Day 0 (the time of	To modify for consistency with the updated study design.

STUDY SYNOPSIS: OTHER	study drug dosing) through Day 35, all randomized participants will be subject to safety assessments including vital signs (including sitting heart rate and blood pressure), laboratory samples include hematology, chemistries and iron indices, and adverse event queries. **Participants receiving oral iron treatment will be assessed for degree of compliance.** **Secondary Endpoints:** **Original Wording**: Change in reticulocyte hemoglobin from baseline to day 35 Changes from baseline to individual time points will be summarized descriptively for hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin. **New Wording:** Changes from baseline in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin **content throughout the study**. **Pharmacokinetic assessments, including C_{max}, T_{max}, $AUC_{0\text{-time last measured concentration}}$, $AUC_{0\text{-infinity}}$, $T_{1/2}$, MRT, Cl, V_D, V_{Dc}, V_{Dss}, and V_{Darea}.** **Study Duration per Participant:** **Original Wording**: Approximately **8** weeks **New Wording:** Approximately **6** weeks **Study Sites:**	To modify for consistency with the updated study design.

	Original Wording: Approximately 12 to 15 **New Wording:** Approximately 20 **<u>Participant Number:</u>** **Original Wording**: Approximately **56** randomized (N=**28** FCM / N=**28** Oral Iron) **New Wording:** Approximately **72** randomized (N=**36** FCM / N=**36** Oral Iron)	A total of 60 participants (30 per treatment group) are required to detect an expected difference in Hgb of 1.0 g/dL (common standard deviation = 1.16 g/dL) at two-sided alpha = 0.05 with 90% power. Assuming 20% attrition of subjects not meeting the definition of modified intention to treat (mITT), approximately 72 participants will be randomized.
1.0 INTRODUCTION	The following subsections were modified as follows: **<u>1.2.2 Ferric Carboxymaltose versus Other Parenteral Iron Agents</u>**	These statements are based on information contained within the following article: Van

	A reference (#19) was added to the following text: "Iron sucrose and iron gluconate preparations carry a significant risk of inducing a bioactive iron reaction when delivered at higher doses. These reactions are characterized by hypotension (without allergic signs) accompanied by pain in the chest, abdomen, flank and/or nausea, vomiting, and diarrhea."	Wyck D, Anderson J, Johnson K. Labile iron in parenteral iron formulations: a quantitative and comparative study. 2004;19(3):561-565.
2.0 TRIAL OBJECTIVE	The following subsections were modified as follows: **2.1 <u>Primary Objective</u>** **Original Wording**: The primary objective of this study is to demonstrate the efficacy and safety of an investigational IV ferric carboxymaltose, (FCM) compared to oral iron in pediatric participants who have IDA **and have been shown to have an unsatisfactory response to oral iron.** **New Wording:** The primary objective of this study is to demonstrate the efficacy and safety of an investigational IV ferric carboxymaltose, (FCM) compared to oral iron in pediatric participants who have IDA.	To modify for consistency with changes in study design.

3.0 OVERALL STUDY DESIGN AND RATIONALE	The following subsections were modified as follows: **<u>3.2 Rationale of Study Design and Choice of Control Groups</u>** • In addition to the following text, Tables 1 "Mean Change from Screening in Hemoglobin, Ferritin, and TSAT (Safety Population)" and 2 "Overview of Treatment-Emergent Adverse Events (Safety Population)" were added. **Original Wording**: **While** the recommended total daily dose of oral elemental iron for the treatment of IDA in pediatric patients ranges between 3-6 mg/kg/day divided into one to three doses, a total daily dose of 3 mg/kg/day divided into 2 doses (maximum daily dose of 130 mg of elemental iron) was selected for all ages **because evidence suggests that low-dose oral iron therapy may be as effective as higher doses.**[11] Additionally, the simplified regimen may minimize adverse effects associated with high-dose oral iron therapy and thus improve medication adherence.[13] **New Wording:** **Per** the recommended total daily dose of oral elemental iron for the treatment of IDA in pediatric patients ranges between 3-6 mg/kg/day divided into one to three doses, a total daily dose of 6 mg/kg/day divided into 2 doses (maximum daily dose of 130 mg of elemental iron) was selected for all ages **based on the most common practice of pediatric hematology physicians in the United States.**[11] Additionally, the simplified regimen may minimize adverse effects associated with high-dose oral iron therapy and thus improve medication adherence.[13] With respect to FCM, doses of 15 mg/kg with a maximum of 750 mg per dose have been selected based off evidence generated from Luitpold's Phase II dose-finding PK/PD study in which cohorts received single, weight-based doses of FCM at either 7.5 mg/kg or 15 mg/kg.[16] Results from this study demonstrate that the higher weight-based dose is both efficacious and safe **(summarized below in Tables 1 and 2)**. **The mean increase from baseline to Day 35 was larger for participants in Cohort 2 receiving 15 mg/kg (2.8±1.15 g/dL) than those in Cohort 1 receiving 7.5 mg/kg (1.9±1.38 g/dL). The mean increase in ferritin and TSAT at Day 35 was**	While the referenced article indicated that no data support iron dosing of 6 mg/kg/day in children, this was the preference of physicians who responded in the survey and has been modified per FDA recommendation. Preliminary PK, PD, and safety data from the dose-finding Phase 2 trial, 1VIT13036, has been provided to further justify the selected dose for FCM.

3.0 OVERALL STUDY DESIGN AND RATIONALE	**35.1±98.22 ng/mL and 9.9±11.54% for Cohort 1 (N=16) and 52.4±31.7 ng/mL and 13.5±6.88% for Cohort 2 (N=18), respectively. Similar percentages of participants in Cohort 1 (56.3%) and Cohort 2 (63.2%) reported at least 1 treatment-emergent adverse event. At least 1 drug-related treatment-emergent adverse event was reported by 3 of 16 participants in Cohort 1 and 6 of 19 participants in Cohort 2. Specifically, the only treatment-emergent AE considered related to study drug that was experienced by >1 participant was urticaria (3 participants in Cohort 2). Other treatment-emergent AEs considered related to study drug and experienced by 1 participant each included infusion site pruritus, thirst, and hot flush in Cohort 1 and abdominal pain upper, gastroduodenitis, hyperthermia, injection site pain, alanine aminotransferase increased, headache, pruritus, rash, and hypertension in Cohort 2. Two participants in Cohort 1 experienced a serious adverse event.** Further justification for the 15 mg/kg dose is provided by internal modeling data, which demonstrated comparable total serum iron clearance profiles between pediatric and adult populations. Lastly, a retrospective cohort study of 72 pediatric patients with IDA refractory to oral iron treatment ranging in age from 9 months to 18 years treated with 15 mg/kg of FCM (maximum single dose of 750 mg; median dose 750 mg) supports this dosing.[12] • **Section "3.3 Rationale for Oral Run-in" has been modified as follows to "3.3 Rationale for Sparse PK Sampling":** **Original Wording:** 3.3 Rationale for Oral Run-in Oral iron represents a cost-effective option for patients with IDA who do not need rapid repletion of iron stores and who are able to tolerate it. The proposed study enables all participants to complete a 14-day trial of oral iron therapy. Those participants who achieve a Hgb increase of ≥1 g/dL in the oral iron run-in period will not be randomized. The 14-day run-in criteria were selected based on a review of adult Phase III studies of IDA among participants with heavy uterine bleeding, inflammatory bowel disease, or postpartum anemia. It was observed that participants who achieved a <1 g/dL increase in 14 days were less likely to achieve satisfactory	

