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IRON CLAD: Can Iron Lessen Anemia Due to Cancer and Chemotherapy: A Study to Investigate the Efficacy and Safety of Injectafer®

LUITPOLD PHARMACEUTICALS, INC.

PROTOCOL
No. 1VIT14039

IND# 63, 243

IRON CLAD: Can **Iron** Lessen Anemia Due to **c**ancer and chemotherapy: A mu**l**ti-center, r**a**ndomized, **d**ouble-blinded, controlled study to investigate the efficacy and safety of Injectafer® (ferric carboxymaltose injection) in adults

SPONSOR

Luitpold Pharmaceuticals, Inc.
Clinical Research and Development
800 Adams Ave
Norristown, PA 19403
(610) 650-4200

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Administrative Amendment 1 Date: 02 November 2017

SIGNATURES OF AGREEMENT FOR PROTOCOL

03 NOV 2017

Mark Falone, MD
Medical Director,
Head of Clinical Research and Development
Luitpold Pharmaceuticals, Inc

Date

07NOV2017

Marsha Simon
Sr. Manager-Regulatory Affairs
Luitpold Pharmaceuticals, Inc.

Date

03NOV2017

Susan Oskins, RN, BSN
Pharmacovigilance Sr. Manager
Luitpold Pharmaceuticals, Inc.

Date

03NOV2017

Nicole Blackman, PhD
Statistician
Luitpold Pharmaceuticals, Inc.

Date

Study Synopsis

Protocol No. 1VIT14039

Title: IRON CLAD: Can **Iron** Lessen Anemia Due to **c**ancer and chemotherapy: A multi-center, **r**andomized, **d**ouble-blinded, controlled study to investigate the efficacy and safety of Injectafer® (ferric carboxymaltose injection) in adults

Study Drugs: Ferric carboxymaltose injection (FCM) and normal saline as placebo

Objective: The primary objective of this study is to compare the efficacy and safety of ferric carboxymaltose (FCM) versus placebo as monotherapy for maintaining hemoglobin (Hgb) levels in patients with cancer- and chemotherapy-related anemia (CRA)

Secondary objectives:

- To evaluate the safety and tolerability of FCM
    - Percentage of adverse events and serious adverse events
- To evaluate the percentage of patients with a hemoglobin stabilized throughout the study
- To evaluate transfusion rate (The decision of when to transfuse will be at the discretion of the Investigator and treating physicians. However, Investigators and treating physicians will be encouraged not to transfuse patients whose measured Hgb is greater than 7.0 g/dL in absence of any evidence of inadequate oxygen delivery to organs that could be due to Hgb.)
    - Percentage of patients receiving a transfusion
- To evaluate quality of life
    - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale
- To evaluate efficacy response based on hepcidin levels

Design: This is a Phase III, multicenter, randomized, double-blinded, prospective study with two parallel treatment groups. Participants who present to the hematologist/oncologist and satisfy all inclusion and exclusion criteria will be eligible for participation in this 18-week study. Participants who meet all inclusion criteria and no exclusion criteria, will be randomized into the trial (Group A or B).

Scheduled study visits will occur on Day -14 to -2 (screening), Day 0 (randomization/first treatment day), Day 7, Week 2, Week 3, Week 6, Week 9, Week 12, Week 15 and Week 18.

All participants, investigators and study personnel will be blinded to the content of study drug with the exception of the un-blinded study personnel who will be responsible for the following:

- Randomizing the participants on Day 0
- Preparing, concealing and administering the study drug on Day 0 and 7 (as FCM is reddish-brown and slightly viscous) note: this includes collection of post dose vital signs.
- Completing the Study Drug Accountability Form, study drug dosing record and applicable case report form pages.

Group A participants will receive 2 doses of FCM, at 15 mg/kg for a maximum single dose of 750 mg given 7 days apart for a total of up to 1500 mg. It will be diluted in no more than 250 mL of normal saline and infused over 15 minutes. **Note: FCM should not be diluted to concentrations less than 2 mg/mL.**

Group B participants will receive placebo, which will be normal saline. It will be administered as an infusion of no more than 250 mL infused over 15 minutes.

Inclusion Criteria:

1. Participants (male or female) ≥ 18 years of age able to give informed consent to the study
2. Participants with non-myeloid malignancies.
3. Receiving chemotherapy as part of their cancer treatment
    - With at least 4 weeks of treatment remaining
4. Screening visit central laboratory Hgb ≤11 g/dL, but ≥8 g/dL
5. Ferritin between 100 and 800 ng/mL and transferrin saturation (TSAT) ≤ 35%
6. Participants must have Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2
7. Life expectancy of at least 6 months
8. Demonstrate the ability to understand the requirements of the study, willingness to abide by study restrictions and to return for the required assessments.

Exclusion Criteria:

1. Previous participation in a ferric carboxymaltose clinical trial
2. Known hypersensitivity reaction to any component of ferric carboxymaltose
3. Any anemia treatment within 4 weeks before inclusion (oral iron, intravenous (IV) iron, red blood cell (RBC) transfusion, or erythropoiesis-stimulating agents (ESAs))
4. Participants on ESAs
5. Requiring dialysis for the treatment of chronic kidney disease (CKD)
6. Any non-viral infection

7. Participants with overt bleeding
8. Known positive hepatitis with evidence of active disease
9. Received an investigational drug within 30 days of screening
10. Alcohol or drug abuse within the past 6 months
11. Hemochromatosis or other iron storage disorders
12. Any other laboratory abnormality, medical condition or psychiatric disorders which in the opinion of the Investigator would put the participant's disease management at risk or may result in the participant being unable to comply with study requirements.
13. Pregnant or actively trying to become pregnant (Female patients who are of childbearing age must have a negative pregnancy test at screening and be practicing an acceptable method of birth control during the study).

Primary Endpoint: Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from Week 3 to Week 18.

Secondary Endpoints:

1. Change in Hgb from baseline to Week 18 or to non-study intervention.

   Non-study intervention is defined as initiation of ESAs, RBC transfusion, and additional IV or oral iron.

2. Percentage of participants who receive non-study intervention.
3. Percentage of participants with Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention.
4. Percentage of participants with Hgb ≥12 g/dL in the absence of non-study intervention.
5. Time to Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention.
6. Percentage of participants requiring a blood transfusion.
7. Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to each study visit.
8. Time to a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to Week 18.
9. Correlation of change in hemoglobin with Day 0 hepcidin level.
10. Total score of the FACIT-Fatigue.
11. AEs

Schedule of Events

VISIT DAY	SCREENING[1]	Day 0	Day 7	Week 2	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18
Informed Consent	X									
Inclusion/exclusion	X	X								
IRT	X[2]	X[3]								
Medical History	X	X								
FACIT-Fatigue Scale		X	X	X	X	X	X	X	X	X
Physical Exam[4]	X									X
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X
Height	X									
Weight	X									
Hematology, chemistry, and iron indices (Central lab)	X	X	X	X	X	X	X	X	X	X[6]
Hepcidin		X		X						X
Serum pregnancy test[7]	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events assessments		X	X	X	X	X	X	X	X	X
Randomization		X								
FCM administration		X	X							
Placebo administration		X	X							

1. Screening period can occur 2 to 14 days prior to Day 0, in order to obtain all clinical assessments needed to qualify the participant.
2. Contact the Interactive Response Technology (IRT) system for participant screening number.
3. Contact the IRT system for randomization.
4. Includes clinical assessment of skin, cardiovascular, pulmonary, abdominal, and central nervous system.
5. Vital signs include sitting blood pressure (BP) and heart rate (HR). On dosing days BP and HR will be collected, pre, immediately post and 30 minutes post dosing.
6. If the participant's phosphorous is below the lower limit of normal (LLN) at Week 18, the participant should return (as directed by the Investigator) for repeat phosphorous until the value is back to within normal limits (WNLs) or the participant's baseline.
7. Serum pregnancy test will be performed for all women of childbearing potential.

Number of Participants: Approximately 222

Study duration per participant: Approximately 18 weeks

Study Sites: Approximately 40

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LIST OF ABBREVIATIONS

AE	Adverse Event
AEs	Adverse Events
AID	Absolute iron deficiency
ALT	Alanine aminotransferase
ANCOVA	Multivariate analysis based on parametric analysis of covariance
AST	Aspartate aminotransferase
ATC System	Anatomical Therapeutic Chemical classification
BP	Blood Pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CMH	Cochran-Mantel-Haenszel
CRA	Cancer- and chemotherapy related anemia
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESAs	Erythropoiesis stimulating agents
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FCM	Ferric carboxymaltose
FDA	Food and Drug Administration
FID	Functional iron deficiency
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
Hct	Hematocrit
Hgb	Hemoglobin
HR	Heart rate
IB	Investigational Brochure
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Iron deficiency
IDA	Iron deficiency anemia
IND	Investigational New Drug
IRB	Institutional Review Board

IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed-effect model for repeated measures
mITT	Modified Intent-to-Treat
NIC-CTC	National Cancer Institute - Common Terminology Criteria
NIC-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
PCS	Potentially clinically significant
PET	Positron emission tomography
RBC	Red blood cell
RDW	Red cell distribution width
RE	Reticuloendothelial
RES	Reticuloendothelial system
SAE	Serious adverse event
SAEs	Serious adverse events
TEAEs	Treatment-emergent adverse events
TIBC	Total iron binding capacity
TSAT	Transferrin saturation
T ½	Half life
USP	United States Pharmacopeia
WBC	White blood cell
WNLs	Within normal limits

1 INTRODUCTION

1.1 Cancer and chemotherapy-related anemia

Anemia is a common complication in patients who have cancer and those who receive chemotherapy.[1] In a survey conducted by Ludwig et al, including more than 15,000 cancer patients, it is estimated that the incidence of anemia was 53.7%. Low Hgb was also correlated with poor performance status. They also found that anemia was treated in only 38.9% of the patients, thus, leaving a lot of patients untreated. In relation to the patient, anemia is a burden as it may affect one's quality of life, contributing to symptoms such as fatigue and weakness.[2] According to the American Cancer Society, in 2014, there is an estimate of 1.67 million new cancer cases diagnosed. Based on the assumption of an incidence of 53.7%, there will be approximately 897,000 patients that would be anemic. Around 61% of cancer patients are treated, this would be an equivalent of approximately 547,000 patients that may benefit from the treatment of IV iron.

The cause of anemia in cancer may be multifactorial. Contributing factors may include blood loss at the tumor site, invasion of the marrow that leads to suppression of hematopoiesis, myelosuppressive chemotherapy, inflammatory cytokines leading to functional iron deficiency, and others.[3]

Of particular interest is iron deficiency (ID). The reported prevalence of ID in cancer is around 32-60% and most are anemic.[4] ID plays a pivotal role in the development of anemia in cancer. ID in cancer may be separated into two components, absolute iron deficiency (AID) and functional iron deficiency(FID). AID is defined as depleted iron stores. Most iron-deficient patients with cancer present with FID.[5] FID is characterized by iron sequestration, and thus, the lack of available iron with normal or elevated ferritin levels.[4] FID is often caused by a chronic inflammatory state which many cancer patients may have. These inflammatory markers include interleukin-6 and tumor necrosis factor. These cytokines also upregulate hepcidin. Hepcidin is a regulator of iron homeostasis and acts to block ferroportin. Ferroportin allows the exchange of iron from the intracellular stores to transferrin. In inflammatory conditions, hepcidin levels increase and locks the iron in cells causing a restricted supply of iron for erythropoiesis.[6] Ferritin is an acute phase reactant and will also increase in the presence of inflammation or metastatic disease.

