1VIT18045 Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients With Iron Deficiency Anemia and Unsatisfactory Response Oral Iron Under Study Protocol 1VIT17044 NCT04269707

03DEC2019

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AMERICAN REGENT, INC.

PROTOCOL

No. 1VIT18045

IND #: 63,243

Evaluating the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia and an Unsatisfactory Response to Oral Iron under Study Protocol 1VIT17044

SPONSOR

American Regent, Inc.
Clinical Research and Development
800 Adams Avenue
Norristown, PA 19403
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Protocol Date: Final 26 April 2019

Administrative Change 1 Date: Final 03 December 2019

SIGNATURES OF AGREEMENT FOR PROTOCOL

03 DEC 2019

Geoffrey Mukwaya, MD, M.Sc., FAAP, FRCPC
Head, Clinical Research and Development
American Regent, Inc.

Date

03-December-2019

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

Date

Study Synopsis

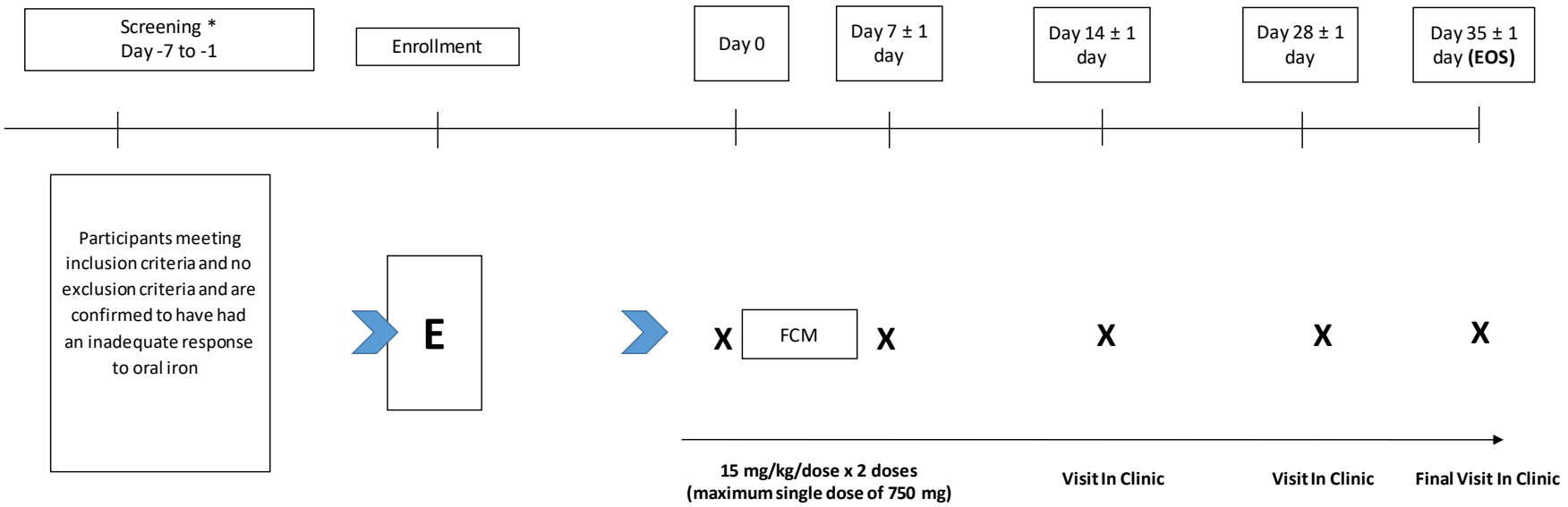
Protocol No. 1VIT18045

Title:	Evaluating the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia and an Unsatisfactory Response to Oral Iron under Study Protocol 1VIT17044
Study Drug:	Injectafer® (Ferric Carboxymaltose [FCM])
Objectives:	• The primary objective of this study is to evaluate the efficacy and safety of intravenous (IV) ferric carboxymaltose (FCM) in pediatric participants who have iron deficiency anemia (IDA).
Nature of Study:	Phase III
Design:	This is a single arm, open-label, multi-center, multi-national, non-randomized study that will evaluate the efficacy and safety of a one course treatment with FCM in participants who had an unsatisfactory response to oral iron in study 1VIT17044. Subjects will have an End of Study (EOS) Visit (Day 35) from the 1VIT17044 study to qualify for entry. Subjects will then be screened, meet all inclusion criteria, no exclusion criteria and have a baseline evaluation. Based on the successful completion of the baseline evaluations, subjects will be enrolled and will receive the first dose of FCM (Day 0). The second FCM dose will occur 7 days from the first dose. Subjects will return to the clinic 14 and 28 days post their first dose for laboratory and safety assessments, and at 35 days post the first dose, participants will return to the clinic for final safety and efficacy assessments. Once all assessments are complete the participant will exit the study. An **unsatisfactory response** to oral iron (i.e., an increase in hemoglobin (Hgb) of <1 g/dL from baseline) will be defined as non-responders to oral iron treatment. Non-responders who continue to meet all inclusion criteria (including Hgb <11 g/dL) and none of the exclusion criteria will receive 1 course of FCM.
Inclusion Criteria:	1. Unsatisfactory response to oral iron or those that required a concomitant intervention, (defined as, blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason [Day 0 thru Day