3.0 OVERALL STUDY DESIGN AND RATIONALE	responses to oral iron at the end of the respective studies than those who achieved a ≥1 g/dL increase in 14 days.[14] Participants who do not have an adequate response to oral iron therapy and are at least 67% compliant, will be randomized to IV FCM or an additional two weeks of oral iron therapy. This design permits an efficacy and safety comparison of switching to FCM *versus* continuing oral iron in a clinical scenario that reflects real life use of parenteral therapy. Participants who have a >2 g/dL Hgb decrease, do not tolerate oral iron, or those deemed by their physicians not appropriate for continued participation in the study will be discontinued and referred to their primary care or GI providers for appropriate evaluation and management. **New Wording:** 3.3 Rationale for Sparse PK Sampling Population-based PK/PD modelling describing the time course of total serum iron (TSI) concentrations and the relationship between TSI and changes of hemoglobin following a single dose of intravenous FCM in pediatric subjects with iron deficiency anemia (IDA) has been performed using intensively sampled data from Study 1VIT13036.[16] It is proposed to supplement this initial modelling with additional sparsely sampled PK data from this study. Based on the anticipated visit duration on the 2 FCM administration days in this study, the following sparse PK sampling scheme is proposed: pre-dose, immediately post-infusion and 60 minutes post-dose on Days 0 and 7, on which subjects will receive 15 mg/kg (up to a maximum dose of 750 mg). This pragmatic approach, which minimizes the number of blood draws compared to a full PK profile, is expected to facilitate exposure-response analysis for the proposed FCM regimen. **Section 3.4 Schedule of Events** The following organizational changes were made to the original table: • Column 3, “Scr 2 (Day -8 or -7)”, was removed. • Row 11, “Hemoglobin Point of Care Testing”, was removed. • Column 2, “Scr 1 (Day -15)”, was changed to “Screening (-7 +1)”. • Row 17, “Pharmacokinetic Sampling”, was added.	

3.0 OVERALL STUDY DESIGN AND RATIONALE	The following assessments were added for the following Visit Days: • Oral Iron Dosing, Oral Iron Dispensing were removed from "Screening (-7 + 1)". • Oral Iron Dosing was added to "Day 28". • Oral Iron Dispensing was added to "Day 14". • Oral Iron Compliance Assessment was added to "Day 28" (Assessment at Day 0 removed). The following footnote was added to Row 12, "Hematology, Chemistry and Iron Indices": • [1] For a full description of central laboratory assessments, refer to Protocol Section 6.4. The following footnote was added to Row 17, "Pharmacokinetic Sampling": • [2] Blood samples for pharmacokinetic analysis will be collected pre-dose, immediately 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.	
4.0 PARTICIPANT SELECTION **4.0 PARTICIPANT SELECTION**	The following subsections were modified as follows: • Subsection 4.7 "Unsatisfactory and Adequate response to the 14 day Oral Iron Run-in Defined" was removed. **4.1 Number and Type of Participants** **Original Wording:**	To modify for consistency with the updated study design.

4.0 PARTICIPANT SELECTION	Approximately 56 participants who have given written informed consent / assent with a diagnosis of IDA who fulfill the inclusion criteria**,** do not meet any of the exclusion criteria, **and completed the 14-day run-in phase as a non-responder** will be randomized to receive either FCM or Oral Iron. **New Wording:** Approximately **72** participants who have given written informed consent/assent with a diagnosis of IDA who fulfill the inclusion criteria **and** do not meet any of the exclusion criteria will be randomized to receive either FCM or Oral Iron. **4.3 Participant Assignment and Randomization Process** **Original Wording:** Participants who have an unsatisfactory response to oral iron, as defined by Hgb value increases <1 g/dL from baseline despite ≥67% compliance based on tablet/drops/elixir count, will be defined as non-responders. Participants who continue to meet the inclusion criteria (including Hgb <12 g/dL) and no exclusion criteria will be entered into the IRT system, stratified by baseline Hgb (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years). Randomization will occur in a 1:1 ratio to either Group A, FCM (oral iron product from the run-in phase will be discontinued) or Group B, continuation of Oral Iron (oral solution drops/elixir or oral tablets) up to day 14. Participants who had an Hgb value increase <1 g/dL from baseline in the run-in period BUT had less than 67% compliance will not be randomized. Participants who have a >2 g/dL decrease in Hgb from the initial screening visit (Day -15) after calculating the point-of-care samples at Day 0 should not be randomized. These participants should be discontinued in the IRT system and assessed and evaluated appropriately by their treating physician. **New Wording:**	

	Participants who satisfy the inclusion requirements and no exclusionary criteria will be eligible to participate in this study and entered into the IRT system. Randomization will occur in a 1:1 ratio to either Group A, participants receiving FCM, or Group B, participants receiving oral iron (oral solution drops, elixir or oral tablets). Randomization will be stratified by baseline Hgb (<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 receive ferrous sulfate elixir, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. Participants who experience adverse clinical symptoms due to the oral iron during the treatment phase may have their weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. If the participant is receiving tablets, the dose will be reduced from one tablet taken twice daily to one tablet per day.	
5.0 STUDY DRUG	The following subsections were modified as follows: **5.2 Drug Administration/Regimen** **Original Wording:** **Group B:** Group B (Ferrous sulfate) will **continue to** receive oral **iron** through the Day **14** visit. **New Wording:** **Group B:** Group B (Ferrous sulfate) will **receive an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age will receive 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 will receive 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) will receive oral ferrous sulfate drops, while children (ages ≥4 to <12 years) will receive oral ferrous sulfate elixir.**	To modify for consistency with the updated study design.