Historically, IV iron agents have been used for the treatment of AID and ESAs have been utilized for the treatment of FID in patients diagnosed with CRA. However, due to safety concerns of ESAs and decline in use[7], the use of IV iron has been studied extensively in combination with ESAs. Iron is essential for Hgb synthesis and can limit the response to ESA treatment.[8] There are a number of clinical trials that have demonstrated positive results in utilizing IV iron and ESAs for treating anemia in cancer patients.[9] Utilization of iron and ESA together as opposed to ESA alone can result in higher and faster response rates (as defined by increase in Hgb), reduction in RBC transfusions, and an ESA dose saving effect.[6,9] The National Comprehensive Cancer

Network (NCCN) has published guidelines in treating CRA. They recommend considering IV iron with ESAs for FID.[10] Thus, the patient of IV iron monotherapy remains to be investigated. Two studies have examined the administration of IV iron without ESAs, and both studies demonstrated that IV iron alone can reduce transfusion rates.[11,12]

A non-interventional, prospective study evaluated the efficacy and tolerability of FCM in routine treatment of anemic cancer patients.[13] A total of 619 patients received FCM, however, only 420 had baseline Hgb measurements. Comparison between the median Hgb increases between FCM alone vs. FCM and ESA were 1.4 g/dL and 1.6 g/dL, respectively. The percentage of patients who received their first transfusion after the initiation of FCM decreased from 13.8% during weeks 1-4 to 9.1% after week 4. The authors concluded IV iron alone may play a role in treatment of anemia in cancer with Hgb stabilization at 11-12 g/dL. Hedenus et al[14] conducted a small trial using ferric carboxymaltose in patients with lymphoid malignancies as sole anemia treatment. The pilot study (n=19) exhibited a significant increase in Hgb for at least 8 weeks in patients with lymphoid malignancies, chemotherapy-induced anemia, and FID.

1.2 FCM

1.2.1 Key Features of FCM

FCM is a stable 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 (reticuloendothelial system – RES), 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 FCM vs Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various parenteral iron preparations available.[15] However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted their use. FCM offers advantages compared to other available IV iron preparations.

More recently approved, non-dextran IV irons like iron sucrose and iron gluconate do not contain the dextran moiety, but they have significant dosage and administration rate limitations. If the body's ability to handle (i.e., sequester, store, and transport) iron is overwhelmed, a reaction to excess free iron referred to as a bioactive iron reaction may occur. These IV iron compounds carry a significant risk of bioactive iron reactions at higher doses. These reactions are characterized by hypotension (without allergic signs) accompanied by pain in the chest, abdomen, flank and/or nausea, vomiting, diarrhea.

Due to its structure, FCM is more stable than iron gluconate and iron sucrose, producing a slow delivery of the complexed iron to endogenous iron binding sites and has an acute toxicity in animals approximately 1/5 that of iron sucrose (data on file). 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 replenish iron stores, consequently making it better suited for outpatient use **(Table 1.2.2.1).** Another recently approved IV iron is ferumoxytol (AMAG Pharmaceuticals) in which 510 mg can be injected rapidly on 2 occasions separated by several days. This formulation, which is currently indicated for IDA associated with CKD, is a modified-dextran derivative and is indicated for a 1020 mg repletion dose.

Table 1.2.2.1 Comparison of the Administration of Intravenous Iron with Currently US Available Iron Preparations

Iron Preparation	Test Dose Required	Maximum Infusion Dose	Infusion Time	Number of Infusions
Iron dextran	Yes	100 mg*	2 minutes	15 + test dose
Iron gluconate	No	125 mg	10 minutes	12
Iron sucrose	No	200 mg	5 minutes	8
Iron sucrose	No	400 mg	2.5 hours	4
Ferumoxytol	No	510 mg	< 1 minute	3
Injectafer®	No	750 to 1000 mg**	8 to 15 minutes	2

* Higher doses are administered off label and are approved outside the US
**1000 mg maximum dose is approved in the European Union; 750 mg maximum is the U.S. FDA approved dose that will be evaluated in this trial

The larger FCM and ferumoxytol doses result in less frequent administration of IV iron and represents an improvement in convenience for patient and physicians, especially for those individuals with conditions amenable to complete replacement dosing in a single setting such as heavy uterine bleeding, inflammatory bowel disease, bariatric surgery, hereditary hemorrhagic telangiectasia or any condition where blood loss exceeds maximum absorption.

1.2.3 FCM Human Experience

The FCM development program demonstrated the safety and effectiveness of IV FCM in the treatment of iron deficiency anemia (IDA). Clinical data are currently available from 20 Phase 2 and 3 studies including 5,799 participants, with IDA or IDA associated with CKD, who received FCM.

A clinical pharmacokinetic study (VIT-IV-CL-001) using positron emission tomography (PET) demonstrated a fast initial elimination of radioactively labeled iron (Fe) $^{52}Fe/^{59}Fe$ FCM from the blood, with rapid transfer to the bone marrow and rapid deposition in the liver and spleen. Eight hours after administration, 5 to 20% of the injected amount was still in the blood, compared with 2 to 13% for iron sucrose. The projected terminal half-life ($t_{½}$) was calculated to be approximately 16 hours, compared to 3 to 4 days for iron dextran and 6 hours for iron sucrose. An ascending dose pharmacokinetic study (VIT-

IV-CL-002), demonstrated that following the 500 and 1,000 mg FCM dose, the majority of the FCM iron complex was utilized or excreted by 72 hours.

Phase III studies demonstrated the effectiveness of FCM in treating IDA secondary to inflammatory bowel disease, heavy uterine bleeding, CKD (hemodialysis and non-hemodialysis) and the postpartum state. Clinically meaningful increases in Hgb, ferritin, and TSAT were observed in each of the studies. Non-inferiority to full therapeutic doses of oral ferrous sulfate was demonstrated in studies of IDA associated with inflammatory bowel disease. Superiority to full therapeutic doses of oral ferrous sulfate was demonstrated in studies of IDA secondary to heavy uterine bleeding, the postpartum state and non-hemodialysis dependent CKD. A head to head comparison of FCM to iron sucrose (Venofer®) in over 2,500 participants with non-dialysis dependent CKD and elevated risk of cardiovascular disease according to the Framingham criteria demonstrated that the recommended dose of FCM, 750 mg x 2 (1500 mg total) was non-inferior to the labeled dose of iron sucrose, 200 mg x 5 (1000 mg total) with regard to Hgb elevation and had a similar cardiovascular (and overall) safety profile, based in part on an independently adjudicated composite cardiovascular safety endpoint.[16] In fact, although the study was not powered for superiority, it did demonstrate statistical superiority. In another large clinical study to investigate the efficacy and safety of FCM, FCM was evaluated against oral iron and IV iron standard of care.[17] This trial was unique, as it had a prospective oral-iron run-in phase. In Cohort 1, FCM demonstrated superiority vs. oral iron in patients who had unsatisfactory response to oral iron. In Cohort 2, FCM demonstrated superiority vs. IV iron standard of care in patients who were inappropriate or intolerant to oral iron.

Important details of pre- and clinical safety and efficacy can be found in the Investigator's Brochure (IB). FCM received Medicines and Healthcare products Regulatory Agency (MHRA) approval on June 15, 2007 for the use of FCM (European Union (EU) Trade name: Ferinject) in 18 EU countries and later in Switzerland. FCM was first approved as a prescription only medicine on July 6, 2007 in The Netherlands. To date, FCM has received regulatory approval for marketing authorization in 72 countries worldwide including the United States.

1.3 Hepcidin

The peptide hormone hepcidin plays a central role in regulating dietary iron absorption and body iron distribution.[18] Hepcidin is secreted by hepatocytes and directly acts on the transmembrane iron efflux transporter ferroportin. When hepcidin is bound to ferroportin, this transporter is internalized and degraded. Ferroportin can down regulate intestinal iron absorption, as well as the release of iron from macrophages and iron stores within hepatocytes. A decrease in hepcidin results in the release of stored iron and an increase in dietary iron absorption. On the other hand, infection and inflammation can cause an increase in hepcidin synthesis. This increased synthesis leads to a deficiency of iron available for erythropoiesis, and is considered to be the mechanism underlying reticuloendothelial (RE) iron sequestration, intestinal iron absorption impairment, and low serum iron concentrations characteristic of anemia of chronic disease. A study evaluated the relationship between hepcidin levels and

outcomes in patients with chemotherapy-associated anemia treated with an ESA alone, ESA and oral iron, or ESA and IV iron.[19] Serum hepcidin was measured in pre-treatment samples of eligible patients. It was concluded that patients who had received 4 or 5 doses of IV iron had the highest overall Hgb response. Patients who had a lower pre-treatment hepcidin level also appeared to have a better clinical response to the combination of ESA and higher doses of IV iron than patients with higher hepcidin levels or patients who did not receive higher-dose IV iron. From these results, hepcidin measurements may help predict response to ESAs and IV iron.

2 PRIMARY OBJECTIVE

The primary objective of this study is to compare the efficacy and safety of FCM versus placebo as monotherapy for maintaining Hgb levels in participants with CRA.

3 OVERALL STUDY DESIGN AND RATIONALE

3.1 Trial Design

This is a Phase III, multicenter, randomized, double-blinded, prospective study with two parallel treatment groups. Participants who present to the hematologist/oncologist and satisfy all inclusion and exclusion criteria will be eligible for participation in this 18-week study. Participants who meet all inclusion criteria and no exclusion criteria, will be randomized into the trial (Group A or B).

Scheduled study visits will occur on Day -14 to -2 (screening), Day 0 (randomization/first treatment day), Day 7, Week 2, Week 3, Week 6, Week 9, Week 12, Week 15 and Week 18.

All participants, investigators and study personnel will be blinded to the content of study drug with the exception of the un-blinded study personnel who will be responsible for the following:

- Randomizing the participant on Day 0
- Preparing, concealing and administering the study drug on Day 0 and 7 (as FCM is reddish-brown and slightly viscous). Note: this includes collection of post dose vital signs.
- Completing the Study Drug Accountability Form, study drug dosing record and applicable case report form pages.

Group A participants will receive 2 doses of FCM, at 15 mg/kg for a maximum single dose of 750 mg given 7 days apart for a total of up to 1500 mg. It will be diluted in no more than 250 mL of normal saline and infused over 15 minutes. **Note: FCM should not be diluted to concentrations less than 2 mg/mL.**

Group B participants will receive placebo, which will be normal saline. It will be administered as an infusion of no more than 250 mL infused over 15 minutes.

No additional iron preparations (IV or oral iron) from 28 days prior to consent are permitted. Multivitamins with iron will be allowed. No prophylactic medications given specifically due to the use of an IV iron may be administered prior to study drug administration without prior approval from Luitpold Pharmaceuticals, Inc. Medications used as prophylaxis to prevent potential side effects of chemotherapies are permitted. Other standard therapies are permitted but must be recorded on the eCRF.

3.2 Rationale

3.2.1 Rationale for Trial Design

FCM is a non-dextran IV iron recently approved by Food and Drug Administration (FDA). This trial is designed to explore the efficacy and safety of IV FCM as sole anemia management in the absence of ESAs or RBC transfusion for anemia stabilization in participants with CRA.