	35 of study protocol 1VIT17044], change in Inflammatory Bowel Disease [IBD] treatment). 2. Hgb <11 g/dL 3. Ferritin ≤300 ng/mL and Transferrin Saturation (TSAT) <30%
Exclusion Criteria:	1. Known history of hypersensitivity reaction to any component of FCM. 2. History of acquired iron overload, hemochromatosis, or other iron accumulation disorders. 3. History of significant diseases of the liver, hematopoietic system, cardiovascular system, psychiatric disorder, or other conditions which, in the opinion of the investigator, may place a subject at added risk for participation in the study. 4. Any existing non-viral infection. 5. Known history of positive hepatitis B surface antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis. 6. Known history of positive human immunodeficiency virus (HIV-1/HIV-2) antibodies (anti-HIV). 7. Anemia due to reasons other than iron deficiency (e.g., hemoglobinopathy and vitamin B12 or folic acid deficiency) that has not been corrected. 8. Administration and / or use of an investigational product (drug or device) within 30 days of screening. 9. Alcohol or drug abuse within the past six months. 10. Female participant who is pregnant or lactating, or sexually active females who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study. 11. Unable to comply with study procedures and assessments.
Study Drug Administration	Participants 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
Endpoints:	**Primary Endpoint:** • Change in Hgb 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 Hgb, ferritin, TSAT, and reticulocyte hemoglobin content (CHr) throughout the study
Participant Duration:	35 Days
Study Sites:	Approximately 25 sites
Participant Number:	Maximum of approximately 36 participants

Figure 1 Study diagram



* Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
Anti-HIV	Antibodies to Human Immunodeficiency Virus
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CHr	Reticulocyte Hemoglobin Content
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
eCRF	Electronic Case Report Form
e.g.	For Example
EOS.	End of Study
FCM	Ferric Carboxymaltose
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
Hct	Hematocrit
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Viral Antibody
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
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
IRT	Interactive Response Technology
IV	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactic Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
m	Meter
mg	Milligram
mL	Milliliter

NCI	National Cancer Institute
ng	Nanogram
PCS	Potentially Clinically Significant
PT	Preferred Term
RBC	Red Blood Cell
RDW	Red (cell) Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
US	United States
WBC	White Blood Cell

1. 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) [Looker, 1997]. 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 [Kulnigg, 2006]. Anemia may also decrease survival rates in adults and children with chronic renal impairment where it is a commonly encountered problem [Foley, 1996; Staples, 2010]. 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 [Kulnigg, 2006].

Non-hematologic consequences of iron deficiency in children include poor weight gain, anorexia, irritability, decreased attention span, exercise intolerance, and decreased physical activity [Wharton, 1999]. 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 [Kazal, 2002].

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 [Kulnigg, 2006]. 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 [Powers, 2014].

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 [Michaud, 2002; Pinsk, 2008; Surico, 2002]. 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 [Michaud, 2002].

Ferric Carboxymaltose has been characterized as an iron complex (Type 1) with a molecular mass of about 150,000 Daltons. 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 completed 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 Hgb, ferritin, and TSAT [Favreau, 2017].

The proposed study will provide safety and efficacy data on the use of FCM in pediatric patients (aged between 1 and 18 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

Ferric Carboxymaltose 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 Hgb 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 [Staples, 2010]. 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% [Michaud, 2002]. Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran [Fishbane, 2003]. 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 iron dextran is associated with a higher rate of life threatening adverse events and anaphylactic reactions in comparison to low molecular weight iron dextran, the US Food and Drug Administration (FDA) was unable to find a clear difference after an examination of post-marketing data, clinical trial data, death certificates, and emergency room diagnoses [Pinsk, 2008]. Iron dextran is limited to second line therapy for treatment of iron deficiency.

More recently approved IV 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 [Van Wyck, 2004].

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. 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. TRIAL OBJECTIVE

2.1. Primary Objective

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

3. OVERALL STUDY DESIGN AND RATIONALE

3.1. Overall Study Design

This is a single arm, open-label, multi-center, multi-national, non-randomized study that will evaluate the efficacy and safety of a one course treatment with FCM in participants who had an unsatisfactory response to oral iron in study 1VIT17044.

