Efficacy of Ferric Carboxymaltose in Patients with Gastrointestinal Stromal Tumor Receiving Systemic Therapy

1.0 Objectives

Primary Objective:
To evaluate the efficacy of Ferric Carboxymaltose (Injectafer) in anemia in gastrointestinal stromal tumor (GIST) patients planned to receive or receiving systemic therapy and presenting with anemia.

Secondary Objectives:
(1) To evaluate the toxicity of Ferric Carboxymaltose in GIST patients planned to receive or receiving systemic therapy and presenting with anemia.
(2) To evaluate effect of Ferric Carboxymaltose on patient reported outcomes (fatigue) by Functional Assessment of Cancer Therapy-Fatigue Scale (FACT-F).

2.0 Background

2.1 Cancer and Chemotherapy-related Anemia
Anemia is a common complication in patients who have cancer and those who receive Chemotherapy [1]. Depending on the type of cancer, 30% to 90% of patients have anemia, defined as a hemoglobin <11.0 g/dL [2, 3]. Results from a survey, including more than 15,000 cancer patients, demonstrated that the incidence of anemia was 53.7%; however, only 38.9% of the patients with anemia were treated. 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 [4, 5]. Anemia in cancer patients is often multifactorial and can be caused by hemolysis, iron deficiency due to blood loss, inadequate nutrition, impaired RBC production due to direct effects of the cancer or myelosuppressive chemotherapy or radiation therapy [5]. The severity of anemia depends on the type and extent of the cancer, the schedule and intensity of therapy, and whether the patient has received prior chemotherapy and/or radiation.

Iron deficiency anemia (IDA), is the top-ranked type of anemia worldwide [6]. The reported prevalence of IDA in cancer is around 32-60%. Iron deficiency (ID) plays a pivotal role in the development of anemia in cancer. ID in cancer may be separated into two components, absolute iron deficiency and functional iron deficiency. Absolute ID is defined as depleted iron stores. Most iron-deficient patients with cancer present with functional ID [7]. Functional ID is characterized by iron sequestration, and thus, the lack of available iron with normal or elevated ferritin levels. Functional ID is often caused by a chronic inflammatory state which many cancer patients may have [8]. Two studies have examined the administration of IV iron without ESAs, and both studies demonstrated that IV iron alone can reduce transfusion rates [9, 10].

2.2 Anemia in GIST Patients Receiving Systemic Therapy
A gastrointestinal stromal tumor (GIST) is a type of tumor that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine [11]. Chronic

blood loss is more common for GIST patients [12]. Many GIST patients are diagnosed with anemia due to chronic blood loss [13]. GIST patients presenting anemia can be due to iron deficiency anemia either from inadequate iron intake or from blood loss (as from a GIST bleeding into the GI tract), surgery, or drug-induced anemia; Gleevec and other Tyrosine Kinase Inhibitors (TKIs) may decrease production of new red blood cells [14].

2.3 Prevention/Treatment for IDA

Iron replacement therapy is essential for replenishing iron stores and raising hemoglobin levels in patients with IDA, regardless of the etiology, and can be administered orally, intramuscularly, or intravenously [6,15]. Patients with IDA should receive iron supplementation and the prescribed use of oral iron is a convenient, inexpensive, and effective treatment regimen in stable patients. However, use of oral iron is limited by side effects, including nausea, vomiting, constipation, and metallic taste, resulting in non-adherence and limited treatment response [6, 15].

There is considerable efficacy and safety experience with the various oral iron preparations available. Intravenous iron replacement therapy is also a treatment alternative. However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted their use [6, 15].

More recently approved, non-dextran intravenous irons, like iron sucrose and iron gluconate, do not contain the dextran moiety, but they have significant dosage and administration rate limitations [16, 17]. 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 [6, 15].

2.4 Injectafer, a Newly Approved Iron Preparation

Injectafer (Ferric Carboxymaltose Injection) is a stable Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as an intravenous iron replacement therapy for the treatment of IDA. After intravenous administration, Injectafer is mainly found in the liver, spleen, and bone marrow. The iron slowly dissociates from the complex and can be efficiently used in the bone marrow for hemoglobin synthesis. The carbohydrate moiety of Injectafer is metabolized by the glycolytic pathway [18-21].