3.3 Schedule of Events

VISIT DAY	SCREENING[1]	Day 0	Day 7	Week 2	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18
Informed Consent	X									
Inclusion/exclusion	X	X								
IRT	X[2]	X[3]								
Medical History	X	X								
FACIT-Fatigue Scale		X	X	X	X	X	X	X	X	X
Physical Exam[4]	X									X
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X
Height	X									
Weight	X									
Hematology, chemistry, and iron indices	X	X	X	X	X	X	X	X	X	X[6]
Hepcidin		X		X						X
Serum pregnancy test[7]	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events assessments		X	X	X	X	X	X	X	X	X
Randomization		X								
FCM administration		X	X							
Placebo administration		X	X							

1. Screening period can occur 2 to 14 days prior to Day 0, in order to obtain all clinical assessments needed to qualify the participant.
2. Contact the IRT system for participant screening number.
3. Contact the IRT system for randomization.
4. Includes clinical assessment of skin, cardiovascular, pulmonary, abdominal, and central nervous system.
5. Vital signs include sitting BP and HR. On dosing days BP and HR will be collected, pre, immediately post and 30 minutes post dosing.
6. If the participant's phosphorous is below the LLN at Week 18, the participant should return (as directed by the Investigator) for repeat phosphorous until the value is back to WNLs or the participant's baseline.
7. Serum pregnancy test will be performed for all women of childbearing potential.

4 PARTICIPANT SELECTION

4.1 Number and Type of Participants

222 participants who meet all the inclusion and exclusion criteria.

4.2 Screening Phase

Once a participant enters the screening phase, they will be assigned, via the IRT system, a unique screening number and will be evaluated for eligibility. From the time of consent until the start of treatment, the participant will not receive any form of iron outside of the study (IV iron from 28 days prior to consent or oral iron from time of consent).

4.2.1 Inclusion Criteria:

1. Participants (male or female) ≥ 18 years of age able to give informed consent to the study
2. Participants with non-myeloid malignancies
3. Receiving chemotherapy as part of their cancer treatment
    - With at least 4 weeks of treatment remaining
4. Screening visit central laboratory Hgb ≤11 g/dL, but ≥ 8 g/dL
5. Ferritin between 100 and 800 ng/mL and TSAT ≤ 35%
6. Participants must have ECOG performance status of 0 - 2
7. Life expectancy of at least 6 months.
8. Demonstrate the ability to understand the requirements of the study, willingness to abide by study restrictions and to return for the required assessments.

Exclusion Criteria:

1. Previous participation in a FCM clinical trial
2. Known hypersensitivity reaction to any component of FCM

3. Any anemia treatment within 4 weeks before inclusion (oral iron, IV iron, RBC transfusion, or ESAs)
4. Participants on ESAs
5. Requires dialysis for the treatment of CKD
6. Any non-viral infection
7. Participants with overt bleeding
8. Known positive hepatitis with evidence of active disease
9. Received an investigational drug within 30 days of screening
10. Alcohol or drug abuse within the past 6 months
11. Hemochromatosis or other iron storage disorders
12. Any other laboratory abnormality, medical condition or psychiatric disorders which in the opinion of the Investigator would put the participant's disease management at risk or may result in the participant being unable to comply with study requirements
13. Pregnant or actively trying to become pregnant (Female participants who are of childbearing age must have a negative pregnancy test at screening and be practicing an acceptable method of birth control during the study).

4.3 Participants Assignment and Randomization Process

Participants that meet all inclusion requirements and no exclusionary criteria will be offered participation in this 18-week study. Participants will be randomized in a 1:1 ratio via the IRT system to either group A or B as listed below.

Group A participants will receive 2 doses of FCM, at 15 mg/kg for a maximum single dose of 750 mg given 7 days apart for a total of up to 1500 mg. It will be diluted in no more than 250 mL of normal saline and infused over 15 minutes. **Note: FCM should not be diluted to concentrations less than 2 mg/mL.**

OR

Group B participants will receive placebo, which will be normal saline. It will be administered as an infusion of no more than 250 mL infused over 15 minutes.

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 the trial at any time if it is felt to be in the best interest of the participant.

At the time of withdrawal, procedures for the Week 18 visit must be immediately

performed regardless of whether the participant has completed study drug treatment. In the event the participant has received any study drug; the participant should be contacted for follow-up 30 days after the last dose to assess adverse events, if possible.

4.5 Non-Study Intervention

Non-study intervention is defined as any of the following:

- Initiation of erythropoietin for any reason, and/or
- RBC transfusion, and/or
- IV iron, and/or
- Prescribed use of oral iron

When non-study intervention occurs, the date of the intervening event should be recorded in the source documents as well as the eCRF, and the participant should continue in the study as scheduled.

5 STUDY DRUG

5.1 Formulation Packaging and Storage

All medication to be used in this study that has been supplied by Luitpold Pharmaceuticals, Inc. will have been prepared according to Good Manufacturing Practices (GMP).

FCM 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.

Placebo (normal saline) will not be supplied but it must be stored under labeled storage conditions.

All IV study drugs supplied by Luitpold Pharmaceuticals, Inc. must be kept in a secure place at the investigational site, and stored at room temperature. Refer to the United States Pharmacopeia (USP)). The study medication should not be frozen. **Vials may not be used for more than 1 dose or for more than 1 participant. All FCM vials (used and unused) should be kept by the study staff and returned to Luitpold Pharmaceuticals, Inc., after drug accountability has been completed by the monitor.**

5.2 Drug Administration/Regimen

Prior to each drug administration participants must be blinded with a sleeping mask, or other method. The Investigator(s) who is conducting the efficacy and safety evaluations will not be present when the study drug is administered to the participant.

Group A participants will receive 2 doses of FCM, at 15 mg/kg for a maximum single dose of 750 mg given 7 days apart for a total of up to 1500 mg. It will be diluted in no more than 250 mL of normal saline and infused over 15 minutes. **Note: FCM should not be diluted to concentrations less than 2 mg/mL.**

OR

Group B participants will receive placebo, which will be normal saline. It will be administered as an infusion of no more than 250 mL infused over 15 minutes.

5.3 IV Iron Precautions

When administering IV Iron, the following precautions will be taken:

- The participant will be clinically evaluated prior to drug administration to assess the development of clinically significant conditions.
- The vials will be visually inspected for particulate matter and discoloration before each use; if noted, the vial will not be used and the Investigator or his/her designee will notify the Sponsor, or Sponsor's designee, for replacement of the study drug and for directions to return the unused vial.
- Sitting BP and HR will be assessed pre-, immediately post, and 30 minutes post administration. If the participant is an outpatient, they will be discharged from the site by the Investigator only if there are no significant signs or symptoms 30 minutes after the administration is completed.
- Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in participants receiving IV iron therapies. Participants may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. If hypersensitivity reactions or signs of intolerance occur during administration, stop IV iron administration immediately. Monitor participants for signs and symptoms of hypersensitivity during and after IV iron administration for at least 30 minutes, and until clinically stable following completion of the infusion. Only administer IV iron when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Most reactions associated with IV iron preparations occur within 30 minutes of the completion of the iron infusion.

5.4 Drug Accountability

Investigators will keep adequate records of the receipt, administration and return of FCM. They will not allow FCM 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 screened and randomized in the study, or to investigators not listed on the Form 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 unused FCM will be returned to Luitpold Pharmaceuticals, Inc. All data regarding

FCM must be recorded on the Drug Accountability Forms provided by the Sponsor.

Investigators will keep adequate records of the administration and disposition of IV iron and normal saline used for participants selected for the trial.

5.5 Concomitant Medication

Concomitant medications along with their route of administration and duration must be recorded in the eCRF.

No additional iron preparations (IV or oral iron) from 28 days prior to consent are permitted. Multivitamins with iron will be allowed. No prophylactic medications given specifically due to the use of an IV iron may be administered prior to study drug administration without prior approval from Luitpold Pharmaceuticals, Inc. Medications used as prophylaxis to prevent potential side effects of chemotherapies are permitted. Other standard therapies are permitted but must be recorded on the eCRF.

5.6 Blinding

All participants, investigators and study personnel will be blinded to the content of study drug, with the exception of the un-blinded study personnel who will be responsible for the following:

- Randomizing the participant on Day 0
- Preparing, concealing and administering the study drug on Day 0 and 7 (as FCM is reddish-brown and slightly viscous). Note: this includes collection of post dose vital signs
- Completing the Study Drug Accountability Form, study drug dosing record and applicable case report form pages.

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 must voluntarily sign an informed consent statement (see: Required Elements of Informed Consent, 21 CFR 50.25). The participant will be given a copy of the signed consent form.

6.2 Screening

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

- Obtain informed consent
- Verify inclusion / exclusion criteria
- Obtain screening number from IRT
- Medical history, including prior iron therapy use, chemotherapy history, and planned regimen and other concomitant medications
- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system
- Vital signs (including sitting BP and HR)
- Height and weight
- Blood samples for central laboratory hematology (complete blood count (CBC)), iron indices, chemistry
- Serum pregnancy test for women of child bearing potential (via central laboratory, negative results must be obtained prior to randomization).

Participants who do not meet the entry criteria should be entered into the electronic data capture (EDC) system as a screen failure. A participant may be re-screened, one time, once it is believed that they would qualify for study entry.

6.3 Study Visits Day 0 – Week 18

6.3.1 Day 0

The following will occur PRIOR to randomizing the participant:

- Re-verify the inclusion and exclusion criteria
- Update any relevant history
- Concomitant medications assessment

Once it is confirmed that the participant continues to meet the entry criteria, all eligible participants will be randomized to either Group A (FCM) or Group B (placebo-normal saline) in a 1:1 ratio based on a pre-determined randomization schedule via the IRT system. After assignment of the treatment group, the following will occur:

All participants (prior to drug administration/dispensing, if applicable) on Days 0:

- Vital signs: temperature, sitting BP and HR will be obtained
- Concomitant medications
- Blood sample for central lab hematology (CBC, iron indices, chemistry, hepcidin levels) prior to study drug administration
- Complete the FACIT-Fatigue scale

Group A:

- Blind the participant (via use of a sleeping mask or other method)
- Verify the amount of single FCM dose (15 mg/kg up to a maximum dose of 750 mg)

- Document the start and stop time of FCM administration, the total dose administered and the volume of saline used for dilution.
- Obtain sitting BP and HR immediately post and 30 minutes post FCM administration
- AE assessment starting at beginning of FCM infusion.

Group B:

- Blind the participants (via use of a sleeping mask or other method)
- Verify the amount of normal saline administered (250 mL)
- Document the start and stop time of saline administration, the total volume administered
- Obtain sitting BP and HR immediately post and 30 minutes post placebo administration
- AE assessment starting at beginning of placebo infusion.

6.3.2 Day 7

The following will occur on Day 7:

- Vital signs: BP, HR
- Blood samples for central lab hematology (CBC), iron indices, and chemistries
- Concomitant medications assessment
- Complete the FACIT-Fatigue scale prior to the study drug administration on Day 7
- AE assessment.

Group A:

- Blind the participant (via use of a sleeping mask or other method)
- Verify the amount of single FCM dose (15 mg/kg up to a maximum dose of 750 mg)
- Document the start and stop time of FCM administration, the total dose administered and the volume of saline used for dilution.
- Obtain sitting BP and HR immediately post and 30 minutes post FCM administration.