	Adolescents (ages ≥12 to 17 years) will receive an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants is 130 mg of elemental iron.	
5.5 Concomitant Medication	**Original Wording:** If receiving treatment for IBD, therapy must be stable for at least **90 days** prior to consent and remain stable through the remaining of the study. **New Wording:** If receiving treatment for IBD, therapy must be stable for at least 8 weeks prior to consent and remain stable through the remaining of the study.	To modify for consistency with the updated inclusion criteria.
6.0 STUDY PROCEDURES	The following subsections were modified as follows: • Section 6.2.2, "Screening Visit 2 (Day -8 ± 1)", was removed. • Section 6.2.3, "Oral iron Dose Reduction in the 14 Day Run-in", was removed and replaced with Section 6.3.5, "Oral Iron Dose Reduction during the Treatment Phase". • Section 6.3.6, "Pharmacokinetic Sampling", was added. **6.2.1 Screening Visit 1** **Original Wording (only affected areas appear below):** 6.2.1 Screening Visit 1 **(Day -15)** **• Hgb by point-of-care testing** **• ** If the point-of-care testing Hgb is >11.0 g/dL all study procedures should be stopped and the participant entered into the IRT as a screen failure.**	

6.0 STUDY PROCEDURES	**After a screening number has been obtained and the POC Hgb ≤11 g/dL is confirmed, the first dose of oral ferrous sulfate will be administered according to the following: infants and toddlers (1 to <5 years of age) will receive ferrous sulfate drops; children (≥5 to <12 years of age) will receive ferrous sulfate elixir; and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets.** **A sufficient quantity of doses for a 7 day period will be dispensed to the parent or guardian of the participant. The parent or guardian of the participant will be responsible for the administration of two daily doses of oral ferrous sulfate to the participant.** **New Wording:** 6.2.1 Screening Visit 1 **(Day -7 ± 1)** Each participant who qualifies for inclusion will undergo the following clinical evaluations to confirm their eligibility for the study: • Obtain screening number from IRT • Medical history, including documented history of an inadequate response after at least 8 weeks of prior oral iron therapy use • Hematology, chemistries and iron indices • Serum pregnancy test for female participants of child bearing potential (negative results must be obtained prior to randomizing the participant for study drug dosing). • Height and weight • Vitals signs (including sitting heart rate and blood pressure) • Concomitant medications assessment • ESA and IBD therapy stability (if applicable) ** Participants who do not meet the entry criteria should be entered into the IRT system as a screen failure. A participant may be re-screened, **only** one time, once it is believed that they would qualify for study entry. The participant will need to re-	

6.0 STUDY PROCEDURES	sign a new consent form and all screening procedures in section 6.2 will need to be repeated. **6.3.1 Day 0 Visit** **Original Wording:** The following will be obtained and/or completed before contacting IRT for randomization: For all participants: • Verify all inclusion and exclusion criteria • **Blood samples for central lab hematology, chemistries, and iron indices** • **Weight** A participant who develops a bacterial infection during the **run-in** phase should be discontinued and treated appropriately. These participants may be re-screened, one time, once the enrolling physician deems the participant would qualify for study entry. The participant will need to re-sign a new consent / assent form and all screening procedures in section 6.2 will need to be repeated. After verifying the eligibility of the participant, the IRT system will then be contacted by a study team member. **Participants** will be stratified by Hgb (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years), and randomization in a 1:1 ratio to either Group A (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) or Group B (Ferrous sulfate will continue to receive oral iron through the Day 14 visit). After assignment of the treatment group the following will occur: Group A: • **Pre-administration evaluation to include measurement of heart rate, blood pressure, and body temperature on Day 0.**	

6.0 STUDY PROCEDURES	Group B: • Oral ferrous sulfate dispensing: • **Pre-administration evaluation to include measurement of heart rate, blood pressure, and body temperature on Day 0.** o Parents or guardians of participants will be responsible for the administration of twice daily dosing of oral ferrous sulfate. Participants that experience adverse events **during the run-in will continue the reduced** regimen [one dose per day] of oral ferrous sulfate. o A record of compliance will be maintained for each participant and reviewed at each study visit. (**see section 6.2.2 for compliance assessment**). • Adverse event assessment (starting once the participant takes the first in-clinic dose). **New Wording:** A participant who develops a bacterial infection during the **screening** phase should be discontinued and treated appropriately. These participants may be re-screened, one time, once the enrolling physician deems the participant would qualify for study entry. The participant will need to re-sign a new consent / assent form and all screening procedures in section 6.2 will need to be repeated. After verifying the eligibility of the participant, the IRT system will then be contacted by a study team member. **Randomization** will be stratified by Hgb (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years), and randomized in a 1:1 ratio to either Group A (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) or Group B (Ferrous sulfate, dose and regimen dependent upon age and weight, twice daily for 28 days). **After a randomization number has been obtained, the first dose of oral ferrous sulfate will be administered in the clinic according to the following: infants and**	

6.0 STUDY PROCEDURES	**children (1 to <4 years of age) will receive ferrous sulfate drops; children (≥4 to <12 years of age) will receive ferrous sulfate elixir; and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets.** **A sufficient quantity of doses for a 7 day period will be dispensed to the parent or guardian of the participant. The parent or guardian of the participant will be responsible for the administration of two daily doses of oral ferrous sulfate to the participant.** After assignment of the treatment group the following will occur: **All participant's (prior to study drug administration/dispensing, if applicable) on Day 0:** • **Blood samples for central lab hematology, chemistries, and iron indices (Group A participants will have an additional blood sample for PK prior to dosing)** • **Vital signs: temperature, sitting heart rate and blood pressure** • **Weight** Group A: • **Blood samples for PK immediately post-dose and 60 minutes post-dose.** Group B: • Oral ferrous sulfate dispensing: o Parents or guardians of participants will be responsible for the administration of twice daily dosing of oral ferrous sulfate. Participants that experience adverse events **may** continue **with a dose-reduced** regimen [**3 mg/kg twice daily**] of oral ferrous sulfate **after a consult with the investigator. (See section 6.3.5 for oral iron dose reduction)**	