Due to its structure, Injectafer 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. These characteristics of Injectafer 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 below).

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

Compared to other available intravenous iron preparations, the larger Injectafer doses result in less frequent administration of intravenous iron and represents an improvement in convenience for patients 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 [18-21].

2.4.1 Pharmacodynamics

A clinical pharmacokinetic study (VIT-IV-CL-001) using positron emission tomography (PET) demonstrated a fast initial elimination of radioactively labeled iron (Fe) $^{52}Fe/^{59}Fe$ Injectafer 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 (t½) 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 Injectafer dose, the majority of the Injectafer iron complex was utilized or excreted by 72 hours [18-21].

Using PET it was demonstrated that red cell uptake of ^{59}Fe and ^{52}Fe from Injectafer ranged from 61% to 99%. In patients with iron deficiency, red cell uptake of radio-labeled iron ranged from 91% to 99% at 24 days after Injectafer dose. In patients with renal anemia, red cell uptake of radio-labeled iron ranged from 61% to 84% after 24 days Injectafer dose.

After administration of a single dose of Injectafer of 100 to 1000 mg of iron in iron deficient patients, maximum iron levels of 37 µg/mL to 333 µg/mL were obtained respectively after 15 minutes to 1.2 hours post dose. The volume of distribution was estimated to be 3 L. The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours. Renal elimination of iron was negligible [18-21].

2.4.2 Clinical Experience

The efficacy of Injectafer® for the treatment of IDA was demonstrated in 2 randomized, open-label, controlled clinical studies (1VIT09030 and 1 VIT09031). In these 2 studies, Injectafer® was administered at a dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on 2 occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron [21-23].

Study 1 VIT09031 enrolled subjects with iron-deficiency anemia who had an unsatisfactory response to oral iron or who were intolerant to or inappropriate for oral iron therapy during the 14-day, oral iron run-in period. Study 1VIT09030 enrolled subjects with iron-deficiency anemia and impaired renal function [21-23].

The overall incidence of treatment-emergent serious adverse events in the 2 studies was 12.8% in the Injectafer® group and 12.5% in the pooled comparators group. No notable differences (1.0% and at least a 2-fold difference in incidence) were observed between the Injectafer® group and the pooled comparators groups for specific events.

The overall incidence of treatment-emergent adverse events resulting in premature discontinuation of study drug was 2.9% in the Injectafer® group and 2.1% in the pooled comparators group. The most common treatment-emergent adverse events resulting in premature discontinuation of study drug in the Injectafer® group were flushing and hypertension (0.5% and 0.6%, respectively) [21-23].

The percentage of subjects with treatment-emergent low phosphorus, defined as a baseline value that was Grade 0, 1, or 2 and decreased to a value defined as Grade 3 (<2.0 to 1.0 mg/dL) or Grade 4 (<1.0 mg/dL) per Common Terminology Criteria for Adverse Event version 3.0, was the only notable difference between the Injectafer® (29.6%) and the pooled comparators (0.7) groups. Mean decreases from baseline in phosphorus in the Injectafer® group were highest at Day 14 and were returning toward baseline at Day 28/35 in Studies 1VIT09030 and 1VIT09031. The trend toward baseline continued through Day 56 in Study 1VIT09030 [21-23].

Safety results for 5799 Injectafer®-treated subjects treated in 20 short-term Phase 2/3 studies of iron-deficiency anemia or congestive heart failure (CHF) were similar to studies 1VIT09030 and 1VIT09031 [21-23].

In summary, Injectafer® is a safe and effective treatment of IDA in adult patients who are [20]:

- Intolerance to oral iron or have had unsatisfactory response to oral iron;
- Non-dialysis-dependent chronic kidney disease.

2.5 Rationale for the Study

The incidence of anemia in patients with gastrointestinal stromal tumor (GIST) receiving TKIs therapy is high [13]. Anemia in GIST patients can be multifactorial such as: anemia of chronic disease, primary therapy, surgery, blood loss and Iron/vitamin deficiency [6].