Group B:

- Blind the participants (via use of a sleeping mask or other method)
- Verify the amount of normal saline administered (250 mL)
- Document the start and stop time of saline administration, the total volume administered
- Obtain sitting BP and HR immediately post and 30 minutes post placebo administration.

6.3.3 Week 2, 3, 6, 9, 12, 15

- Vital signs: sitting BP, HR
- Blood samples for central lab hematology (CBC), iron indices, chemistries
- Blood sample collection for hepcidin (**only at Week 2**)
- Concomitant medications assessment
- Complete the FACIT-Fatigue scale
- AE assessment.

6.3.4 Week 18

- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system
- Vital signs: sitting BP, HR
- Blood samples for central lab hematology (CBC), iron indices, chemistries, and hepcidin
- Concomitant medications assessment
- Complete the FACIT-Fatigue scale
- AE assessment.

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 Week 18 laboratory, this laboratory may be obtained after notification of the Sponsor. If a participant's phosphorous is below the LLN at Week 18 the participants should return (as directed by the Investigator) for repeat phosphorous until the value is back WNL's or returns to the participant's baseline levels. The laboratory assessments will be determined as listed in Section 6.0.

Hematology:	Hgb, hematocrit (Hct), white blood cells (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets, differential count, and reticulocyte count.
Chemistry:	sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, albumin, alkaline phosphatase, total bilirubin, gamma-glutamyl-transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), calcium, phosphorus, glucose, and bicarbonate.

Iron indices:	serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT).
Other:	Serum pregnancy tests, serum hepcidin

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, must be recorded on the Adverse Event page of the eCRF.

For any laboratory abnormality, the physician 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 AE and should be recorded on the Adverse Events page of the eCRF. If the laboratory value is outside the normal range, but not an AE, the Investigator should comment on the findings (i.e. "not clinically significant" or "unchanged from baseline") in the source documentation [laboratory report].

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 AEs. Anemia or ID will be considered end points if an intervention is required.

To quantify the severity of AEs, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version 4 should be used to grade all events. These criteria are provided in the procedure manual.

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

Table 7.1.1 Grading of Adverse Event Severity as per CTCAE v 4

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 adverse events will be reported from the initial treatment with study drug* through the completion of the study. All ongoing AEs related to study drug (i.e., FCM or Placebo) should be followed until they are no longer related, have taken a confounding medication or return to baseline grade.

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

- NONE There is *no* evidence of any causal relationship.
- UNLIKELY There is *little* evidence to suggest there is a causal relationship. There is *another reasonable explanation* for the event (e.g., the participant's clinical condition, other concomitant treatments).
- POSSIBLE There is *some* evidence to suggest a causal relationship (i.e. there is a reasonable possibility that the adverse experience may have been caused by the agent). However, the influence of *other factors may have contributed* to the event (e.g., the participant's clinical condition, other concomitant events).
- PROBABLE There *is evidence* to suggest a causal relationship, and the influence of other factors is *unlikely*.

* For the purposes of this trial, "study drug" is defined as: **FCM or normal saline.**

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 AEs 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 / 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 severe AE is a major experience of its type. A severe AE 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: SAEs as well as AEs will be elicited during study visits and contact with participant. These AEs/SAEs as well as SAEs discovered through passive reporting from the time of initial treatment with study drug up to the completion of the study will be reported. Hospitalizations resulting from historical conditions (present prior to initial treatment with study drug or prescheduled prior to treatment with study drug) that have not increased in severity or led to prolongation of hospital stay should not be considered SAEs. All reported SAEs 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 (by the end of the next business day) to Luitpold Pharmaceuticals, Inc. by telephone, email and/or fax of the written SAE report form to the contacts listed below:**

Safety Monitor

Luitpold Pharmaceuticals, Inc.
pv@luitpold.com
Tel: (610) 650-4200 Fax: (610) 650-0170

In addition to the above reporting, all SAEs must be recorded on the Adverse Event page of the eCRF and reported immediately to your Institutional Revie Board (IRB) and/or Ethics Committee (EC) per their reporting guidelines.

The responsible Investigator must determine whether the degree of any untoward event warrants removal of any participant from the study. He/she should, in any case, institute appropriate diagnostic and/or therapeutic measures, and keep the participant under observation for as long as is medically indicated.

7.4 Other Reportable Information

As part of the continuous assessment of the risk-benefit profile for the life cycle of pharmaceutical products regulatory agencies require monitoring of occurrences that while not considered AEs, are considered "other reportable information". For this protocol, other reportable information refers to: drug exposure during pregnancy and / or lactation exposure (irrespective of any reported fetal abnormalities or any AE in mother and/or child). Pregnancy exposure and lactation exposure should be reported to the Luitpold's Pharmacovigilance Department by email and/or fax using the pregnancy tracking form to the contact listed below:

Safety Monitor
Luitpold Pharmaceuticals, Inc.
pv@luitpold.com
Tel: (610) 650-4200 Fax: (610) 650-0170

8 STATISTICS

This section provides an overview of planned statistical methods. A detailed Statistical Analysis Plan will be finalized prior to study completion.

All statistical tests will be 2-sided with Type I error of 0.05.

8.1 Stratification and Randomization

Participants will be randomized on Day 0 to FCM or placebo in a 1:1 ratio. The randomization will be stratified by study site and the randomization schedule will be generated prior to study initiation.

8.2 Sample Size Rationale

The study is powered to demonstrate a clinically meaningful difference between FCM and placebo with respect to the percentage with decrease in Hgb ≥0.5 g/dL (i.e., with respect maintenance of Hgb levels) from Week 3 to Week 18. Determination of sample size was based on the following assumptions:

- The proportion of placebo participants not maintaining Hgb levels will be 65%.[1]
- A relative reduction of 35%, i.e., a reduction from 65% with placebo to 42% with FCM, would be clinically meaningful.[10]
- The study would have 90% power to detect a clinically meaningful treatment difference at two sided alpha=0.05.
- Test statistic is continuity corrected chi-squared test.
- Treatments will be allocated on a 1:1 ratio.

Then a sample size of 106 participants per treatment group is required. Assuming 5% of participants will not meeting the definition of modified Intent-to-Treat (mITT), 111 participants per treatment group (222 participants in total) should be randomized.

The key secondary efficacy endpoint is the change in Hgb from baseline to Week 18 or to non-study intervention. This sample size of 106 participants per treatment group will have 99% power to demonstrate superiority of FCM over placebo in the mean change in Hgb from baseline to Week 18 in the absence of non-study intervention, using a t-test at two-sided alpha=0.05. This assumes a difference in means of Hgb of 1.0 g/dL with common standard deviation = 1.5 g/dL.

8.3 Analysis Populations

Intent-to-Treat Population (ITT)

The ITT population will comprise all randomized participants. Participants will be evaluated according to the treatment to which they were randomized. Any participant who receives a treatment randomization number will be considered to have been randomized.

Modified Intent-to-Treat Population (mITT)

The mITT population will comprise all subjects in the ITT population who receive at least one dose of study drug, have a baseline Hgb measurement, and at least one corresponding post-baseline measurement. Participants will be evaluated according to the treatment to which they were randomized. The primary population for the assessing efficacy will be the mITT population.

Safety Population

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

8.4 Disposition and Baseline Characteristics

The number and percent of participants who are randomized, treated with randomized therapy, prematurely discontinue, and complete the study will be summarized. The

number and percent of participants will be summarized for each reason for premature discontinuation.

Categorical baseline characteristics (e.g., sex and race) will be summarized with the number and percent of participants in each treatment group with the characteristic. Quantitative characteristics (e.g., age and weight) will be summarized with the mean, median, standard deviation, minimum value, and maximum value.

8.5 Endpoints and Definitions

8.5.1 Primary Endpoint

Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from Week 3 to Week 18

8.5.2 Secondary Endpoints

1. Change in Hgb from baseline to Week 18 or to non-study intervention.

   Non-study intervention is defined as initiation of ESAs, RBC transfusion, and additional IV or oral iron.

2. Percentage of participants who receive non-study intervention.
3. Percentage of participants with Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention.
4. Percentage of participants with Hgb ≥12 g/dL in the absence of non-study intervention.
5. Time to Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention.
6. Percentage of participants requiring a blood transfusion.
7. Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to each study visit.
8. Time to a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to Week 18.
9. Correlation of change in hemoglobin with Day 0 hepcidin level.
10. Total score of the FACIT-Fatigue.
11. AEs.

8.6 Efficacy Analyses

8.6.1 Primary Efficacy Analysis

The following participants will be considered to have met the primary endpoint:

- Participants with observed Hgb decrease from baseline between 0.5 g/dL to 1.0 g/dL on two consecutive visits between Weeks 3 and 18.
- Participants with observed Hgb decrease from baseline ≥1.0 g/dL at one visit.

- Participants who have a non-study intervention prior to Week 18.
- Participants who discontinue prior to Week 18 for lack of efficacy or adverse events.

All other randomized participants will be considered to have not met primary endpoint, i.e., will be considered to have maintained Hgb levels.

The primary endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for pooled site. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages and associated 95% confidence intervals will be presented.

The primary endpoint will be analyzed for the mITT population.

8.6.2 Secondary Efficacy Analyses

Key secondary endpoint

Change in Hgb from baseline to Week 18 or to non-study intervention is the key secondary endpoint. The analysis of the key secondary endpoint will be based on a mixed-effect model for repeated measures (MMRM). Missing data will be handled assuming a missing at random (MAR) mechanism. The model will include terms of pooled site, baseline Hgb, as well as treatment group.

The key secondary endpoint will be analyzed for the mITT population.

Other secondary endpoints

Treatment group differences for proportions will be analyzed using the CMH chi-square test adjusting for pooled site Continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM). Missing data will be handled assuming a missing at random (MAR) mechanism. Time to hemoglobin response and time to Hgb decrease from baseline ≥ 0.5 g/dL will be analyzed using a stratified logrank test.

The correlation of baseline hepcidin level with change in hemoglobin will be analyzed within each treatment group. Spearman rank correlation and Pearson product-moment correlation will be summarized.

Subgroup Analyses

Univariate analyses
The primary and key secondary endpoint will be analyzed separately for the following subgroups:

- Geographic Region: United States, Europe.

- Cancer Stage.
- Baseline hemoglobin: <10 g/dL, ≥ 10 g/dL.

Estimates of treatment effect and corresponding 95% confidence intervals will be displayed graphically.

Multivariate analyses
Multiple logistic regression will be used to evaluate the effect of treatment on maintenance of Hgb level while simultaneously controlling for the important subgroups. Multivariate analysis based on parametric analysis of covariance (ANCOVA) will be conducted for the Hgb change from baseline endpoint. Details will be provided in the SAP.

Subgroup analyses will be conducted for the mITT population.

8.6.3 Control of Type I error

Type I error will be maintained at 0.05 for the primary efficacy endpoint by pre-specifying the single primary endpoint and single primary efficacy analysis. There will be no control of Type I error for the secondary endpoints.

8.6.4 Handling of Missing Data

Methods for handling missing data are specific for each endpoint to be analyzed. Details will be provided in the SAP. *Sections 8.6.1* and *Section 8.6.2* outline how missing data will be handled for the primary endpoint, and the key secondary endpoint, respectively.