6.0 STUDY PROCEDURES	○ Parents or guardians of participants will be dispensed oral iron on Day**s** 0, 7, **and 14**. Used dispensing packs/blisters/**syringes** will be returned and are to include both the empty containers and any unused medication. ○ A record of compliance will be maintained for each participant and reviewed at each study visit. **(See** section 6.**3**.2 for compliance assessment). **6.3.2 Day 7 and Day 14 Visit** **Original Wording:** For Group A participants the following will be performed on **Day 7 only**: • Pre-administration evaluation to include **measurement of heart rate, blood pressure,** and body temperature. For Group B participants the following will be performed: • Oral iron dispensing **(Day 7 only).** • **Oral iron compliance assessment (see section 6.2.2 for compliance assessment).** **New Wording:** All participants will return to the clinic on Day 7 and 14. Prior to the administration of the study drug (if applicable), the participant will be evaluated clinically to assess for the development of clinically significant conditions that may contraindicate dosing. • **Blood samples for central lab hematology, chemistries and iron indices (Group A participants will have an additional blood sample for PK prior to dosing).**	

6.0 STUDY PROCEDURES	**For Group A participants the following will be performed on Day 7 only:** • **Blood samples for PK immediately post-dose and 60 minutes post dose.** • Pre-administration evaluation to include body temperature. For Group B participants the following will be performed: • Oral iron dispensing **(**Day 7 **and Day 14).** **Compliance will be assessed according to the following:** **For ferrous sulfate tablets:** o **Used blister packs will be returned and are to include both the empty containers and any unused medication.** o **The blister packs will be examined to assess compliance (the number taken divided by the number of pills expected to be taken). A record of compliance will be maintained for each participant and reviewed.** o **If the participant took less than the number of tablets expected, document the reason(s) for dose reduction and counsel the participant about the importance of taking the study drug as prescribed.** **For ferrous sulfate drops and elixir:** o **Used oral syringes will be returned which will include any unused medication.** o **The oral syringes will be examined to assess compliance (the volume remaining in the oral syringes divided by the expected amount to be taken). A record of compliance will be maintained for each participant and reviewed.** o **If the participant took less than the volume expected, document the reason(s) for dose reduction and counsel the participant about the importance of taking the study drug as prescribed.**	

6.0 STUDY PROCEDURES	**<u>6.3.5 Oral Iron Dose Reduction during the Treatment Phase</u>** **New Wording:** Participants who experience AE possibly or probably due to the oral iron during the treatment phase will have their dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg while maintaining the same frequency of twice per day. If the participant is receiving tablets, the dose will be reduced from one tablet taken twice daily to one tablet per day. **6.3.6 Pharmacokinetic Sampling** **New Wording:** Blood samples will be collected for PK assessment pre-dose, immediately post-dose, and 60 minutes post-dose for participants receiving FCM on Days 0 and 7. Blood samples should be taken at approximately the same time of day on Day 7 as Day 0. The pharmacokinetic parameters to be analyzed in this study are as follows: the maximum serum concentration (C_{max}) and the time at which C_{max} occurs (T_{max}), the area under the serum concentration-time curve from time zero to the last sampling time with a quantifiable concentration ($AUC_{0\text{-time last measured concentration}}$), the extrapolated area under the serum concentration- time curve from time zero to infinity ($AUC_{0\text{-infinity}}$), and the half-life ($T_{1/2}$). The secondary parameters are the mean residence time (MRT), the apparent serum clearance (Cl), and the apparent volume of distribution (V_D), which includes the initial volume of distribution following the injection (V_{Dc}), the volume of distribution at the steady state (V_{Dss}), and the volume of distribution at the final elimination (V_{Darea}). **<u>6.4 Central Laboratory Assessments</u>** **Original Wording:**	

	Hematology: Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, reticulocyte count, and reticulocyte hemoglobin (**ret-he %**) **New Wording:** Hematology: Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, reticulocyte count, and reticulocyte hemoglobin **content** (**CHr**)	
8.0 STATISTICS **8.0 STATISTICS**	The following subsections were modified as follows: • Section 8.5.3, "Clinical Laboratory Findings", was changed to Section 8.5.4. • Section 8.5.4, "Vital Signs", was changed to Section 8.5.5. **New Wording:** **All hypothesis tests and confidence intervals will be two-sided. No correction for multiple testing will be applied amongst the secondary endpoints. Except where otherwise noted, the statistical model on which inference is based will include terms for randomization strata.** **Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, Q1, Q3, minimum and maximum. Other descriptive statistics (e.g., coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages.** **Generally, data will be summarized by nominal visit. However, data from both unscheduled and scheduled will be used for determination of last observed value, and in worst- or best-case changes and/or shifts from baseline. Assessment**	To modify for consistency with the updated study design.

8.0 STATISTICS	**windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.** **A complete description of the statistical analyses and methods will be available in a Statistical Analysis Plan (SAP), which will be finalized before the database is locked.** **<u>8.2 Analysis Populations</u>** **Original Wording:** **The Oral Iron Run-In Population will include all participants who receive oral iron during the oral iron run-in period.** **All participants who receive at least 1 dose of randomized study drug will be included in the Safety Population. If a participant receives the wrong study drug, the participant will be analyzed under the study drug that was received. All safety analyses will be performed with the Safety Population.** **All participants in the Safety Population who have a hemoglobin measurement at baseline and at least 1 hemoglobin measurement after receiving study drug will be included in the Efficacy Population. If a participant receives the wrong study drug, the participant will be analyzed under the randomized study drug. All efficacy analyses will be performed with the Efficacy Population.** **New Wording:** **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.** **Modified Intent-to-Treat Population**	

8.0 STATISTICS	**The modified Intent-to-Treat (mITT) population will comprise all participated in the ITT population who receive at least one dose of study drug, have a baseline Hgb measurement, and at least one corresponding post-baseline measurement. Participants will be evaluated according to the treatment to which they were randomized. The primary population for the assessing efficacy will be the mITT population.** **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.** **Pharmacokinetics Population** **The Pharmacokinetics (PK) population will consist of all participants in the Safety population with at least one measurable concentration of FCM.** **<u>8.3 Disposition and Baseline Characteristics</u>** **Original Wording:** **For the oral iron run-in period, the number and percentage of participants who are treated with oral iron, discontinue oral iron, respond to oral iron, and enter the randomized portion of the study will be summarized.** **For the randomized portion of the study,** the number **and percentage** of participants who are randomized, treated, prematurely discontinue, and complete the study will be summarized **by treatment group**. **Participants with clinically important protocol deviations will be identified by treatment group and type of deviation.** The clinical team will identify deviations and the deviations will be identified in the database.	