In our experience, GIST patients with anemia and IDA do response to oral iron if they can tolerate it. In our observations in patients with GIST on iron therapy, approximately 29% of patients tolerated and had response to oral iron vs 75% had response to IV iron such as iron sucrose. This experience is similar to response rate (73%-77%) reported with iv iron in clinical trials in cancer patients receiving chemotherapy [27]. However, the GIST patients seem to have lower tolerance to oral iron due to the underlying disease and treatment with TKIs. This can explain lower success rate (~29%) in our experience as compared to ~45% reported in clinical trials to oral drugs in cancer patients receiving chemotherapy. Also, multiple infusions of iron sucrose are needed to deliver the total dose of iron. Patients with GIST often present with IDA and anemia often worsens during therapy with TKIs like Gleevac [14]. These patients often have nausea from their systemic therapy and not all patients tolerate oral iron well. Also there is a time lag for response to oral iron. Injectafer is a newly approved, non-dextran IV iron that can be administered in a large dose of 2 infusions 1 week apart (15 mg/kg for a maximum single dose of 750 mg, a total of up to 1500 mg). The safety profile is excellent and has been found effective in correcting IDA. Based on these observations, we are proposing a clinical trial of IV injectafer vs oral iron (to avoid patient selection bias) in GIST patients with IDA planning to start or have recently started systemic therapy to evaluate efficacy and safety with IV injectafer.

3.0 Background Drug Information

3.1 Ferric Carboxymaltose (Injectafer)

Injectafer® (ferric carboxymaltose injection) is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron [20].

A. Physical Description of Study Drug

Injectafer® is a dark brown, non-transparent amorphous powder that is readily soluble in water. The active pharmaceutical ingredient of Injectafer® contains about 28% weight to weight (w/w) of iron, equivalent to about 53% w/w iron (III) hydroxide, about 37% w/w of ligand, ≤ S6% w/w of sodium chloride and ≤ S10% w/w of water [20].

B. Formulation Packaging, Labeling and Storage

Ferric carboxymaltose, an iron replacement product, is an iron carbohydrate complex with the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-O-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. It has a relative molecular weight of approximately 150,000 Da corresponding to the following empirical formula: $[FeO_x(OH)_y(H_2O)_z]_n$ $[\{(C_6H_{10}O_5)_m$ $(C_6H_{12}O_7)\}_l]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$ (l represents the mean branching degree of the ligand)[20].

Injectafer will be supplied as 15 mL vials, containing 750 mg of iron as 5% w/v iron solution in water for injection.

The dosage of Injectafer® is expressed in mg of elemental iron. Each mL of Injectafer® contains 50 mg of elemental iron. Injectafer® is intended for intravenous (IV) administration, either as a slow IV push or by IV infusion. When administered as a slow IV push, Injectafer® can be injected without dilution at a rate of 100 mg/minute. When

administered as an infusion, up to 750 mg of Injectafer® is diluted in no more than 250 mg of sterile 0.9% weight to volume (w/v) sodium chloride, such that the concentration of the infusion is not less than 2 mg of iron/mL and administered over 15 minutes. No other IV dilution solutions should be used and no other therapeutic agent should be added, as there is a potential for interaction.

All IV study drugs will be supplied by Luitpold Pharmaceuticals, Inc. They should be kept in a secure place at the investigational site, and stored at room temperature (see: USP). The study medication should not be frozen. **Vials may not be used for more than 1 dose or for more than 1 subject.**

C. Drug Accountability
Ferric Carboxymaltose (Injectafer®) will be provided by Luitpold Pharmaceuticals, Inc. from the commercial drug supply according to Good Manufacturing Practices (GMP).

It is the responsibility of the clinical investigator or trained designee to ensure that all study drug received at the site is inventoried and accounted for throughout the study by the designated personnel and is recorded in the inventory log kept with the pharmacy study documentation. The drug accountability will be verified by a trained designee upon completion of the study. Study drug will be stored in a secured area with restricted access to the dosing preparers only.

The clinical investigator or trained designee must store all study drugs pending reconciliation. The investigator agrees that study drug(s) will be dispensed by the investigator or sub-investigator(s) named on the Investigator Agreement or their qualified designees. The investigator, sub-investigators, or qualified designees also agree that the study drug(s) will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria and in accordance with the instructions provided in the pharmacy manual.

After study drug reconciliation, the clinical site may destroy used/unused study drug product locally in accordance with all applicable institutional standard operating procedures, local and federal laws. Documentation of such destruction must be recorded and provided Luitpold Pharmaceuticals, Inc.