8.7 Safety Analyses

No formal statistical hypothesis tests for treatment group differences will be performed.

Categorical endpoints will be summarized with the number and percent of participants in each treatment group. Quantitative endpoints will be summarized with the mean, median, standard deviation, minimum value, and maximum value.

8.7.1 Extent of Exposure

The total administered dose of iron will be summarized for the FCM group with the mean, median, standard deviation, minimum value, and maximum value. The number of doses of study drug will be summarized for each treatment group.

8.7.2 Adverse Events

The number and percent of participants who report treatment-emergent adverse events (TEAEs) will be summarized for each treatment group. A TEAE is an event that begins after receipt of randomized treatment. The Medical Dictionary for Regulatory Activities (MedDRA) Terminology will be used to classify all AEs with respect to system organ class and preferred term.

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/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 AEs. Anemia or iron deficiency will be considered end points if an intervention is required.

The AE profile will be characterized with severity (as graded by Version 4.0 of the NCI-CTCAE) and relationship (unrelated and related) to study drug. Related AEs will be events that are possibly or probably related to treatment in the Investigator's judgment. Events with unknown severity or relationship will be counted as unknown.

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 system organ class, the participant will be counted only once for that system organ class.

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 TEAEs resulting in discontinuation of study drug will be similarly summarized for each treatment group.

8.7.3 Clinical Laboratory Tests

Clinical laboratory variables will be presented in 2 ways. First, change from baseline to each scheduled study visit will be summarized descriptively. 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 post-baseline value is abnormal (i.e., meets Grade III or Grade IV toxicity criteria from the National Cancer Institute - Common Terminology Criteria (NCI-CTC)) and the baseline value is not abnormal.

Laboratory values will be converted to the project-defined unit of measurement before analysis.

8.7.4 Vital Signs

The number and percent of participants with treatment-emergent PCS vital signs will be identified with the criteria in Table 8.8.4.1 and summarized descriptively. No formal statistical comparisons will be made.

Table 8.8.4.1 Criteria for Potentially Clinically Significant Vital Signs on Dosing Days

Vital Sign	Criterion	Definition of PCS at immediately, 30, and 60 minutes post-dose
Systolic blood pressure	Low	Value ≤90 mmHg and decreased ≥20 mmHg from initial value
	High	Value ≥180 mmHg and increased ≥20 mmHg from initial value
Diastolic blood pressure	Low	Value ≤50 mmHg and decreased ≥15 mmHg from initial value
	High	Value ≥105 mmHg and increased ≥15 mmHg from initial value
Pulse	Low	Value ≤50 bpm and decreased ≥15 bpm from initial value
	High	Value ≥120 bpm and increased ≥15 bpm from initial value

Initial value is the value obtained pre-dosing on the dosing day

8.8 Concomitant Medications

The Concomitant Medications World Health Organization drug dictionary will be used to classify all concomitant medications with respect to the Anatomical-Therapeutic-Chemical classification (ATC system) and preferred drug name. Concomitant drug usage will be summarized by ATC level 3 and preferred drug name. The summary will provide the number and percent of participants in each treatment group who receive at least 1 non-study medication. No statistical testing will be performed.

8.9 Interim Analyses

No formal interim analysis is planned.

9 ADMINISTRATIVE CONSIDERATIONS

9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including eCRFs that will be provided to the Investigator after database lock, informed consent documents and adequate records for the receipt and disposition of study medications, for a period of two years following the completion of the study. Permission should be obtained from Luitpold Pharmaceuticals Inc. prior to destroying any study records.

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, that includes the signed informed consent form and copies of all study documentation related to that participant. The Investigator must ensure the availability of source documents 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 AEs that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the IB, 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 (IND) safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the 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 Luitpold Pharmaceuticals, 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 advertisements for participant recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisements may include but are not limited to newspaper, fliers, radio, television, etc. 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 Luitpold Pharmaceuticals, Inc. with the following documentation:

- Curriculum Vitae and medical license for Principal Investigators and co-investigators.
- Form FDA 1572.
- Financial disclosure form.
- 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 well organized support staff.
- Availability of diagnostic facilities to support study data 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.

Luitpold Pharmaceuticals, Inc. 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 of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practices (GCPs), 21CFR Part 312. Each study site will be visited by the Clinical Monitor as outlined in the study specific Monitoring Plan. At this time, the progress of the study will be discussed with the Principle Investigator and the eCRFs will be checked for completeness and accuracy. Source documents from which the data are obtained will be made available at the time of review. Interim checks on progress will be made when deemed appropriate (i.e. telephone or email).

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 Luitpold Pharmaceuticals, 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 may also include review of facilities, equipment, pertinent site documentation, and personnel qualifications. Notification of these audits will be sent to all investigators in advance.

9.7 Ethics

9.7.1 Ethical and Legal Issues

This study will be performed in accordance with the FDA Code of Federal Regulations (CFR) on Protection of Human Subjects (21 CFR 50), IRB regulations (21 CFR 56), the most current revision of the Declaration of Helsinki (October 2013), 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 on institutional letterhead must be provided to the Sponsor or designee. The IRB must comply with current FDA Regulations (21 CFR 56). 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 within 10 days or per their reporting guidelines of all SAEs that occur or are reported to you by the Sponsor.

9.7.3 Informed Consent

Informed consent must be obtained from each participant prior to study participation. The informed consent will be provided to the participant in their native language. The consent form must be signed by the participant or the participant's legally authorized representative. Each investigational site must provide the Sponsor (or designee) with a copy of the informed consent approved by that site's IRB. The original signed consent 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 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 must be certified by a qualified translator and their use must be documented.

The informed consent documents the information the Investigator provides to the participant and the participant's 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 must be signed and dated by each participant 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 human participants as set out in the most current revision of the Declaration of Helsinki, the local legal requirements and the guidelines on "GCP, [21 CFR Part 312 and ICH guidelines].

9.8 Data Handling and Record Keeping

9.8.1 Electronic Case Report Form (eCRF)

- eCRFs will be provided for each participant on this study. The participants in this study will be identified only by initials and participant number on these forms.
- eCRF used will be 21 CFR 11 compliant. The system used for 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).
- eCRFs must be reviewed and verified for accuracy by the Principal Investigator. A copy of the eCRF will remain at the site at the completion of the study.
- All eCRF are to be reviewed by the Clinical Monitor at Luitpold Pharmaceuticals, Inc. to insure accuracy, completeness and compliance with the protocol.

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: 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 by Luitpold Pharmaceuticals, Inc. for the purpose of the trial shall remain the sole property of Luitpold Pharmaceuticals, Inc. They will be used 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 Luitpold Pharmaceuticals, Inc., and no assistance should be given to any third party to make such an application without the written authorization of Luitpold Pharmaceuticals, Inc.

9.8.3 Termination of the Study

The study may be terminated if the Sponsor, Investigator, or Clinical Monitor 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, 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 Luitpold Pharmaceuticals, 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.

The IRB Chairperson may approve minor changes, or may designate one or more members of the IRB to approve a protocol amendment.

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 an administrative change. Administrative changes do not require the Investigator's signature or IRB approval, but do require IRB notification. Administrative changes will be transmitted to the Investigator and a copy provided to the IRB for completeness.

9.9 Publication Policy

All information resulting from this study is the Proprietary Information of Luitpold Pharmaceuticals, Inc., as per the Confidentiality Section of this protocol. Luitpold Pharmaceuticals, Inc., alone will own the copyrights in any publication of the results of the study in its entirety.

Luitpold Pharmaceuticals, Inc., alone shall have the right to publish the results of the study in its entirety, or on data involving multiple sites provided, however, that at least 10 days prior to any submission of a work for publication, Luitpold Pharmaceuticals, Inc. shall provide any potential authors with a copy of same for the authors' and if indicated Institutions' review and comments. Any publication based upon the study in its entirety or on data involving multiple sites will be submitted at the discretion of the Sponsor. Authorship will include the Investigator assigned with the primary responsibility to write the manuscript, whom will be listed first. Additional authors will be listed according to site enrollment, with one author listed per site at Luitpold Pharmaceuticals, Inc.'s sole discretion. The Principal Investigator at each site may designate an alternate for authorship at his/her discretion. If required for publication, the number of authors may be limited by the Sponsor.

Luitpold Pharmaceuticals, Inc. and the Publication 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 Luitpold Pharmaceuticals, 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 Luitpold Pharmaceuticals, Inc. to make constructive comments about the manuscript or text and to give the opportunity of assessing whether patent protection should be sought by Luitpold Pharmaceuticals, 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 ICH guidelines.

_____

Investigator's signature

_____

Date

_____

Investigator's Name (Please print)

References

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APPENDIXES
APPENDIX A:

SUMMARY OF CHANGES from original Protocol dated 04 December 2014 to Protocol Amendment 1 dated 18 February 2015	
Title	
Original Wording	**A Multi-center, Randomized, Double-blinded, Controlled Study to Investigate the Efficacy and Safety of Injectafer® (ferric carboxymaltose injection) in Patients with Cancer- and Chemotherapy-related Anemia**
New Wording	IRON CLAD: Can **Iron** Lessen Anemia Due to **c**ancer and chemotherapy: A mu**l**ti-center, **r**andomized, **d**ouble-blinded, controlled study to investigate the efficacy and safety of Injectafer® (ferric carboxymaltose injection).
Inclusion Criteria	
#5	
Original Wording	Screening visits central laboratory hemoglobin (Hgb) 12 ≤ g/dl, but 8 g/dL
New Wording	Screening visits central laboratory hemoglobin (Hgb) ≤ 11g/dL, but ≥ 8 g/dL
#6	
Original Wording	Ferritin 50 ng/mL and transferrin saturation (TSAT) ≤ 25%
New Wording	Ferritin between 100 and 800g/mL and transferrin saturation (TSAT) 25%
Exclusion Criteria	
#6	
Original Wording	Patients with renal failure on erythropoiesis-stimulating agents.
New Wording	Patients on erythropoiesis-stimulating agents.
Primary Endpoint	
Original Wording	Percentage of patients with a decrease in Hgb ≥ 0.5 g/dL from baseline between Day 0 to 18 Week 18.
New Wording	Percentage of patients with a decrease in Hgb ≥ 0.5 g/dL from baseline (Day 0 value) beginning at Week 3 through Week 18.
Original Wording	If the patient's Hgb decrease is between 0.5-1.0 gL from baseline, two consecutive Hgb will be notified Hgb will be needed to qualify as part of the primary endpoint.
New Wording	If the patient's Hgb decrease is between 0.5-1.0 gL from baseline, two consecutive Hgb will be needed to qualify as part of the primary endpoint.