Subjects will have an EOS Visit (Day 35) from the 1VIT17044 study to qualify for entry. Subjects will then be screened, meet all inclusion criteria, no exclusion criteria and have a baseline evaluation. Based on the successful completion of the baseline evaluations, subjects will be enrolled and will receive the first dose of FCM (Day 0). The second FCM dose should occur 7 days from the first dose. Subjects will return to the clinic 14 and 28 days post their first dose for laboratory and safety assessments, and at 35 days post the first dose, participants will return to the clinic for final safety and efficacy assessments. Once all assessments are complete the participant will exit the study.

An **unsatisfactory response** to oral iron (i.e., an increase in Hgb of <1 g/dL from baseline) will be defined as non-responders to oral iron treatment. Non-responders who continue to meet all inclusion criteria (including Hgb <11 g/dL) and none of the exclusion criteria will receive 1 course of FCM.

3.2. Rationale of Study Design

The primary objective in this study is to allow participants who were randomized to receive oral iron in the 1VIT17044 trial and who had an unsatisfactory response to oral iron or those that required a concomitant intervention, (defined as, blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason [Day 0 thru Day 35 of study protocol 1VIT17044], change in IBD treatment) to receive one course of FCM. This course of FCM will consist of two doses of FCM at 15 mg/kg (maximum single dose of 750 mg), separated by seven days.

This study is a rollover for study 1VIT17044 which is an open label, multi-center, multi-national, randomized, active-control parallel group study that will evaluate the efficacy and safety of FCM in pediatric participants, ages 1 to 18 years with iron deficiency anemia.

3.3. Schedule of Events

Table 1 Schedule of Activities

Procedures	Screening[1] Day -7 to -1	Enrollment Visit 1, Day 0	Study Visit 2 Day 7 ± 1 day	Study Visit 3 Day 14 ± 1 day	Study Visit 4 Day 28 ± 1 day	Study Visit 5 Day 35 ± 1 day
Informed Consent / Assent	X					
Medical History	X					
Physical Exam		X				X
Inclusion/Exclusion Criteria	X	X				
Interactive Response Technology (IRT)	X	X				X
Vital Signs	X	X	X	X	X	X
Weight	X	X				
Height	X					
Temperature		X	X			
Blood sampling for Hematology, Chemistry and Iron Indices (5.5 mL) [1]	X	X	X	X	X	X
Blood sampling for Serum Pregnancy Test (1.5 mL), if applicable	X					X
Concomitant Medications	X	X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X
FCM Dosing		X	X			

1. Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening

2. For a full description of central laboratory assessments, refer to Protocol Section 6.4.

4. PARTICIPANT SELECTION

4.1. Number and Type of Participants

A maximum of approximately 36 participants from study 1VIT17044 who had an unsatisfactory response to oral iron.

4.2. Screening Phase

A subject who enters the screening phase will be assigned, via the IRT system, a unique screening number. 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).

4.2.1. Inclusion Criteria

1. Unsatisfactory response to oral iron or those that required a concomitant intervention, (defined as, blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason [Day 0 thru Day 35 of study protocol 1VIT17044], change in IBD treatment).
2. Hgb <11 g/dL
3. Ferritin ≤300 ng/mL and TSAT <30%

4.2.2. Exclusion Criteria

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

4.3. Participant Assignment Process

Participants who satisfy the inclusion requirements and no exclusionary criteria will be eligible to participate in this study. This is an open label study.

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.

5. STUDY DRUG

5.1. Formulation, Packaging and Storage

The 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.

FCM must be kept in a secure place at the investigational site, and stored at room temperature (see United States Pharmacopeia). 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 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. All subjects will be dosed with FCM based on the Hgb, TSAT and ferritin values from the last scheduled visit in the 1VIT17044 study.

Participants 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.

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 post (within 5 minutes), 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 normal saline, 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). 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.

6. 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 -18 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 informed consent form, 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 to -1)

Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening.

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
- Hematology, chemistries and iron indices. For a full description of central laboratory assessments, refer to Protocol Section 6.4.
- Serum pregnancy test for female participants of child bearing potential (negative results must be obtained prior to study drug dosing).
- Height and weight
- Vitals signs (sitting heart rate and blood pressure)
- Concomitant medications assessment

Participants who do not meet the entry criteria should be entered into the IRT system as a screen failure.

6.3. Treatment Phase (Day 0 to Day 35)

6.3.1. Enrollment: Visit 1 Day 0

The following will be obtained and/or completed before contacting IRT for a subject number:

For all participants:

- Verify all inclusion and exclusion criteria (**see Sections 4.2.1 and 4.2.2**)
- Physical exam
- Review concomitant medications.