D. Contraindications
Hypersensitivity to Injectafer® or any of its inactive components.

3.2 Oral Iron Supplement
Oral iron supplement like Ferrous sulphate, Ferrosequels will be used from the commercial source.

3.3 Other Drugs
TKIs like Imatinib/Gleevec, sunitinib are all commercially available drugs.

4.0 Patient Eligibility

Inclusion Criteria

1) GIST patients with IDA planned to start or receiving systemic therapy with TKIs

2) Evidence of iron deficiency anemia including, Hgb $\leq$ 11 g/dL, but $\geq$ 8 g/dL; and transferrin saturation (TSAT) < 20%.

3) No H/O allergic reaction to iron therapy.

4) No clinical signs active of bleeding.

5) Adequate hematologic (ANC > 1500/mm^3, platelet count > 100,000/mm^3), renal (serum creatinine < 1.5mg/dL), hepatic (serum bilirubin count < 1.5 x normal and SGOT or SGPT < 3 x normal) functions.

6) Patients must have Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 2.

7) Signed informed consent to the study.

8) Male and Females of child bearing potential must use acceptable methods of birth control which include oral contraceptives, spermicide with either a condom, diaphragm or cervical cap, use of an intrauterine device (IUD) or abstinence.

9) Patients are required to read and understand English to comply with protocol requirements.

10) Age $\geq$18 years old.

11) Life expectancy of at least 6 months.

Exclusion Criteria

1) Pregnant or lactating women.

2) Patients with any co-morbid condition which renders patients at high risk of treatment complication.

3) Patient has uncontrolled angina, congestive heart failure (New York Heart Association > class II or known ejection fraction < 40%), uncontrolled cardiac arrhythmia or hypertension, or acute myocardial infarction within 3 months.

4) Patient has an active seizure disorder. (Patients with a previous history of seizure disorders will be eligible for the study, if they have had no evidence of seizure activity, and they have been free of antiseizure medication for the previous 5 years).

5) Psychological, social, familial, or geographical reasons that would prevent scheduled visits and follow-up.

6) Prior surgery or radiotherapy (RT) within 2 weeks of study entry.

7) Known hypersensitivity reaction to any component of ferric carboxymaltose.

8) Any anemia treatment within 4 weeks before inclusion (oral iron, IV iron,

or erythropoiesis-stimulating agents), or transfusion of PRBCs in 2 weeks.

9) Hemochromatosis or other iron storage disorders.

10) Known positive hepatitis with evidence of active disease.

11) Patients with overt bleeding.

12) Ferritin $\geq$ 800 ng/mL.

5.0 Treatment Plan

5.1 Study Drug Treatment

This is an open label, randomized, phase II trial. Approximately 50 evaluable subjects will be randomly assigned to arm A and arm B (1:1).
Prior to randomization, all patients will be stratified into < 10g/dL vs. $\geq$10g/dL.

Treatment Plan:
Fifty patients with GIST will be randomized 1:1 into two treatment arms; total 25 patients in each of the two arms:

Arm A/ investigational arm: all subjects (n=25) will receive 2 doses of Injectafer® at15 mg/kg for a maximum single dose of 750 mg, given 7 days apart for a total of up to 1500 mg. The first IV infusion will be given prior to starting systemic therapy. The dose will be repeated 1 week later. It will be diluted in no more than 250 mL of normal saline and infused over 15 minutes.

Arm B/control arm: all patients (n=25) will receive oral iron (dose equivalent of 150-200 mg of elemental iron/day) supplement daily (such as Ferrosequels, BID, or ferrous sulphate, TID) for 3 months. Different iron preparation can be used based on patient's tolerance/preference.

5.2 Chemotherapy
Standard treatment for GIST with TKI-based therapy.

5.3 Duration of Therapy:
Patients can receive 2 doses of Injectafer® IV, given 7 days apart for a total of up to 1500 mg, or oral iron supplement e.g. Ferrosequels, BID, or ferrous sulphate, TID for 3 months, whichever arm they were assigned originally. If the patient on arm B does not tolerate oral preparations (even one dose of oral iron per day), then the patient can come off the protocol and receive IV iron as per standard of care.