Schedule of Events	
Footnote #1	
Original Wording	Screening period can occur 7 to 14 days prior to Day 0, in order to obtain all clinical assessments needed to qualify the patient.
New Wording	Screening period can occur 2 to 14 days prior to Day 0, in order to obtain all clinical assessments needed to qualify the patient.
Footnote #6	
Original Wording	If the patient's phosphorous is below the LLN at Day 42 the patient should return (as directed by the investigator) for repeat phosphorous until the value is back to WNL's or the patient's baseline
New Wording	If the patient's phosphorous is below the LLN at Week 18 the patient should return (as directed by the investigator) for repeat phosphorous until the value is back to WNL's or the patient's baseline
Footnote #7	
Original Wording	There will be 3 hepcidin samples drawn. One on Day 0 (prior to administration of study drug, Week 2 and either at Week 18 or time of intervention (e.g. administration of oral or IV Iron, ESAs, or transfusion)
New Wording	Screening and all hepcidin laboratory samples should be collected as fasting samples.
Footnote #8	
Added	There will be 3 hepcidin samples drawn. One on Day 0 (prior to administration of study drug). Week 2 and either Week 18 or the time of intervention (e.g. administration, of oral or IV Iron, FRAs or transfusion.
Introduction – 1.3	
Original Wording	A study evaluated the relationship between hepcidin levels and outcomes in patients with chemotherapy-associated anemia in treated with an ESA alone, ESA and oral iron, or ESA and IV iron.
New Wording	A study evaluated the relationship between hepcidin levels and outcomes in patients with chemotherapy-associated anemia treated with an ESA alone, ESA and oral iron, or ESA and IV iron.
Trial Design 3.1	
Original Wording	Preparing, concealing and administering the study drug on Day 0 and 5 (as Injectafer® is reddish-brown and slightly viscous).
New Wording	Preparing, concealing and administering the study drug on Day 0 and 7 (as Injectafer® is reddish-brown and slightly viscous).

Study Procedures	
6.2	
Original Wording	Central laboratory collection for Hematology (complete blood count [CBC]), iron indices, chemistry
New Wording	Fasting central laboratory collection for hematology (complete blood count [CBC]), iron indices, chemistry
6.3.3	
Original Wording	Blood samples for hepcidin (**only at Week 2)**
New Wording	Fasting blood samples for hepcidin (**only at Week 2)**
6.3.4	
Original Wording	Blood samples for central lab hematology (CBC), iron indices, chemistry and hepcidin
New Wording	Fasting blood samples for central lab hematology (CBC), iron indices, chemistry and hepcidin
6.4	
Added	Screening and all hepcidin samples should be collected as fasting samples
Statistics	
8.1	
Original Wording	The randomization will be stratified by major types of cancer and the randomization schedule will be generated prior to study initiation
New Wording	The randomization will be stratified by study site and the randomization schedule will be generated prior to study initiation
8.5.1	
Original Wording	Percentage of patients with a decrease in Hgb $\geq$ 0.5 g/dL from baseline between Day 0 to Week 18
New Wording	Percentage of patients with a decrease in Hgb $\geq$ 0.5 g/dL from baseline (Day 0 value) beginning at Week 3 through Week 18
8.6.1	
Original Wording	The treatment group difference for the percentage of patients with Hgb decrease ≥0.5 g/dL from baseline (between 0.5 to 1.0 g/dL on 2 consecutive measurements or > 1.0 g/dL decrease on a single measurement) will be assessed with the continuity-corrected chi-square test.
New Wording	The treatment group difference for the percentage of patients with Hgb decrease ≥ 0.5 g/dL from baseline (Day 0 value) beginning at Week 3 through Week 18 (between 0.5 to 1.0 g/dL on 2 consecutive measurements or > 1.0 g/dL decrease on a single measurement) will be assessed with the continuity-corrected chi-square test for patients who discontinue prior to Week 3, change in Hgb will be calculated from baseline to the last Hgb measurement after baseline.

8.7.2	
Original Wording	The adverse event profile will be characterized with severity (as graded by Version 3.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) and relationship (unrelated and related) to study drug.
New Wording	The adverse event profile will be characterized with severity (as graded by Version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) and relationship (unrelated and related) to study drug.

APPENDIX B:

SUMMARY OF CHANGES from Protocol Amendment 1 dated 18 February 2015 to Protocol Amendment 2 dated 20 December 2016	
Signatures of Agreement for Protocol	
Original Wording	Sylvan Hurewitz, MD Medical Director, Clinical Development Syed Quadri, MD Medical Director, Pharmacovigilance
New Wording	Sumita Chowdhury, MD, MPH Senior Medical Director, Head of Clinical Research and Development Patricia Campbell, RN Manager, Pharmacovigilance
Protocol Date	
Original Wording	Protocol Date: 04 November 2014 Amendment 1 Date: 18 February 2015
New Wording	Protocol Date: 04 November 2014 Amendment 1 Date: 18 February 2015 Amendment 2 Date: 20 December 2016
Design	
Original Wording	Preparing, concealing and administering the study drug on Day 0 and 7 (as Injectafer® is reddish-brown and slightly viscous)
New Wording	Preparing, concealing and administering the study drug on Day 0 and 7 (as Injectafer® is reddish-brown and slightly viscous) note: this includes collection of post dose vital signs.
Inclusion Criteria	
#2	
Original Wording	Patient whose cancer treatment is considered non-curative
New Wording	*Criteria removed*

#3	
Original Wording	Receiving non-adjuvant chemotherapy as part of their cancer treatment • With at least 2 cycles remaining
New Wording	Receiving chemotherapy as part of their cancer treatment • With at least 4 weeks of treatment remaining
#5	
Original Wording	Ferritin between 100 and 800 ng/mL and transferrin saturation (TSAT) ≤ 25%
New Wording	Ferritin between 100 and 800 ng/mL and transferrin saturation (TSAT) ≤ 35%
Exclusion Criteria	
#3	
Original Wording	Patients receiving adjuvant chemotherapy
New Wording	*Criteria removed*
Schedule of Events	
Footnote #2	
Original Wording	Contact the IWRS (interactive web response system) for patient screening number.
New Wording	Contact the IRT (interactive response technology) system for patient screening number.
Footnote #3	
Original Wording	Contact the IWRS for randomization
New Wording	Contact the IRT system for randomization
Footnote #7	
Original Wording	Screening and all hepcidin laboratory samples should be collected as fasting samples.
New Wording	*Footnote removed*
Footnote #8	
Original Wording	There will be 3 hepcidin samples drawn. One on day 0 (prior to administration of study drug), Week 2, and either at Week 18 or the time of intervention (e.g. administration of oral IV Iron, ESAs, or transfusion)
New Wording	*Footnote removed*
Trial Design 3.1	
Original Wording	Preparing, concealing and administering the study drug on Day 0 and 7 (as Injectafer® is reddish-brown and slightly viscous)
New Wording	Preparing, concealing and administering the study drug on Day 0 and 7 (as Injectafer® is reddish-brown and slightly viscous) note: this includes collection of post dose vital signs.
Original Wording	**No additional iron preparations (IV or oral iron) from 28 days prior to consent are permitted.**

	Multivitamins with iron will be allowed. No prophylactic medications may be administered prior to study drug administration without prior approval from Luitpold Pharmaceuticals, Inc. Other standard therapies are permitted but must be recorded on the electronic case report form.
New Wording	**No additional iron preparations (IV or oral iron) from 28 days prior to consent are permitted. Multivitamins with iron will be allowed. No prophylactic medications given specifically due to the use of an IV iron may be administered prior to study drug administration without prior approval from Luitpold Pharmaceuticals, Inc.** Medications used as prophylaxis to prevent potential side effects of chemotherapies are permitted. Other standard therapies are permitted but must be recorded on the electronic case report form.
Schedule of Events 3.3	
Footnote #2	
Original Wording	Contact the IWRS (interactive web response system) for patient screening number.
New Wording	Contact the IRT (interactive response technology) system for patient screening number.
Footnote #3	
Original Wording	Contact the IWRS for randomization
New Wording	Contact the IRT system for randomization
Footnote #7	
Original Wording	Screening and all hepcidin laboratory samples should be collected as fasting samples.
New Wording	*Footnote removed*
Footnote #8	
Original Wording	There will be 3 hepcidin samples drawn. One on day 0 (prior to administration of study drug), Week 2, and either at Week 18 or the time of intervention (e.g. administration of oral IV Iron, ESAs, or transfusion)
New Wording	*Footnote removed*
Patient Selection	
4.2	
Original Wording	Once a patient enters the screening phase, they will be assigned, via the IWRS system, a unique screening number and will be evaluated for eligibility. From the time of consent until the start of treatment, the patient will not receive any form of iron outside of the study (intravenous iron from 28 days prior to consent or oral iron including multivitamins with iron from time of consent).

New Wording	Once a participant enters the screening phase, they will be assigned, via the IRT system, a unique screening number and will be evaluated for eligibility. From the time of consent until the start of treatment, the patient will not receive any form of iron outside of the study (intravenous iron from 28 days prior to consent or oral iron from time of consent).
4.2.1	
Inclusion Criteria	
#2	
Original Wording	Patients whose cancer treatment is considered non-curative
New Wording	*Criteria removed*
#3	
Original Wording	Receiving non-adjuvant chemotherapy as part of their cancer treatment • With at least 2 cycles remaining
New Wording	Receiving chemotherapy as part of their cancer treatment • With at least 4 weeks of treatment remaining
#5	
Original Wording	Ferritin between 100 and 800 ng/mL and transferrin saturation (TSAT) ≤ 25%
New Wording	Ferritin between 100 and 800 ng/mL and transferrin saturation (TSAT) ≤ 35%
Exclusion Criteria	
#3	
Original Wording	Patients receiving adjuvant chemotherapy
New Wording	*Criteria removed*
Study Drug	
5.2	
Drug Administration/Regimen	
Original Wording	Prior to each drug administration participants must be blinded with a sleeping mask, and the investigator(s) who is conducting the efficacy and safety evaluations will not be present when the study drug is administered to the participant.
New Wording	Prior to each drug administration participants must be blinded with a sleeping mask, or other method. The investigator(s) who is conducting the efficacy and safety evaluations will not be present when the study drug is administered to the participant.
5.5	

Original Wording	**No additional iron preparations (IV or oral iron) from 28 days prior to consent are permitted. Multivitamins with iron will be allowed. No prophylactic medications may be administered prior to study drug administration without prior approval from Luitpold Pharmaceuticals, Inc.** Other standard therapies are permitted but must be recorded on the eCRF
New Wording	**No additional iron preparations (IV or oral iron) from 28 days prior to consent are permitted. Multivitamins with iron will be allowed. No prophylactic medications given specifically due to the use of an IV iron may be administered prior to study drug administration without prior approval from Luitpold Pharmaceuticals, Inc.** Medications used as prophylaxis to prevent potential side effects of chemotherapies are permitted. Other standard therapies are permitted but must be recorded on the eCRF
5.6	
Original Wording	Preparing, concealing and administering the study drug on Day 0 and 7 (as Injectafer® is reddish-brown and slightly viscous)
New Wording	Preparing, concealing and administering the study drug on Day 0 and 7 (as Injectafer® is reddish-brown and slightly viscous) note: this includes collection of post dose vital signs.
Study Procedures	
6.2	
Original Wording	Obtain screening number from IWRS
New Wording	Obtain screening number from IRT
Original Wording	Fasting central laboratory collection for hematology (complete blood count [CBC]), iron indices, chemistry
New Wording	Blood samples for central laboratory hematology (complete blood count [CBC]), iron indices, chemistry
6.3.1	
Original Wording	Once it is confirmed that the patient continues to meet the entry criteria, all eligible patients will be randomized to either Group A (Injectafer) or Group B (placebo-normal saline) in a 1:1 ratio based on a pre-determined randomization schedule via the IWRS system
New Wording	Once it is confirmed that the patient continues to meet the entry criteria, all eligible patients will be randomized to either Group A (Injectafer) or Group B (placebo-normal saline) in a 1:1 ratio based on a pre-

	determined randomization schedule via the IRT system
Original Wording	Fasting central labs for hematology (complete blood count [CBC]), iron indices, chemistry, hepcidin levels (prior to study drug administration)
New Wording	Blood sample for central lab hematology (complete blood count [CBC]), iron indices, chemistry, hepcidin levels (prior to study drug administration)
Group A	
Original Wording	Blind the patient via use of a sleeping mask
New Wording	Blind the patient (via use of a sleeping mask or other method)
Group B	
Original Wording	Blind the patient via use of a sleeping mask
New Wording	Blind the patient (via use of a sleeping mask or other method)
6.3.2	
Group A	
Original Wording	Blind the patient via use of a sleeping mask
New Wording	Blind the patient (via use of a sleeping mask or other method)
Group B	
Original Wording	Blind the patient via use of a sleeping mask
New Wording	Blind the patient (via use of a sleeping mask or other method)
6.3.3	
Original Wording	Fasting blood sample for hepcidin (**only at Week 2**)
New Wording	Blood sample collection for hepcidin (**only at Week 2**)
6.3.4	
Original Wording	Fasting blood samples for central lab hematology (CBC), iron indices, chemistries, and hepcidin
New Wording	Blood samples for central lab hematology (CBC), iron indices, chemistries, and hepcidin
6.4	
Original Wording	Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. Screening and all hepcidin samples should be collected as fasting samples. All serum laboratory testing will be provided to the physician for review and assessment.
New Wording	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.