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. After assignment of the subject number, 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 (prior to study drug administration)
- Vital signs: temperature, sitting heart rate and blood pressure
- Weight
- Verify amount of single FCM dose (15 mg/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 (SAE) assessment (starting at beginning of FCM injection).

6.3.2. Visit 2 Day 7 ± 1 day

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

- Vital signs (temperature, sitting heart rate and blood pressure)
- Blood samples for central lab hematology, chemistries and iron indices (prior to study drug administration).
- Concomitant medications assessment
- Verify amount of single FCM dose (15 mg/kg up to a maximum 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 / SAE assessment (starting at beginning of FCM injection).

6.3.3. Visit 3 Day 14 ± 1 day

All participants will return to the clinic on Day 14. The participant will be evaluated clinically to assess for the development of clinically significant conditions.

- Vital signs (sitting heart rate and blood pressure)
- Blood samples for central lab hematology, chemistries and iron indices
- Concomitant medications assessment
- Adverse events assessment

6.3.4. Visit 4 Day 28 ± 1 day

- Vitals signs (sitting heart rate and blood pressure)
- Hematology, chemistries and iron indices
- Concomitant medications assessment
- Adverse events assessment

6.3.5. Visit 5 Day 35 ± 1 day (End of Study)

- Physical exam

- Vitals signs (sitting heart rate and blood pressure)
- Blood samples for central lab hematology, chemistries and iron indices
- Serum pregnancy test for female participants of child bearing potential
- Concomitant medications assessment
- 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.

6.4. 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 3.3.

Hematology:	Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, reticulocyte count, and 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 TSAT
Other:	Serum pregnancy test

7. 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 electronic case report form (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 EOS/Day 35 that have been deemed clinical significant by the Investigator should be followed until they are back into normal range.

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 NCI-CTCAE criterion does not exist, the investigator should use Table 2 to assign the adverse event grade.

Table 2 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 FCM 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 FCM 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 purpose of this trial, study drug is defined as FCM.

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 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:

Safety Monitor

American Regent, Inc.

Phone: (800) 734-9236
Fax: (610) 650-0170
Email: pv@americanregent.com

The local investigator is responsible for reporting SAEs to their local Institutional Review Board (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. STATISTICS

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation (SD), 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

This is a non-randomized, single arm study.

8.2. Analysis Populations

Safety Population

The safety population will consist of all participants who received at least one dose of study drug.

8.3. Disposition and Baseline Characteristics

The number of participants in each investigative site will be summarized. The number of participants who are screened, 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 Hgb from baseline to day 35. Descriptive statistics will be provided for the baseline Hgb, the day 35 Hgb, and the within-participant change from baseline. The change in Hgb from baseline to day 35 will be analyzed using paired t-tests.

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 in Hgb, ferritin, TSAT, and CHr throughout the study

Details of analyses for these endpoints will be outlined 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. Missing data will not be imputed for descriptive statistical summaries in safety or efficacy. Details will be provided in the SAP.

8.5. Analyses of Safety

8.5.1. Study Drug Exposure

The number of infusions and total administered 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 treatment emergent AE (TEAE) will be summarized. 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 Hgb/hematocrit (Hct) and low iron indices. 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.

The adverse event profile will be characterized with severity (as graded by the 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 potentially clinically significant (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-CTCAE Version 5 or higher). Baseline will be defined as the last value obtained before receiving study drug.

No formal statistical tests will be performed.

8.5.5. Vital Signs

The change in vital signs (sitting heart rate and blood pressure) from pre-infusion to each post-infusion time point will be summarized descriptively on each dosing day.

8.5.6. Sample Size Rationale

There were no sample size estimations for this study. The current study is a rollover for study 1VIT17044. There will be a maximum of approximately 36 participants from study 1VIT17044 who had an unsatisfactory response to oral iron or required an intervention.

9. 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 Investigational New Drug Application (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 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 to 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 Sponsor 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, Inc. 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 Regent, Inc. on any results or ideas connected with the study.

10. 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)

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12. APPENDIX 1: AMENDMENT/ADMINISTRATIVE CHANGES

12.1. 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.: 1VIT18045 CONFIDENTIAL **Final version: 1.0 26 April 2019** **New Wording:** American Regent, Inc. Protocol No.: 1VIT18045 CONFIDENTIAL **Administrative Change 1 Date: Final 03 December 2019**	To reflect the updated version of the protocol.
TITLE PAGE	Protocol Date was changed. **Original Wording**: Protocol Date: 26 April 2019 **New Wording:** Protocol Date: 26 April 2019 **Administrative Change 1 Date: Final 03 December 2019**	To reflect the date of the current protocol version.

AMERICAN REGENT, INC.