8.0 STATISTICS	**The number of participants will be summarized for each investigative site**. Baseline characteristics **(e.g., sex, race, and age)** will be summarized descriptively **by treatment group and overall**. **New Wording:** **The number of participants in each investigative site will be summarized**. The number of participants who are **screened**, randomized, treated, prematurely discontinue, and complete the study will be summarized. The clinical team will identify deviations and the deviations will be identified in the database. **Participants with clinically important protocol deviations will be summarized.** **Demographics and** baseline characteristics will be summarized **using** descriptive **statistics or frequency counts**. **8.4.1 Primary Endpoint** **Original Wording:** The change in hemoglobin from baseline to day 35 will be assessed with an analysis of covariance **(ANCOVA) model with baseline stratification factors** (Hgb and age categories), **treatment, and a covariate of** baseline hemoglobin. Baseline hemoglobin will be defined as the last hemoglobin obtained before randomization. **New Wording:** **Primary analysis** The primary endpoint is the change in hemoglobin from baseline to day 35. The change in hemoglobin from baseline to day 35 **will be analyzed using parametric** analysis of covariance **(ANCOVA). The model will include terms for the randomization strata** (Hgb and age categories), baseline **Hgb, as well as treatment**	

8.0 STATISTICS	**group**. Baseline hemoglobin will be defined as the last hemoglobin obtained before randomization. **The primary endpoint will be analyzed for the mITT population**. **Subgroup analyses** **The change in hemoglobin from baseline to day 35 will be summarized separately for the following subgroups:** • **Cause of IDA: inflammatory bowel disease (IBD), not IBD** • **Baseline hemoglobin: <10, ≥10 g/dL** • **Age: 1 to <12, ≥12 to 17 years** **Estimates of treatment effect together with 95% confidence intervals will be displayed graphically.** **Subgroup analyses will be conducted for the mITT population.** **<u>8.4.2 Secondary Endpoint</u>** **Original Wording:** The change in ferritin, TSAT, and reticulocyte hemoglobin content from baseline to day 35 will be assessed with an ANCOVA model with baseline stratification factors (Hgb and age categories), treatment, and a covariate of baseline value. Baseline will be defined as the last value obtained before randomization. Change from baseline to individual time points will be summarized descriptively for Hgb, ferritin, TSAT, and reticulocyte hemoglobin content. **New Wording:**	

8.0 STATISTICS	**Secondary Efficacy Endpoints** Secondary efficacy endpoints include: • Change in ferritin from baseline to Day 35 • Change in TSAT from baseline to Day 35 • Changes from baseline in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin content throughout the study. • Pharmacokinetic assessments, including C_{max}, T_{max}, $AUC_{0\text{-time last measured concentration}}$, $AUC_{0\text{-infinity}}$, $T_{1/2}$, MRT, Cl, V_D, V_{Dc}, V_{Dss}, and V_{Darea}. Continuous efficacy endpoints will be analyzed using ANCOVA as described for the primary endpoint. Binary efficacy variables will be analyzed using stratified Cochran-Mantel-Haenszel chi-square tests.. All secondary endpoints will be analyzed for the mITT population. Details of analyses for these endpoints will be outlined in the SAP. **Pharmacokinetics and Pharmacodynamics (PK/PD) Endpoints** **The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin®. All calculations of non-compartmental parameters will be based on actual sampling times. The actual sampling times and doses will be used for the analysis. The PK parameters will be calculated with and without adjustment for baseline. All derived PK parameters will be listed. The following summary statistics will be calculated: n, mean, standard deviation [SD], coefficient of variation (CV) , median, minimum, and maximum, along with geometric mean, geometric mean SD, geometric percent coefficient of variation [%CV], and 95%**	

8.0 STATISTICS	**Cis around the geometric mean. For T_{max}, only n, median, minimum and maximum will be presented.** **In addition, nonlinear mixed effects modelling will be used derive population PK parameters and/or models. The influence of various covariates (e.g., age, weight, sex, race) on the variability will be examined. Further details will be provided in the SAP.** **The relationship between FCM exposure and clinical outcome may be explored graphically. If appropriate, a relationship may be established between FCM exposure and effect or any special interest adverse events. Further details will be provided in the SAP.** **8.4.3 Missing Data** **Original Wording:** The effect of missing data on the primary efficacy endpoint may be examined with sensitivity analyses to be described in the Statistical Analysis Plan. **New Wording:** 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. Details will be provided in the SAP. **8.5.2 Adverse Events** **Original Wording:** **Oral Iron Run-In Period** **The number and percent of participants who report treatment-emergent adverse events will be summarized. A treatment-emergent adverse event is an event that begins after receipt of oral iron.** The Medical Dictionary for Regulatory	

8.0 STATISTICS	Activities [MedDRA] Terminology **will be used to classify all adverse events with respect to system organ class (SOC) and preferred term.** **Randomized Period** The number and percent of participants who report treatment-emergent adverse events will be summarized for each treatment group. A treatment-emergent adverse event is an event that begins after receipt of randomized treatment. **The Medical Dictionary for Regulatory Activities [MedDRA] Terminology will be used to classify all adverse events with respect to system organ class (SOC) and preferred term.** **New Wording:** Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percent of participants who report treatment-emergent adverse events will be summarized for each treatment group. A treatment-emergent adverse event is an event with onset date on or after the study drug start **date**.. **8.5.3 Adverse Events of Special Interest** Adverse events of special interest (AESI) include hypersensitivity, hypersensitivity-like reactions, and cardiovascular events. Hypersensitivity and hypersensitivity-like reactions will be identified using standardized MedDRA queries. Cardiovascular events will be identified using the SOCs for cardiac disorders and vascular disorders. The overviews and summaries that are provided for all TEAEs will also be provided for the AESIs. In addition, the time to onset and time to recovery will be summarized. 8.6 **Sample** Size Rationale	

	Original Wording: Enrollment is planned for approximately 56 randomized participants (28 per treatment group). Based on Study 1VIT09031, a mean difference in change from baseline for hemoglobin of 1.0 g/dL between FCM and oral iron and a pooled standard deviation of 1.0 g/dL, 23 participants/group will achieve 90% power for the primary endpoint. Up to 56 participants/group will be randomized in order to account for premature discontinuations. **New Wording:** A total of 60 participants (30 per treatment group) are required to detect an expected difference in Hgb of 1.0 g/dL (common standard deviation = 1.16 g/dL) at two-sided alpha=0.05 with 90% power. Assuming 20% attrition of subjects not meeting the definition of mITT, approximately 72 participants will be randomized.	
REFERENCES	The following reference was added: 19. Van Wyck D, Anderson J, Johnson K. Labile iron in parenteral iron formulations: a quantitative and comparative study. 2004;19(3):561-565.	To support the claim that other parenteral iron preparations carry a significant risk of inducing a bioactive iron reaction when delivered at higher doses.