6.0 Pretreatment Evaluation

- Standard History and Physical examination including weight and height and performance status (appendix D)
- Laboratory studies will include a CBC with differential, and platelet count, electrolytes and serum chemistries.
- Serum beta hCG or urinary pregnancy test (when indicated).
- All screening labs/pretreatment evaluations can be done within 1 week before registration.

7.0 Evaluation During Study

- Interim History and Physical examination including weight will be done before and after 3 months of the initiation of treatment.
- CBC differential and platelet counts will be monitored at least once a week for 3 months.
- Serum electrolytes and chemistries will be performed prior to and as frequently as needed during the treatment.
- Serum iron, serum ferritin, and total iron binding capacity (TIBC),and percentage serum transferrin saturation (TSAT) will be done at baseline, and every month for 3 months and then at 6 months.
- Patients will report the FACT-Fatigue and energy score at baseline and every month for 3 months and then at 6 months. In addition, patients will continue to report on daily symptom record diary the adverse events for 3 months [24].
- Management of hypersensitivity to the study drug: Patients with allergic reactions can be symptomatically managed. All patients with grade 4 hypersensitivity reactions (anaphylaxis) will be removed from the study.

8.0 End of Study/Early Withdrawal

Standard History and Physical examination including weight will be documented. Laboratory studies will include a CBC with differential, and platelet count.

9.0 Criteria for Response

9.1 Response

All patients who receive one dose of study drugs under this protocol will be evaluable for toxicity.All patients randomized will be considered evaluable for response in the intent-to-treat analysis.

Efficacy assessments will include:
- Hemoglobin, TSAT, and other iron panel test measures
- Patient reported outcomes questionnaires (FACT-Fatigue)
- The use (or lack of use) of other therapies for anemia (eg, RBC or whole blood transfusions, ESA, or both)

9.2 Response will be defined as proportion of achieving an increase in hemoglobin at any time from baseline to end of 3 months, as described below:

Complete response (CR): increase in HGB $\geq$2.0 g/dL above baseline, and/ or transfusion free.
Partial response (PR): increase in HGB ($\geq$1g/dL-2g/dL) above baseline
Minor response (MR): increase in HGB ($\geq$ 0.5 g/dL-1g/dL) above baseline

9.3 Toxicity: Toxicities will be graded using the Common Terminology Criteria for Adverse Events v4.03 – CTCAE (see Appendix C). Uncomplicated, severe, or life threatening neutropenia and thrombocytopenia are expected toxicities of the systemic therapy and as such will not be collected as adverse events in this study since the data is already captured through the CORe.

10.0 Criteria for Discontinuation from Treatment

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing treatment include the following:

- Serious or life-threatening adverse event
- Risk to patients as judged by the Investigator and/or Sponsor
- Severe noncompliance with protocol as defined by not receiving at least 70% of the planned treatment (judged by the Investigator and/or Sponsor).
- Request of the patient
- Patient becomes pregnant
- Progressive disease
- Investigator becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues

10.1 Discontinuation from Study

Patients who discontinue from treatment will continue to receive follow-up assessments as part of the study unless they are discontinued from study by one of the following events:

- Withdrawal of consent
- Loss to follow-up
- Death from any cause
- Termination of the study

11.0 Statistical Consideration and Sample Size

Statistical Considerations and Analysis

This study will assess the efficacy of IV Injectafer in improving HGB level in GIST patients planned to receive or receiving systemic therapy and presenting with anemia.

Design and Sample Size/Power

This is a randomized, open label, 2-arm trial of 2-dose IV Injectafer in patients with GIST planned to receive or receiving systemic therapy and presenting with anemia. Arm A patients will receive 2 doses of IV Injectafer over 15 min infusion (prior to start systemic therapy and another same dose 1 week later). Arm B patients will receive oral iron supplement (such as Ferrosequels BID, or ferrous sulphate TID) for 3 months. The primary objective is to evaluate the efficacy of IV Injectafer in patients with GIST planned to receive or receiving systemic therapy and presenting with anemia as compared to the effect of oral iron supplement.