PROTOCOL

No. 1VIT18045

IND #: 63,243

Evaluating the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia and an Unsatisfactory Response to Oral Iron under Study Protocol 1VIT17044

SPONSOR

American Regent, Inc.
Clinical Research and Development
800 Adams Avenue
Norristown, PA 19403
631-772-3500

Protocol Date: Final 26 April 2019

SIGNATURES OF AGREEMENT FOR PROTOCOL

Dr Linda M. Mundy on behalf of GM Clinical R+D

~~Geoffrey Mukwaya, MD, M.Se., FAAP, FRCPC~~ Date
29 APR 2019
Head, Clinical Research and Development
American Regent, Inc.

26 APR 2019

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

29APR2019

Anthony DiGuglielmo, DPM Date
Medical Director, Head of Pharmacovigilance
American Regent, Inc.

29APR2019

Marsha Simon Date
Director of Regulatory Affairs
American Regent, Inc.

26APR2019

Nicole Blackman, PhD Date
Head of Quantitative Sciences
American Regent, Inc.

Study Synopsis

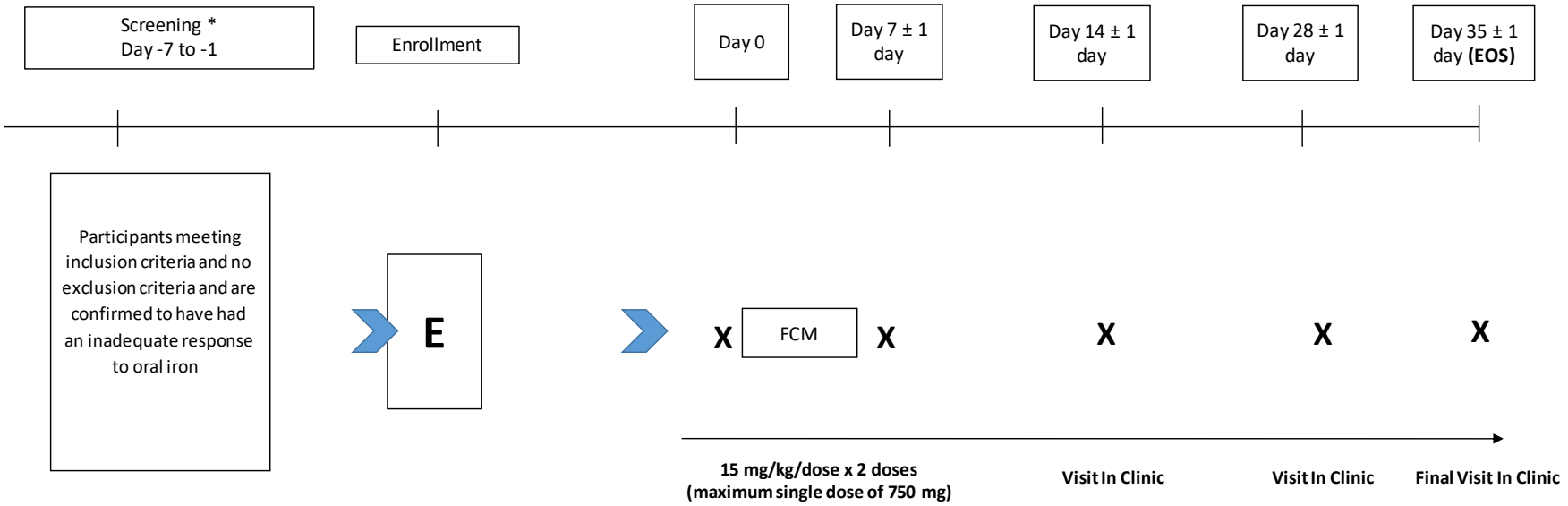
Protocol No. 1VIT18045

Title:	Evaluating the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia and an Unsatisfactory Response to Oral Iron under Study Protocol 1VIT17044
Study Drug:	Injectafer® (Ferric Carboxymaltose [FCM])
Objectives:	• The primary objective of this study is to evaluate the efficacy and safety of intravenous (IV) ferric carboxymaltose (FCM) in pediatric participants who have iron deficiency anemia (IDA).
Nature of Study:	Phase III
Design:	This is a single arm, open-label, multi-center, multi-national, non-randomized study that will evaluate the efficacy and safety of a one course treatment with FCM in participants who had an unsatisfactory response to oral iron in study 1VIT17044. Subjects will have an End of Study (EOS) Visit (Day 35) from the 1VIT17044 study to qualify for entry. Subjects will then be screened, meet all inclusion criteria, no exclusion criteria and have a baseline evaluation. Based on the successful completion of the baseline evaluations, subjects will be enrolled and will receive the first dose of FCM (Day 0). The second FCM dose will occur 7 days from the first dose. Subjects will return to the clinic 14 and 28 days post their first dose for laboratory and safety assessments, and at 35 days post the first dose, participants will return to the clinic for final safety and efficacy assessments. Once all assessments are complete the participant will exit the study. An **unsatisfactory response** to oral iron (i.e., an increase in hemoglobin (Hgb) of <1 g/dL from baseline) will be defined as non-responders to oral iron treatment. Non-responders who continue to meet all inclusion criteria (including Hgb <11 g/dL) and none of the exclusion criteria will receive 1 course of FCM.
Inclusion Criteria:	1. Unsatisfactory response to oral iron or those that required a concomitant intervention, (defined as, blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason [Day 0 thru Day