AMENDMENT 2 CHANGES

Affected Section(s)	Summary of Revisions Made	Rationale
HEADER	The heading was changed to reflect the change in company name and the current protocol version number and date of version. **Original Wording**: **Luitpold Pharmaceuticals**, Inc. Protocol No.: 1VIT17044 CONFIDENTIAL **Amendment 1 Date: 14 September 2017** **New Wording:** **American Regent,** Inc. Protocol No.: 1VIT17044 CONFIDENTIAL **Amendment 2 Date: 13 March 2019**	To reflect the updated version of the protocol.
Many sections throughout the protocol	**Luitpold Pharmaceuticals, Inc.** was changed to **American Regent, Inc.**	To reflect the current name of the company
TITLE PAGE and STUDY SYNOPSIS: TITLE	Title was changed. **Original Wording**: A Multicenter, Randomized, Active-Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia **New Wording:** A Multicenter, **Multinational,** Randomized, Active-Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia	To reflect that it is a global study

TITLE PAGE and STUDY SYNOPSIS	Protocol Date was changed. **Original Wording**: Protocol Date: 20 April 2017 Amendment I Protocol Date: 14 September 2017 **New Wording:** Protocol Date: 20 April 2017 Amendment 1 Protocol Date: 14 September 2017 **Amendment 2 Protocol Date: 13 March 2019**	To reflect the date of the current protocol version.
SIGNATURES OF AGREEMENT FOR PROTOCOL	**Removal of:** Linda M. Mundy, MD, PhD, FACP Susan Oskins, RN, BSN, Pharmacovigilance Manager Nicole Blackman, PhD, Statistician **Addition of:** Geoffrey Mukwaya, MD, Head, Clinical R&D Mark Falone, MD, Medical Director, Clinical R&D Anthony DiGuglielmo, DPM, Head of Pharmacovigilance Nicole Blackman, PhD, Head of Quantitative Sciences	To reflect current reviewers.
Many sections throughout the protocol	**Luitpold Pharmaceuticals, Inc.** was changed to **American Regent, Inc.**	To reflect the current name of the company
STUDY SYNOPSIS: DESIGN and 3.1 OVERALL STUDY DESIGN	**Original Wording**: This is a Phase III, multicenter, 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 randomization. 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 receive ferrous sulfate elixir, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. Participants who experience adverse clinical symptoms due to the oral iron during the treatment phase may have a weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. If	To allow children (≥4 to <12 years of age) the option to receive either ferrous sulfate elixir or ferrous sulfate tablets.

	the participant is receiving tablets, the dose will be reduced from one tablet taken twice daily to one tablet per day. **New Wording:** 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 randomization. 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. Participants who experience adverse clinical symptoms due to the oral iron during the treatment phase may have a weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. If the participant is receiving tablets, the dose will be reduced from one tablet taken twice daily to one tablet per day.	
STUDY SYNOPSIS: INCLUSION CRITERIA **and** **4.2.1 INCLUSION CRITERIA**	**Original Wording**: 4. Documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to **randomization**. **New Wording:** 4. Documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to **screening**.	Section 4.1 states no oral iron from time of consent so the sentence was changed screening instead of randomization.
STUDY SYNOPSIS: EXCLUSION CRITERIA **and** **4.2.2 EXCLUSION CRITERIA**	**Original Wording**: 2. Previous randomization and treatment in this study or any other clinical study of FCM **or VIT-45**. 4. **Chronic kidney disease participants on hemodialysis**.	FDA requested that children with chronic kidney disease on hemodialysis be

	New Wording: 2. Previous randomization and treatment in this study or any other clinical study of FCM. 4. ~~Chronic kidney disease participants on hemodialysis.~~	allowed to participate in the study
STUDY SYNOPSIS: STUDY DRUG ADMINISTRATION and 5.2 DRUG ADMINISTRATION/REGIMEN	**Original Wording**: **Group A (FCM)** will receive 2 doses (Day 0 and Day 7) of FCM at 15 mg/kg to a maximum **of** single dose of 750 mg (whichever is smaller) up to a maximum total dose of 1500 mg. FCM will be administered as either an undiluted IV push at a rate of 100 mg (2 mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes. **Group B:** Group B (Ferrous sulfate) will receive an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age will receive 6 mg (elemental iron)/kg/day divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 will receive 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) will receive oral ferrous sulfate drops, while children (ages ≥4 to <12 years) will receive oral ferrous sulfate elixir. Adolescents (ages ≥12 to 17 years) will receive an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants is 130 mg of elemental iron **New Wording:** **Group A (FCM)** will receive 2 doses (Day 0 and Day 7) of FCM at 15 mg/kg to a maximum ~~of~~ single dose of 750 mg (whichever is smaller) up to a maximum total dose of 1500 mg. FCM will be administered as either an undiluted IV push at a rate of 100 mg (2 mL)/minute OR in no more than 250 mL of normal saline and infused over 15 minutes. **Group B:** Group B (**Oral** Ferrous sulfate) will receive an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows: participants <12 years of age will receive 6 mg (elemental iron)/kg/day	To allow children (≥4 to <12 years of age) the option to receive either ferrous sulfate elixir or ferrous sulfate tablets.

	divided into 2 daily doses of an oral liquid formulation, either drops or elixir, and participants ≥12 will receive 2 daily doses of oral tablets. Infants and children (ages 1 to <4 years) will receive oral ferrous sulfate drops, while children (ages ≥4 to <12 years) will **have the option** receive oral ferrous sulfate elixir **or oral ferrous sulfate tablets**. Adolescents (ages ≥12 to 17 years) will receive an oral ferrous sulfate tablet (65 mg of elemental iron/tablet/dose) twice a day (BID). The maximum daily dose for all participants is 130 mg of elemental iron.	
STUDY SYNOPSIS: STUDYSITES	**Original Wording**: Approximately **20** **New Wording:** Approximately **30**	To reflect anticipated number of sites
STUDY SYNOPSIS, FIGURE 1	**Original Wording**: Ferrous Sulfate Oral Solution (Drops: <4y.o.; Elixer ≥4 y.o.) **New Wording**: Ferrous Sulfate Oral Solution (Drops: <4y.o.; Elixer **or Oral** Tablets ≥4 y.o.)	
3.3 RATIONALE FOR SPARSE PHARMACOKINETIC SAMPLING	**Original Wording**: Population-based PK/PD modelling describing the time course of total serum iron (TSI) concentrations and the relationship between TSI and changes of hemoglobin following a single dose of intravenous FCM in pediatric subjects with IDA has been performed using intensively sampled data from Study 1VIT13036.[16] It is proposed to supplement this initial modelling with additional sparsely sampled PK data from this study. Based on the anticipated visit duration on the 2 FCM administration days in this study, the following sparse PK sampling scheme is proposed: pre-dose, immediately post-infusion and 60 minutes post-dose on Days 0 and 7, on which subjects will receive 15 mg/kg (up to a maximum dose of 750 mg). This pragmatic approach, which minimizes the number of blood draws	To provide a timeframe for what immediately means.