A patient will be considered as to have a complete response (CR) if his/her HGB level increase $\geq$ 2 g/dL from baseline to any time during 3 months following initiation of the study drug, and/or transfusion free. The primary endpoint is CR rate in 3 months. A total of 50 patients, 25 in each arm, will provide the study 93% power to detect the differences of response between the two arms using a Chi-square test with a 0.05 two-sided significance level when the respective CR rates are 75% (6/8) and 28.6% (8/28) in Arm A, and B (according to our clinical experience). All patients who are randomized will be evaluable for response in the intent-to-treat analysis. nQuery 7.0 was used for the sample size or power calculation.

Analysis Plans

Patients' demographic and clinical characteristics at baseline will be summarized using descriptive statistics such as mean, standard deviation, median, interquartile range (IQR), frequency where appropriate. We will apply Student t-test/Wilcoxon test and Kruskal-Wallis test/ANOVA to compare continuous variables between different patient group, and the chi-square test or the Fisher's exact test to assess the association between two categorical variables [25].

For the analysis of the primary endpoint, Chi-square test will be used to test the difference of CR rates between the two arms. CR rates along with their 95% confidence intervals (CIs) will be estimated by study arm. We will use logistic regression model [26] to assess the effect of patient specific covariates, such as treatment group, gender, etc. on the complete response.

Toxicity data will be summarized by frequency tables for all patients and by treatment arm. For the efficacy endpoint, intent-to-treat analysis will be applied to all randomized patients. For the toxicity endpoint, per-treated analysis will be used to include any patient who received one dose of the treatment regardless of the eligibility nor the duration or dose of the treatment received.

We will analyze patient reported outcomes using standard statistical methods for analyzing continuous data, discrete data, and survival data whenever appropriate. Additional analyses in furtherance of the stated objectives may be conducted as warranted.

Randomization
Stratified randomization will be carried out via CORe. The stratification factor is baseline hemoglobin level <10 g/dL vs ≥10 g/dL.

12.0 Data and Protocol Management

Data will be collected and entered in CORe by the research staff assigned to the study.

12.1 Good Clinical Practice
The conduct of the study will conform to the recommendations for clinical studies in human subjects as per the guidelines on “Good Clinical Practice”, [21 CFR Part 312 and ICH guidelines].

13.0 Serious Adverse Events and Reporting Requirement

13.1 Adverse Events

An adverse event (AE) is any new, undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs during or after treatment, whether or not considered to be product related. Therefore, adverse events are treatment-emergent signs or symptoms.

For the purposes of this study, non-serious anemia (Hgb or Hct below the normal range or worsened from baseline) or iron deficiency (iron indices below the normal range or worsened from baseline) will not be considered adverse events. Anemia or iron deficiency will be considered end points if an intervention is required.

In this study, the following adverse effects are expected and will not be reported. They will be summarized in the updated and final analysis. Myelosuppression and its associated complications are part of the treatment of sarcoma. Therefore, low blood counts and related complications such as infections, bleeding and hospitalizations due to myelosuppression will not be reported as severe adverse drug reactions related to Injectafer.

AEs will be collected from the time of informed consent to 30 days after last study drug administration. AEs that occur before the first study drug administration, concomitant illnesses, which existed before study entry, but did not worsen during the treatment period and any pre-existing conditions are known as "pre-treatment AEs" and by definition are "unrelated" to study drug. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, electrocardiograms [ECG], reported by patient), must be documented.

Each AE will be assessed by the Investigator with regard to the intensity.
Intensity should be assessed in accordance with the Common Terminology Criteria for Adverse Events (CTCAE v.4.03, Appendix C). Attribution of AE to study treatment will be recorded as follows:

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 subject'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 subject's clinical condition, other concomitant events).
- PROBABLE There *is evidence* to suggest a causal relationship, and the influence of other factors is *unlikely*.

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

***** For the purposes of this trial, "study drug" is defined as: **Injectafer, oral iron supplement**.

Follow-up of Adverse Events
All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to

baseline or stabilized at a level acceptable to the Investigator, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has expired.

For the purposes of this study, non-serious anemia (Hgb or Hct below the normal range or worsened from baseline) or iron deficiency (iron indices below the normal range or worsened from baseline) will not be considered adverse events. Anemia or iron deficiency will be considered end points if an intervention is required.

13.2 Serious Adverse Events

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

- **Death**
- **Life-Threatening:** The subject 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 subject'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 subject'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 subject 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 subject. 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 serious adverse events 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

All serious adverse events will be reported to the University of Texas M.D. Anderson Cancer Center IRB within 24 hours of knowledge of the event.