	35 of study protocol 1VIT17044], change in Inflammatory Bowel Disease [IBD] treatment). 2. Hgb <11 g/dL 3. Ferritin ≤300 ng/dL and Transferrin Saturation (TSAT) <30%
Exclusion Criteria:	1. Known history of hypersensitivity reaction to any component of FCM. 2. History of acquired iron overload, hemochromatosis, or other iron accumulation disorders. 3. History of significant diseases of the liver, hematopoietic system, cardiovascular system, psychiatric disorder, or other conditions which, in the opinion of the investigator, may place a subject at added risk for participation in the study. 4. Any existing non-viral infection. 5. Known history of positive hepatitis B surface antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis. 6. Known history of positive human immunodeficiency virus (HIV-1/HIV-2) antibodies (anti-HIV). 7. Anemia due to reasons other than iron deficiency (e.g., hemoglobinopathy and vitamin B12 or folic acid deficiency) that has not been corrected. 8. Administration and / or use of an investigational product (drug or device) within 30 days of screening. 9. Alcohol or drug abuse within the past six months. 10. Female participant who is pregnant or lactating, or sexually active females who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study. 11. Unable to comply with study procedures and assessments.
Study Drug Administration	Participants 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
Endpoints:	**Primary Endpoint:** • Change in Hgb 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 Hgb, ferritin, TSAT, and reticulocyte hemoglobin content (CHr) throughout the study
Participant Duration:	35 Days
Study Sites:	Approximately 25 sites
Participant Number:	Maximum of approximately 36 participants

Figure 1 Study diagram



* Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
Anti-HIV	Antibodies to Human Immunodeficiency Virus
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CHr	Reticulocyte Hemoglobin Content
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
eCRF	Electronic Case Report Form
e.g.	For Example
EOS.	End of Study
FCM	Ferric Carboxymaltose
FDA	Food and Drug Administration
Fe	Iron
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
Hct	Hematocrit
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Viral Antibody
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
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
IRT	Interactive Response Technology
IV	Intravenous
Kg	Kilogram
L	Liter
LDH	Lactic Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
m	Meter
mg	Milligram
mL	Milliliter

NCI	National Cancer Institute
ng	Nanogram
PCS	Potentially Clinically Significant
PT	Preferred Term
RBC	Red Blood Cell
RDW	Red (cell) Distribution Width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TIBC	Total Iron Binding Capacity
TSAT	Transferrin Saturation
US	United States
WBC	White Blood Cell

1. 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) [Looker, 1997]. 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 [Kulnigg, 2006]. Anemia may also decrease survival rates in adults and children with chronic renal impairment where it is a commonly encountered problem [Foley, 1996; Staples, 2010]. 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 [Kulnigg, 2006].

Non-hematologic consequences of iron deficiency in children include poor weight gain, anorexia, irritability, decreased attention span, exercise intolerance, and decreased physical activity [Wharton, 1999]. 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 [Kazal, 2002].

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 [Kulnigg, 2006]. 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 [Powers, 2014].

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 [Michaud, 2002; Pinsk, 2008; Surico, 2002]. 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 [Michaud, 2002].

Ferric Carboxymaltose has been characterized as an iron complex (Type 1) with a molecular mass of about 150,000 Daltons. 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 completed 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 Hgb, ferritin, and TSAT [Favreau, 2017].

The proposed study will provide safety and efficacy data on the use of FCM in pediatric patients (aged between 1 and 18 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

Ferric Carboxymaltose 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 Hgb 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 [Staples, 2010]. 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% [Michaud, 2002]. Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran [Fishbane, 2003]. 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 iron dextran is associated with a higher rate of life threatening adverse events and anaphylactic reactions in comparison to low molecular weight iron dextran, the US Food and Drug Administration (FDA) was unable to find a clear difference after an examination of post-marketing data, clinical trial data, death certificates, and emergency room diagnoses [Pinsk, 2008]. Iron dextran is limited to second line therapy for treatment of iron deficiency.

More recently approved IV 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 [Van Wyck, 2004].