	compared to a full PK profile, is expected to facilitate exposure-response analysis for the proposed FCM regimen. **New Wording:** Population-based PK/PD modelling describing the time course of total serum iron (TSI) concentrations and the relationship between TSI and changes of hemoglobin following a single dose of intravenous FCM in pediatric subjects with IDA has been performed using intensively sampled data from Study 1VIT13036.[16] It is proposed to supplement this initial modelling with additional sparsely sampled PK data from this study. Based on the anticipated visit duration on the 2 FCM administration days in this study, the following sparse PK sampling scheme is proposed: pre-dose, immediately **(within 5 minutes)** post-infusion and 60 minutes post-dose on Days 0 and 7, on which subjects will receive 15 mg/kg (up to a maximum dose of 750 mg). This pragmatic approach, which minimizes the number of blood draws compared to a full PK profile, is expected to facilitate exposure-response analysis for the proposed FCM regimen.	
3.4 SCHEDULE OF EVENTS	**Footnote #2** **Original Wording**: Blood samples for pharmacokinetic analysis will be collected pre-dose, immediately 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. **New Wording**: 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.	To provide a timeframe for what immediately means.

4.3 PARTICIPANT ASSIGNMENT AND RANDOMIZATION PROCESS	**Original Wording**: 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 receive ferrous sulfate elixir, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. **New Wording:** 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 receive ferrous sulfate elixir **or ferrous sulfate tablets**, and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets.	To allow children (≥4 to <12 years of age) the option to receive either ferrous sulfate elixir or ferrous sulfate tablets.
5.3 MEDICATION PRECAUTION	**Original Wording**: When administering FCM, the following precautions will be taken: • Heart rate and blood pressure will be assessed pre-, immediately post, and 30 minutes post administration. Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed. **New Wording:** When administering FCM, the following precautions will be taken: • Heart rate and blood pressure will be assessed pre-, immediately **(within 5 minutes)** post, and 30 minutes post administration. Participants will be discharged from the site by the Investigator or his or her designee only if there are no significant signs or symptoms 30 minutes after the administration is completed.	To provide a timeframe for what immediately means.
5.5 CONCOMITANT MEDICATION	**Original Wording**:	For clarification.

	If receiving treatment for IBD, therapy must be stable for at least 8 weeks prior to consent and remain stable through the **remaining** of the study. **New Wording:** If receiving treatment for IBD, therapy must be stable for at least 8 weeks prior to consent and remain stable through the **duration** of the study.	
6.1 INFORMED CONSENT	**Original Wording**: Prior to any study specific procedures, the investigator must explain to each participant the nature of the study, its purpose, procedures to be performed, expected duration, and the benefits and risks of study participation. After this explanation, the participant (who for this trial is 1 -17 years old) must assent, if appropriate, and his/her legal guardian (who is above age of legal consent) voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The Code of Federal Regulations (CFR) is a codification of rules and regulations of the US government. The participant's legal guardian will be given a copy of the signed consent form. **New Wording:** Prior to any study specific procedures, the investigator must explain to each participant the nature of the study, its purpose, procedures to be performed, expected duration, and the benefits and risks of study participation. After this explanation, the participant (who for this trial is 1 -17 years old) must assent, if appropriate, and his/her legal guardian (who is above age of legal consent) voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The Code of Federal Regulations (CFR) is a codification of rules and regulations of the US government. **Subjects who are too young to sign an ICF, but mature enough to understand the study, will provide informed assent per local law. The subject must be able to understand that he or she can withdraw from the trial at any time and for any reason.** The participant's legal guardian will be given a copy of the signed consent form.	To provide additional guidance about informed assent

6.3.1 DAY 0 VISIT	**Original Wording**: After a randomization number has been obtained, the **first dose** of oral ferrous sulfate will be administered in the clinic according to the following: infants and children (1 to <4 years of age) will receive ferrous sulfate drops; children (≥4 to <12 years of age) will receive ferrous sulfate elixir; and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. Group A: • Blood samples for PK immediately post-dose and 60 minutes post dose. • Post-administration, obtain sitting heart rate and blood pressure immediately after and 30 minutes after FCM administration. Group B • Oral ferrous sulfate dispensing: o If the participant took less than the amount of oral iron expected, document the reason(s) for **dose reduction** and counsel the participant/parents/guardians about the importance of taking the study drug as prescribed. **New Wording:** After a randomization number has been obtained, the **first dose** of oral ferrous sulfate will be administered in the clinic according to the following: infants and children (1 to <4 years of age) will receive ferrous sulfate drops; children (≥4 to <12 years of age) will receive ferrous sulfate elixir **or ferrous sulfate tablets**; and adolescents (≥12 to 17 years of age) will receive ferrous sulfate tablets. Group A: • Blood samples for PK immediately **(within 5 minutes)** post-dose and 60 minutes post dose.	To allow children (≥4 to <12 years of age) the option to receive either ferrous sulfate elixir or ferrous sulfate tablets. To provide a timeframe for what immediately means. To correct a typo: missed doses instead of dose reduction.

	• Post-administration, obtain sitting heart rate and blood pressure immediately **(within 5 minutes)** after and 30 minutes after FCM administration. Group B • Oral ferrous sulfate dispensing: o If the participant took less than the amount of oral iron expected, document the reason(s) for **missed doses** and counsel the participant/parents/guardians about the importance of taking the study drug as prescribed. • For ferrous sulfate drops and elixir: o If the participant took less than the volume expected, document the reason(s) for **missed doses** and counsel the participant/parent/guardian about the importance of taking the study drug as prescribed.	
6.3.2 DAY 7 AND DAT 14 VISIT	**Original Wording**: Group A: • Blood samples for PK immediately post-dose and 60 minutes post dose. • Post-administration, obtain sitting heart rate and blood pressure immediately after and 30 minutes after FCM administration. Group B • Oral ferrous sulfate dispensing: o If the participant took less than the number of tablets expected, document the reason(s) for **dose reduction** and counsel the	To provide a timeframe for what immediately means. To correct a typo: missed doses instead of dose reduction.