Statistics	
8.5.2	
#11	
Original Wording	
New Wording	Adverse Events

APPENDIX C:

SUMMARY OF CHANGES from Protocol Amendment 2 dated 20 December 2016 to Administrative amendment 1 dated 2 November 2017	
Title of the study	
Original Wording	IRON CLAD: Can Iron Lessen Anemia Due to cancer and chemotherapy: A multi-center, randomized, double-blinded, controlled study to investigate the efficacy and safety of Injectafer® (ferric carboxymaltose injection).
New Wording	IRON CLAD: Can Iron Lessen Anemia Due to cancer and chemotherapy: A multi-center, randomized, double-blinded, controlled study to investigate the efficacy and safety of Injectafer® (ferric carboxymaltose injection) in adults
Signatures of Agreement for Protocol	
Original Wording	Sumita Chowdhury, MD, MPH Senior Medical Director, Head of Clinical Research and Development Patricia Campbell, RN Manager, Pharmacovigilance
New Wording	Mark Falone, MD, Medical Director, Head of Clinical Research and Development Luitpold Pharmaceuticals, Inc
Original Wording	Patricia Campbell, RN Manager, Pharmacovigilance Luitpold Pharmaceuticals, Inc
New Wording	Susan Oskins, RN, BSN Pharmacovigilance Sr. Manager Luitpold Pharmaceuticals, Inc.
Original Wording	David Morris, PhD Senior Director, Statistics WebbWrites, LLC
New Wording	Nicole Blackman, PhD Statistician Luitpold Pharmaceuticals, Inc.

Terminology/ Defining first time used abbreviations	
Original Wording	Injectafer®
New Wording	FCM
Original Wording	Adverse Events
New Wording	Adverse Events (AE), AE
Original Wording	Serious Adverse Events
New Wording	Serious Adverse Events (SAE), SAE
Original Wording	FACIT-Fatigue Scale
New Wording	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
Original Wording	cancer- and chemotherapy-related anemia
New Wording	cancer- and chemotherapy-related anemia (CRA), CRA
Original Wording	IV
New Wording	intravenous (IV), IV
Original Wording	erythropoiesis-stimulating agents
New Wording	erythropoiesis-stimulating agents (ESAs), ESAs
Original Wording	BP
New Wording	Blood pressure (BP), BP
Original Wording	Heart Rate
New Wording	Heart Rate (HR), HR
Original Wording	LLN
New Wording	Lower limit of normal (LLN), LLN
Original Wording	WNL'S
New Wording	Within normal limits (WNLs), WNLs
Original Wording	IDA
New Wording	Iron deficiency anemia (IDA), IDA
Original Wording	Iron deficiency
New Wording	Iron deficiency (ID), ID
Original Wording	Absolute ID
New Wording	Absolute iron deficiency (AID), AID
Original Wording	Functional ID
New Wording	Functional iron deficiency (FID), FID
Original Wording	The National Comprehensive Cancer Network
New Wording	The National Comprehensive Cancer Network (NCCN), NCCN
Original Wording	RES
New Wording	Reticuloendothelial system – RES, RES
Original Wording	Investigator's Brochure
New Wording	Investigator's Brochure (IB), IB
Original Wording	investigator
New Wording	Investigator
Original Wording	sponsor
New Wording	Sponsor

Original Wording	International Conference on Harmonisation
New Wording	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH
Original Wording	US Regulations
New Wording	FDA Regulations
Original Wording	Informed Consent
New Wording	informed consent
Original Wording	Study monitor
New Wording	Clinical Monitor
Original Wording	institution
New Wording	Institution
Original Wording	treatment-emergent adverse events
New Wording	treatment-emergent adverse events (TEAEs), TEAEs
Font of the document	
Original Wording	Times New Roman
New Wording	Arial
Protocol Date	
Original Wording	Protocol Date: 04 November 2014 Amendment 1 Date: 18 February 2015 Amendment 2 Date: 20 December 2016
New Wording	Protocol Date: 04 November 2014 Amendment 1 Date: 18 February 2015 Amendment 2 Date: 20 December 2016 Administrative Amendment 1 Date: 2 November2017
Header	
Original Wording	Luitpold Pharmaceuticals, Inc. 1VIT14039 CONFIDENTIAL Amendment 2: 20 December 2016
New Wording	Luitpold Pharmaceuticals, Inc. Protocol:1VIT14039 CONFIDENTIAL Amendment 1,2 and Administrative Amendment 1: 2 November 2017
STUDY SYNOPSIS	
Original Wording	Patients
New Wording	Participants
Exclusion Criteria	
Original Wording	Any anemia treatment within 4 weeks before inclusion (oral iron, intravenous iron, transfusion, or erythropoiesis-stimulating agents)

New Wording	Any anemia treatment within 4 weeks before inclusion (oral iron, intravenous (IV) iron, red blood cell (RBC) transfusion, or erythropoiesis-stimulating agents (ESAs))
Primary Endpoint	
Original Wording	Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from baseline (Day 0 value) beginning at Week 3 through Week 18 •If the participant's Hgb decrease is between 0.5-1.0 g/dL from baseline, two consecutive Hgb values will be needed to qualify as part of the primary endpoint •If the participant's Hgb decrease is > 1.0 g/dL from baseline, one single measurement will be needed to qualify as part of the primary endpoint
New Wording	Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from Week 3 to Week 18.
Secondary Endpoints	
Original Wording	**Major Secondary Endpoints:** 1. Percentage of participants with avoidance of anemia progression as defined as initiation of other anemia management at any time during the study (i.e. ESAs, blood transfusions, and iron) 2. Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to each study visit 3. Time to a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to Week 18 4. Percentage of participants requiring a blood transfusion 5. Mean change in Hgb from baseline to week 18 or time of intervention 6. Percentage of participants with Hgb >1 g/dL increase at any time point in the absence of any blood transfusion or ESA treatment 7. Percentage of participants with Hgb >12 at any time point in the absence of any blood transfusion or ESA treatment 8. Time to hemoglobin response defined as ≥ 1 g/dL increase 9. Correlation of change in hemoglobin with Day 0 hepcidin level 10. Total score of the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue) 11. Adverse events
New Wording	**Secondary Endpoints:**

Order was changes and first secondary endpoint was paraphrased for clarity.	12. Change in Hgb from baseline to Week 18 or to non-study intervention. Non-study intervention is defined as initiation of ESAs, RBC transfusion, and additional IV or oral iron. 13. Percentage of participants who receive non-study intervention. 14. Percentage of participants with Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention. 15. Percentage of participants with Hgb ≥12 g/dL in the absence of non-study intervention. 16. Time to Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention. 17. Percentage of participants requiring a blood transfusion. 18. Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to each study visit. 19. Time to a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to Week 18. 20. Correlation of change in hemoglobin with Day 0 hepcidin level. 21. Total score of the FACIT-Fatigue. 22. AEs
Number of Participants:	
Original Wording	400
New Wording	222
Schedule of Events	
Footnote #7	
Original Wording	No existing footnote
New Wording	Serum pregnancy test will be performed for all women of childbearing potential.
Table of Content	
Original Wording	2. Main trial Objective
New Wording	2. Primary Objective
Original Wording	4.5 Intervention
New Wording	4.5 Non-Study Intervention
List of Abbreviations	

New wording	*Addition of following abbreviations:* AID – absolute iron deficiency ANCOVA – Multivariate analysis based on parametric analysis of covariance BP – blood pressure CRA – cancer- and chemotherapy related anemia CFR – Code of Federal Regulations CMH – Cochran-Mantel-Haenszel EC – Ethics Committee FID – functional iron deficiency HR – heart rate IB – Investigational Brochure ITT – Intent-to-Treat LLN – lower limit of normal MAR – Missing at random MMRM – Mixed-effect model for repeated measures mITT – modified Intent-to-Treat WNLs – within normal limits TEAEs – treatment-emergent adverse events T ½ - half life *Deletion of following unused or standardized abbreviations:* Bmp – beats per minute dL – deciliter g – gram mg – milligram ml – milliliter mmHg – milliliter of mercury US – United States
Introduction	
Original Wording	Historically, erythropoiesis-stimulating agents (ESAs) have been utilized for the treatment of cancer- and chemotherapy-related anemia.
New Wording	Historically, IV iron agents have been used for the treatment of AID and ESAs have been utilized for the treatment of FID in patients diagnosed with CRA.
1.2.3 FCM Human Experience	
Original Wording	Patients
New Wording	Participants
Schedule of Events 3.3	
Footnote #7	
Original Wording	No footnote present
New Wording	Serum pregnancy test will be performed for all women of childbearing potential.