13.3 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 adverse events, 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 adverse effect 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

14.0 Monitoring Plan

All protocol participants will be registered in CORe. The principal investigator will be responsible for submitting SAE's to the IRB. SAE's will be submitted to OPR and entered into CORe.

15. References

1. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer. 2004;40:2293-306.
2. Dicato M, Plawny L, Diederich M. Anemia in cancer. Ann Oncol. 2010; Oct;21 Suppl 7:vii167-72.
3. Knight K, Wade S, Balducci L. Prevalence and outcomes of anaemia in cancer: a systematic review of the literature. Am J Med. 2004; 116 Suppl 7A: 11S–26S.
4. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. Semin Oncol. 1998;25:43-6.
5. Gilreath JA, Stenehjem DD, and Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Heamtol. 2014;89:203-12.
6. Camaschella, C. Iron-Deficiency Anemia. N Engl J Med 2015; 372:1832-1843
7. Ludwig H, Muldur E, Endler G, et al. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status, and anemia. Ann Oncol. 2013;24:1886-92.
8. Aapro M, Osterborg A, Gascon P, et al. Prevalence and management of cancer-related anaemia, iron deficiency, and the specific role of i.v. iron. Ann Oncol. 2012; 23:1954-62.
9. Kim Y, Kim S, Yoon B, et al. Effect of intravenously administered iron sucrose on the prevention of anemia in the cervical cancer patients treated with concurrent chemoradiotherapy. Gyn Oncol. 2007;105:199-204.
10. Dangsuwan P, Manchana T. Blood transfusion reduction with intravenous iron in gynecologic cancer patients receiving chemotherapy. Gyn Oncol. 2010;116:522-5.
11. Søreide K, Sandvik OM, Søreide JA, et al. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. Cancer Epidemiol. 2016; 40:39-46.
12. Rammohan A1, Sathyanesan J, Rajendran K, et al. A gist of gastrointestinal stromal tumors: A review. World J Gastrointest Oncol. 2013; 5(6):102-12.
13. https://liferaftgroup.org/2012/12/anemia-has-multiple-causes-and-treatments/
14. Duffaud F1, Even C, Ray-Coquard I, et al. Recombinant erythropoietin for the anaemia of patients with advanced Gastrointestinal Stromal Tumours (GIST) receiving imatinib: an active agent only in non progressive patients. Clin Sarcoma Res. 2012; 2(1):11.
15. Lopez A, Cacoub P, Macdougall IC, et al. Iron deficiency anaemia. Lancet. 2015; pii: S0140-6736(15)60865-0.
16. Vadhan-Raj S, Strauss W, Ford D, et al. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. Am J Hematol. 2014; 89(1):7-12.
17. Vadhan-Raj S, Ford DC, Dahl NV, et al. Safety and efficacy of ferumoxytol for the episodic treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy: Results of a phase III, open-label, 6-month extension study. Am J Hematol. 2016; 91(2):E3-5.

18.http://www.centerwatch.com/drug-information/fda-approved drugs/drug/1280/injectafer-ferric-carboxymaltose-injection
19.Lyseng-Williamson KA, Keating GM. Ferric Carboxymaltose: A Review of its Use in Iron-Deficiency Anaemia. Drugs. 2009; 69 (6): 739-756
20. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203565s000lbl.pdf
21. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4337b1-01-fda.pdf
22. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. Nephrol Dial Transplant. 2014;54:306-15.
23. Onken JE, Bregman DB, Harrington RA, et al. A multicenter, randomized, active controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia.Transfusion. 2014;29:833-42.
24. Jean-Pierre P, Figueroa-Moseley CD, Kohli S, Fiscella K, et al. Assessment of cancer-related fatigue: implications for clinical diagnosis and treatment. Oncologist. 2007;12 Suppl 1:11-21.
25. Woolson, RF and Calrke, WR. Statistical Methods for the Analysis of Biomedical Data. 2nd Edition, John Wiley & Sons, New York, 2000.
26. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd Edition, Wiley, New York, 2000.
27. Henry D, Dahl NV, Auerbach M, Tchekmedyian, Laufman LR. Intravenous Ferric Gluconate significantly improves response to Epoietin Alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. The Oncologist 207; 12:231-242.