	participant/parent/guardian about the importance of taking the study drug as prescribed. • For ferrous sulfate drops and elixir: o If the participant took less than the volume expected, document the reason(s) for **dose reduction** and counsel the participant/parent/guardian about the importance of taking the study drug as prescribed. **New Wording:** Group A: • Blood samples for PK immediately **(within 5 minutes)** post-dose and 60 minutes post dose. • Post-administration, obtain sitting heart rate and blood pressure immediately **(within 5 minutes)** after and 30 minutes after FCM administration. Group B • Oral ferrous sulfate dispensing: o If the participant took less than the number of tablets expected, document the reason(s) for **missed doses** and counsel the participant/parent/guardian about the importance of taking the study drug as prescribed. • For ferrous sulfate drops and elixir: o If the participant took less than the volume expected, document the reason(s) for **missed doses** and counsel the participant/parent/guardian about the importance of taking the study drug as prescribed.	
6.3.6 PHARMACOKINETIC SAMPLING	**Original Wording**: Blood samples will be collected for PK assessment pre-dose, immediately post-dose, and 60 minutes post-dose for participants receiving FCM on Days	To clarify the time for blood sampling.

	0 and 7. Blood samples should be taken at approximately the same time of day on Day 7 as Day 0. **New Wording:** Blood samples will be collected for PK assessment pre-dose, immediately **(within 5 minutes)** post-dose, and 60 minutes post-dose for participants receiving FCM on Days 0 and 7. Blood samples should be taken at approximately the same time of day **(within 1 hour)** on Day 7 as Day 0.	
7.1 ADVERSE EVENTS	**Original Wording**: To quantify the severity of adverse events, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version **4** should be used to grade all events. These criteria are provided in the procedure manual. **New Wording:** To quantify the severity of adverse events, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version **5 or higher** should be used to grade all events. These criteria are provided in the procedure manual.	To make sure the latest version of the NCI CTCAE is used
7.3 SERIOUS ADVERSE EVENTS	**Original Wording**: Email: pv@**luitpold**.com **New Wording:** Email: pv@**americanregent**.com	To reflect the change in the e-mail for Pharmacovigilance
8.4.1 PRIMARY ENDPOINTS **Subgroup analyses**	**Original Wording**: The change in hemoglobin from baseline to day 35 will be summarized separately for the following subgroups: • Cause of IDA: IBD, not IBD • Baseline hemoglobin : <10, ≥10 g/dL	Since children with chronic kidney disease on hemodialysis are allowed to participate in the study, they

	• Age: 1 to <12, ≥12 to 17 years **New Wording**: The change in hemoglobin from baseline to day 35 will be summarized separately for the following subgroups: • Cause of IDA: IBD, not IBD • ***CKD, not CKD*** • Baseline hemoglobin : <10, ≥10 g/dL • Age: 1 to <12, ≥12 to 17 years	were included in the subgroup analyses
8.4.2 SECONDARY ENDPOINTS	**Original Wording**: Secondary efficacy endpoints include: • Change in ferritin from baseline to Day 35 • Change in TSAT from baseline to Day 35 • Changes from baseline to in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin content. • Pharmacokinetic assessments, including C_{max}, T_{max}, $AUC_{0\text{-time last measured concentration}}$, $AUC_{0\text{-infinity}}$, $T_{1/2}$, MRT, Cl, V_D, V_{Dc}, V_{Dss}, and V_{Darea}. **New Wording**: Secondary efficacy endpoints include: • Change in ferritin from baseline to Day 35 • Change in TSAT from baseline to Day 35 • Changes from baseline to in hemoglobin, ferritin, TSAT, and reticulocyte hemoglobin content. • Pharmacokinetic assessments, including C_{max}, T_{max}, $AUC_{0\text{-time last measured concentration}}$, $AUC_{0\text{-infinity}}$, $T_{1/2}$, MRT, Cl, V_D, V_{Dc},	To clarify pharmacokinetic assessment

	V_{Dss}, and V_{Darea}. **These assessments will be based on a population pharmacokinetic analysis using data from this study and 1VIT13036.**	
8.5.4 CLINICAL LABORATORY FINDINGS	**Original Wording**: Clinical laboratory variables will be presented in two ways. First, the mean change from baseline to each scheduled visit will be summarized. Second, the number and percent of participants with treatment-emergent PCS laboratory values will be tabulated. Treatment-emergent PCS laboratory tests are those in which the baseline value is normal and post-baseline value is abnormal (i.e., meets Grade III or Grade IV toxicity criteria from the NCI-CTC). Baseline will be defined as the last value obtained before randomization. **New Wording:** Clinical laboratory variables will be presented in two ways. First, the mean change from baseline to each scheduled visit will be summarized. Second, the number and percent of participants with treatment-emergent PCS laboratory values will be tabulated. Treatment-emergent PCS laboratory tests are those in which the baseline value is normal and post-baseline value is abnormal (i.e., meets Grade III or Grade IV toxicity criteria from the NCI-CTC **Version 5 or higher**). Baseline will be defined as the last value obtained before randomization.	To update the version of NCI-CTC to be used.

ADMINISTRATIVE CHANGE 1

Affected Section(s)	Summary of Revisions Made	Rationale
HEADER	The heading was changed to reflect the current protocol version number and date of version. **Original Wording**: American Regent, Inc. Protocol No.: 1VIT17044 CONFIDENTIAL **Amendment 2 Date: 13 March 2019** **New Wording:** **American Regent,** Inc. Protocol No.: 1VIT17044 CONFIDENTIAL **Administrative Change 1 Date: 26 September 2019**	To reflect the updated version of the protocol.
TITLE PAGE	Protocol Date was changed. **Original Wording**: Protocol Date: 20 April 2017 Amendment I Protocol Date: 14 September 2017 Amendment 2 Protocol Date: 13 March 2019 **New Wording:** Protocol Date: 20 April 2017 Amendment 1 Protocol Date: 14 September 2017 Amendment 2 Protocol Date: 13 March 2019 **Administrative Change 1 Date: 26 September 2019**	To reflect the date of the current protocol version.
SIGNATURES OF AGREEMENT FOR PROTOCOL	**Removal of:** Anthony DiGuglielmo, DPM, Medical, Director, Head of Pharmacovigilance Marsha Simon, Director of Regulatory Affairs Nicole Blackman, PhD, Head of Quantitative Sciences	An Administrative Change does not need all functions to approve.

Section 4.2.1 INCLUSION CRITERIA	**Original Wording**: 4. Documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to **screening**. **New Wording:** 4. Documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to **randomization**.	To revert back to the inclusion criteria # 4 sentence in the original protocol and Amendment 1.