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. 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. TRIAL OBJECTIVE

2.1. Primary Objective

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

3. OVERALL STUDY DESIGN AND RATIONALE

3.1. Overall Study Design

This is a single arm, open-label, multi-center, multi-national, non-randomized study that will evaluate the efficacy and safety of a one course treatment with FCM in participants who had an unsatisfactory response to oral iron in study 1VIT17044.

Subjects will have an EOS Visit (Day 35) from the 1VIT17044 study to qualify for entry. Subjects will then be screened, meet all inclusion criteria, no exclusion criteria and have a baseline evaluation. Based on the successful completion of the baseline evaluations, subjects will be enrolled and will receive the first dose of FCM (Day 0). The second FCM dose should occur 7 days from the first dose. Subjects will return to the clinic 14 and 28 days post their first dose for laboratory and safety assessments, and at 35 days post the first dose, participants will return to the clinic for final safety and efficacy assessments. Once all assessments are complete the participant will exit the study.

An **unsatisfactory response** to oral iron (i.e., an increase in Hgb of <1 g/dL from baseline) will be defined as non-responders to oral iron treatment. Non-responders who continue to meet all inclusion criteria (including Hgb <11 g/dL) and none of the exclusion criteria will receive 1 course of FCM.

3.2. Rationale of Study Design

The primary objective in this study is to allow participants who were randomized to receive oral iron in the 1VIT17044 trial and who had an unsatisfactory response to oral iron or those that required a concomitant intervention, (defined as, blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason [Day 0 thru Day 35 of study protocol 1VIT17044], change in IBD treatment) to receive one course of FCM. This course of FCM will consist of two doses of FCM at 15 mg/kg (maximum single dose of 750 mg), separated by seven days.

This study is a rollover for study 1VIT17044 which is an open label, multi-center, multi-national, randomized, active-control parallel group study that will evaluate the efficacy and safety of FCM in pediatric participants, ages 1 to 18 years with iron deficiency anemia.

3.3. Schedule of Events

Table 1 Schedule of Activities

Procedures	Screening[1] Day -7 to -1	Enrollment Visit 1, Day 0	Study Visit 2 Day 7 ± 1 day	Study Visit 3 Day 14 ± 1 day	Study Visit 4 Day 28 ± 1 day	Study Visit 5 Day 35 ± 1 day
Informed Consent / Assent	X					
Medical History	X					
Physical Exam		X				X
Inclusion/Exclusion Criteria	X	X				
Interactive Response Technology (IRT)	X	X				X
Vital Signs	X	X	X	X	X	X
Weight	X	X				
Height	X					
Temperature		X	X			
Blood sampling for Hematology, Chemistry and Iron Indices (5.5 mL) [1]	X	X	X	X	X	X
Blood sampling for Serum Pregnancy Test (1.5 mL), if applicable	X					X
Concomitant Medications	X	X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X
FCM Dosing		X	X			

1. Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening

2. For a full description of central laboratory assessments, refer to Protocol Section 6.4.

4. PARTICIPANT SELECTION

4.1. Number and Type of Participants

A maximum of approximately 36 participants from study 1VIT17044 who had an unsatisfactory response to oral iron.

4.2. Screening Phase

A subject who enters the screening phase will be assigned, via the IRT system, a unique screening number. 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).

4.2.1. Inclusion Criteria

1. Unsatisfactory response to oral iron or those that required a concomitant intervention, (defined as, blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason [Day 0 thru Day 35 of study protocol 1VIT17044], change in IBD treatment).
2. Hgb <11 g/dL
3. Ferritin ≤300 ng/dL and TSAT <30%

4.2.2. Exclusion Criteria

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

4.3. Participant Assignment Process

Participants who satisfy the inclusion requirements and no exclusionary criteria will be eligible to participate in this study. This is an open label study.

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.

5. STUDY DRUG

5.1. Formulation, Packaging and Storage

The 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.

FCM must be kept in a secure place at the investigational site, and stored at room temperature (see United States Pharmacopeia). 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 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. All subjects will be dosed with FCM based on the Hgb, TSAT and ferritin values from the last scheduled visit in the 1VIT17044 study.

Participants 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.

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 post (within 5 minutes), 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 normal saline, 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). 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.

6. 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 -18 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 informed consent form, 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 to -1)

Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening.

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
- Hematology, chemistries and iron indices. For a full description of central laboratory assessments, refer to Protocol Section 6.4.
- Serum pregnancy test for female participants of child bearing potential (negative results must be obtained prior to study drug dosing).
- Height and weight
- Vitals signs (sitting heart rate and blood pressure)
- Concomitant medications assessment

Participants who do not meet the entry criteria should be entered into the IRT system as a screen failure.