4.1 Number and Type of Participants	
Original Wording	Approximately 400
New Wording	Approximately 222
4.5 Non-Study Intervention	
Original Wording	Intervention is defined as any of the following: •Initiation of erythropoietin for any reason •RBC transfusion •IV iron •Prescribed use of oral iron When intervention occurs, the date of the intervening event should be recorded in the source documents as well as the electronic Case Report Form (eCRF), and the participant should continue in the study as scheduled.
New Wording	Non-study intervention is defined as any of the following: •Initiation of erythropoietin for any reason, and/or •RBC transfusion, and/or •IV iron, and/or •Prescribed use of oral iron When non-study intervention occurs, the date of the intervening event should be recorded in the source documents as well as the eCRF, and the participant should continue in the study as scheduled.
Study Drug	
5.1 Formulation Packaging and Storage	
Original Wording	See USP.
New Wording	Refer to the United States Pharmacopeia (USP)).
5.6 Blinding	
Original Wording	Note: this includes collection of post does vital signs
New Wording	Note: this includes collection of post dose vital signs
Study Procedures	
6.3.1 Day 0	
Original Wording	Blood sample for central lab hematology (complete blood count [CBC]), iron indices, chemistry, hepcidin levels (prior to study drug administration)
New Wording	Blood sample for central lab hematology (CBC, iron indices, chemistry, hepcidin levels) prior to study drug administration
6.4 Central Laboratory Assessments	

Original Wording	Hematology: Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, and reticulocyte count Chemistry: sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, GGT, AST, ALT, LDH, calcium, phosphorus, glucose, and bicarbonate Iron indices: serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT)
New Wording	Hematology: Hgb, hematocrit (Hct), white blood cells (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets, differential count, and reticulocyte count. Chemistry: sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, albumin, alkaline phosphatase, total bilirubin, gamma-glutamyl-transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), calcium, phosphorus, glucose, and bicarbonate. Iron indices: serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT).
Original Wording	Blind the patient via use of a sleeping mask
7.3 Serious Adverse Events	
Original Wording	In addition to the above reporting, all SAEs must be recorded on the Adverse Event page of the eCRF and reported immediately to your IRB/Ethics Committee per their reporting guidelines.
New Wording	In addition to the above reporting, all SAEs must be recorded on the Adverse Event page of the eCRF and reported immediately to your Institutional Revie Board (IRB) and/or Ethics Committee (EC) per their reporting guidelines.
STATISTICS	
8.2 Sample Size Rationale	

Original Wording	No published information was found for the primary endpoint. For sample size estimation, the percentages of participants with Hgb decrease ≥ 0.5 g/dL from baseline (between 0.5 to 1.0 g/dL on 2 consecutive measurements or > 1.0 g/dL decrease on a single measurement) in the treatment groups were hypothesized to bracket 0.50 symmetrically. These percentages provide the lowest power with the chi square test for a given sample size and treatment difference. A sample size of 200 participants per group (400 participants in total) provides > 90% power for a 2 sided, continuity-corrected, chi-square test with Type I error of 0.05 when the percentages of participants meeting the primary endpoint are 41% and 59% in the FCM and placebo groups, respectively. A treatment difference of 18 percentage points is clinically relevant, as evidenced by a number-needed-to-treat of 5.6.

New Wording	The study is powered to demonstrate a clinically meaningful difference between FCM and placebo with respect to the percentage with decrease in Hgb ≥0.5 g/dL (i.e., with respect maintenance of Hgb levels) from Week 3 to Week 18. Determination of sample size was based on the following assumptions: •The proportion of placebo participants not maintaining Hgb levels will be 65%.[1] •A relative reduction of 35%, i.e., a reduction from 65% with placebo to 42% with FCM, would be clinically meaningful.[10] •The study would have 90% power to detect a clinically meaningful treatment difference at two sided alpha=0.05. •Test statistic is continuity corrected chi-squared test. •Treatments will be allocated on a 1:1 ratio. Then a sample size of 106 participants per treatment group is required. Assuming 5% of participants will not meeting the definition of modified Intent-to-Treat (mITT), 111 participants per treatment group (222 participants in total) should be randomized. The key secondary efficacy endpoint is the change in Hgb from baseline to Week 18 or to non-study intervention. This sample size of 106 participants per treatment group will have 99% power to demonstrate superiority of FCM over placebo in the mean change in Hgb from baseline to Week 18 in the absence of non-study intervention, using a t-test at two-sided alpha=0.05. This assumes a difference in means of Hgb of 1.0 g/dL with common standard deviation = 1.5 g/dL.
8.3 Analysis Populations	
Original Wording	The Full Analysis population will consist of all participants who received a dose of randomized treatment. All efficacy and safety analyses will be performed with the Full Analysis population. Treatment assignments will be analyzed according to the actual treatment received.
New Wording	Intent-to-Treat Population (ITT) The ITT population will comprise all randomized participants. Participants will be evaluated according to the treatment to which they were randomized. Any

	participant who receives a treatment randomization number will be considered to have been randomized. Modified Intent-to-Treat Population (mITT) The mITT population will comprise all subjects in the ITT population who receive at least one dose of study drug, have a baseline Hgb measurement, and at least one corresponding post-baseline measurement. Participants will be evaluated according to the treatment to which they were randomized. The primary population for the assessing efficacy will be the mITT population. Safety Population The Safety population will consist of all participants in the ITT population who received at least one dose of study drug. Participants will be evaluated according to treatment received. This population will be used for assessing safety.
8.5 Endpoints and Definitions	
8.5.1 Primary Endpoint	
Original Wording	Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from baseline (Day 0 value) beginning at Week 3 through Week 18 •If the participant's Hgb decrease is between 0.5-1.0 g/dL from baseline, two consecutive Hgb values will be needed to qualify as part of the primary endpoint •If the participant's Hgb decrease is > 1.0 g/dL from baseline, one single measurement will be needed to qualify as part of the primary endpoint
New Wording	Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from Week 3 to Week 18.
8.5.2 Major Secondary Endpoints	
Original Wording	**Major Secondary Endpoints:** 1. Percentage of participants with avoidance of anemia progression as defined as initiation of other anemia management at any time during the study (i.e. ESAs, blood transfusions, and iron) 2. Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to each study visit 3. Time to a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to Week 18

	4. Percentage of participants requiring a blood transfusion 5. Mean change in Hgb from baseline to week 18 or time of intervention 6. Percentage of participants with Hgb >1 g/dL increase at any time point in the absence of any blood transfusion or ESA treatment 7. Percentage of participants with Hgb >12 at any time point in the absence of any blood transfusion or ESA treatment 8. Time to hemoglobin response defined as ≥ 1 g/dL increase 9. Correlation of change in hemoglobin with Day 0 hepcidin level 10. Total score of the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue) 11. Adverse events
New Wording *Order of secondary endpoints was changed to prioritize them (2nd and third endpoint was transferred after 6th secondary endpoint). First secondary endpoint was paraphrased for clarity.*	**Secondary Endpoints:** 1. Change in Hgb from baseline to Week 18 or to non-study intervention. Non-study intervention is defined as initiation of ESAs, RBC transfusion, and additional IV or oral iron. 2. Percentage of participants who receive non-study intervention. 3. Percentage of participants with Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention. 4. Percentage of participants with Hgb ≥12 g/dL in the absence of non-study intervention. 5. Time to Hgb increase ≥1 g/dL (change from baseline) in the absence of non-study intervention. 6. Percentage of participants requiring a blood transfusion. 7. Percentage of participants with a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to each study visit. 8. Time to a decrease in Hgb ≥ 0.5 g/dL from their baseline between Day 0 to Week 18. 9. Correlation of change in hemoglobin with Day 0 hepcidin level. 10. Total score of the FACIT-Fatigue. 11. AEs.

8.6.1 Primary Efficacy Analysis	
Original Wording	The treatment group difference for the percentage of participants with Hgb decrease ≥ 0.5 g/dL from baseline (Day 0 value) beginning at Week 3 through Week 18 (between 0.5 to 1.0 g/dL on 2 consecutive measurements or > 1.0 g/dL decrease on a single measurement) will be assessed with a logistic regression model with factors for treatment, cancer stage, region (United States, Europe), and baseline hemoglobin. For participants who discontinue prior to Week 3, change in Hgb will be calculated from baseline to the last Hgb measurement after baseline. Any cancer stage with <40 participants will be combined for the analysis with a clinically similar cancer stage
New Wording	The following participants will be considered to have met the primary endpoint: • Participants with observed Hgb decrease from baseline between 0.5 g/dL to 1.0 g/dL on two consecutive visits between Weeks 3 and 18. • Participants with observed Hgb decrease from baseline ≥1.0 g/dL at one visit. • Participants who have a non-study intervention prior to Week 18. • Participants who discontinue prior to Week 18 for lack of efficacy or adverse events. All other randomized participants will be considered to have not met primary endpoint, i.e., will be considered to have maintained Hgb levels. The primary endpoint will be analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for pooled site. Estimates of treatment effect will be presented via the test-based odds-ratio and 95% confidence interval. In addition, the absolute difference in the percentages and associated 95% confidence intervals will be presented. The primary endpoint will be analyzed for the mITT population.
8.6.2 Secondary Efficacy Analyses	
Original Wording	Treatment group differences for proportions will be assessed with the same logistic regression model

	specified for the primary efficacy endpoint. Continuous endpoints (e.g., change in hemoglobin) and the total score of the FACIT-Fatigue will be assessed by the analysis of covariance with treatment, cancer stage, and region (United States, Europe) as fixed effects and baseline value as covariate. Time to hemoglobin response and time to Hgb decrease from baseline ≥ 0.5 g/dL will be assessed by the Cox proportional hazards model with factors for treatment, cancer stage, region (United States, Europe), and baseline hemoglobin
New Wording	**Key secondary endpoint** Change in Hgb from baseline to Week 18 or to non-study intervention is the key secondary endpoint. The analysis of the key secondary endpoint will be based on a mixed-effect model for repeated measures (MMRM). Missing data will be handled assuming a missing at random (MAR) mechanism. The model will include terms of pooled site, baseline Hgb, as well as treatment group. The key secondary endpoint will be analyzed for the mITT population. **Other secondary endpoints** Treatment group differences for proportions will be analyzed using the CMH chi-square test adjusting for pooled site Continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM). Missing data will be handled assuming a missing at random (MAR) mechanism. Time to hemoglobin response and time to Hgb decrease from baseline ≥ 0.5 g/dL will be analyzed using a stratified logrank test. The correlation of baseline hepcidin level with change in hemoglobin will be analyzed within each treatment group. Spearman rank correlation and Pearson product-moment correlation will be summarized. **Subgroup Analyses** Univariate analyses The primary and key secondary endpoint will be analyzed separately for the following subgroups:

	• Geographic Region: United States, Europe. • Cancer Stage. • Baseline hemoglobin: <10 g/dL, ≥ 10 g/dL. Estimates of treatment effect and corresponding 95% confidence intervals will be displayed graphically. Multivariate analyses Multiple logistic regression will be used to evaluate the effect of treatment on maintenance of Hgb level while simultaneously controlling for the important subgroups. Multivariate analysis based on parametric analysis of covariance (ANCOVA) will be conducted for the Hgb change from baseline endpoint. Details will be provided in the SAP. Subgroup analyses will be conducted for the mITT population
8.6.4 Handling of Missing Data	
Original Wording	*Text was removed.*
New Wording	Methods for handling missing data are specific for each endpoint to be analyzed. Details will be provided in the SAP. *Sections 8.6.1* and *Section 8.6.2* outline how missing data will be handled for the primary endpoint, and the key secondary endpoint, respectively.
9.7.1 Ethical and Legal Issues	
Original Wording	This study will be performed in accordance with the United States (US) Code of Federal Regulations on Protection of Human Subjects (21 CFR 50), IRB regulations (21 CFR 56), the most current revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312 and applicable ICH guidelines.
New Wording	This study will be performed in accordance with the FDA Code of Federal Regulations (CFR) on Protection of Human Subjects (21 CFR 50), IRB regulations (21 CFR 56), the most current revision of the Declaration of Helsinki (October 2013), all applicable local and state

	regulations, 21 CFR Part 312 and applicable ICH guidelines.
APPENDEXIS	
APPENDIX A	
Original Wording	SUMMARY OF CHANGES
New Wording	SUMMARY OF CHANGES from original Protocol dated 04 December 2014 to Protocol Amendment 1 dated 18 February 2015
APPENDIX B	
Original Wording	SUMMARY OF CHANGES
New Wording	SUMMARY OF CHANGES from Protocol Amendment 1 dated 18 February 2016 to Protocol Amendment 2 dated 20 December 2016
APPENDIX C	
New Wording	*Addition of this table*