6.3. Treatment Phase (Day 0 to Day 35)

6.3.1. Enrollment: Visit 1 Day 0

The following will be obtained and/or completed before contacting IRT for a subject number:

For all participants:

- Verify all inclusion and exclusion criteria (**see Sections 4.2.1 and 4.2.2**)
- Physical exam
- Review concomitant medications.

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. After assignment of the subject number, 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 (prior to study drug administration)
- Vital signs: temperature, sitting heart rate and blood pressure
- Weight
- Verify amount of single FCM dose (15 mg/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 (SAE) assessment (starting at beginning of FCM injection).

6.3.2. Visit 2 Day 7 ± 1 day

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

- Vital signs (temperature, sitting heart rate and blood pressure)
- Blood samples for central lab hematology, chemistries and iron indices (prior to study drug administration).
- Concomitant medications assessment
- Verify amount of single FCM dose (15 mg/kg up to a maximum 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 / SAE assessment (starting at beginning of FCM injection).

6.3.3. Visit 3 Day 14 ± 1 day

All participants will return to the clinic on Day 14. The participant will be evaluated clinically to assess for the development of clinically significant conditions.

- Vital signs (sitting heart rate and blood pressure)
- Blood samples for central lab hematology, chemistries and iron indices
- Concomitant medications assessment
- Adverse events assessment

6.3.4. Visit 4 Day 28 ± 1 day

- Vitals signs (sitting heart rate and blood pressure)
- Hematology, chemistries and iron indices
- Concomitant medications assessment
- Adverse events assessment

6.3.5. Visit 5 Day 35 ± 1 day (End of Study)

- Physical exam

- Vitals signs (sitting heart rate and blood pressure)
- Blood samples for central lab hematology, chemistries and iron indices
- Serum pregnancy test for female participants of child bearing potential
- Concomitant medications assessment
- 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.

6.4. 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 3.3.

Hematology:	Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, reticulocyte count, and 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 TSAT
Other:	Serum pregnancy test

7. 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 electronic case report form (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 EOS/Day 35 that have been deemed clinical significant by the Investigator should be followed until they are back into normal range.

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 NCI-CTCAE criterion does not exist, the investigator should use Table 2 to assign the adverse event grade.

Table 2 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 FCM 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 FCM 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 purpose of this trial, study drug is defined as FCM.

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 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:

Safety Monitor

American Regent, Inc.

Phone: (800) 734-9236
Fax: (610) 650-0170
Email: pv@americanregent.com

The local investigator is responsible for reporting SAEs to their local Institutional Review Board (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. STATISTICS

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation (SD), 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

This is a non-randomized, single arm study.

8.2. Analysis Populations

Safety Population

The safety population will consist of all participants who received at least one dose of study drug.

8.3. Disposition and Baseline Characteristics

The number of participants in each investigative site will be summarized. The number of participants who are screened, 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 Hgb from baseline to day 35. Descriptive statistics will be provided for the baseline Hgb, the day 35 Hgb, and the within-participant change from baseline. The change in Hgb from baseline to day 35 will be analyzed using paired t-tests.

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 in Hgb, ferritin, TSAT, and CHr throughout the study

Details of analyses for these endpoints will be outlined 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. Missing data will not be imputed for descriptive statistical summaries in safety or efficacy. Details will be provided in the SAP.

8.5. Analyses of Safety

8.5.1. Study Drug Exposure

The number of infusions and total administered 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 treatment emergent AE (TEAE) will be summarized. 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 Hgb/hematocrit (Hct) and low iron indices. 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.

The adverse event profile will be characterized with severity (as graded by the 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 potentially clinically significant (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-CTCAE Version 5 or higher). Baseline will be defined as the last value obtained before receiving study drug.

No formal statistical tests will be performed.

8.5.5. Vital Signs

The change in vital signs (sitting heart rate and blood pressure) from pre-infusion to each post-infusion time point will be summarized descriptively on each dosing day.

8.5.6. Sample Size Rationale

There were no sample size estimations for this study. The current study is a rollover for study 1VIT17044. There will be a maximum of approximately 36 participants from study 1VIT17044 who had an unsatisfactory response to oral iron or required an intervention.

9. 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 Investigational New Drug Application (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 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 to 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 Sponsor 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, Inc. 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 Regent, Inc. on any results or ideas connected with the study.

10. 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)

11. REFERENCES

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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.
Synopsis and Section 4.2.1 INCLUSION CRITERIA	**Original Wording**: 3. Ferritin ≤300 ng/**dL** and Transferrin Saturation (TSAT) <30%. **New Wording:** 3. Ferritin ≤300 ng/**mL** and Transferrin Saturation (TSAT) <30%..	To correct a typo to inclusion criteria # 3.