**LUITPOLD PHARMACEUTICALS, INC.**

**PROTOCOL**

**No. 1VIT13036**

**IND #: 63,243**

# A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Ferric Carboxymaltose in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA)

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**Protocol Date: 27 March 2014**

**Amendment I Date: 29 July 2014**

**Amendment II Date: 08 October 2014**

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## Study Synopsis

## Protocol No. 1VIT13036

**Title:** A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Ferric Carboxymaltose in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA).

**Drug:** Ferric Carboxymaltose

**Objectives:** The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Ferric Carboxymaltose for the pediatric population suffering from iron deficiency (ID) with anemia.

**Study Design:** This is a Phase II, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Ferric Carboxymaltose dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Ferric Carboxymaltose®.

**Treatment**

Cohort 1: 16 subjects will be treated with Ferric Carboxymaltose at 7.5 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Ferric Carboxymaltose at 15 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving an erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Ferric Carboxymaltose.
2. Subject previously randomized and treated in this study or any other clinical study of Ferric Carboxymaltose (FCM or VIT-45).
3. Body mass index (BMI) $\leq 5^{th}$ percentile for age (see APPENDIX 2)
4. Male or Female subject 1 year of age weighing < 12kg.
5. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
6. Chronic kidney disease subjects on hemodialysis.
7. Screening Ferritin level > 300ng/mL
8. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
9. Any active infection.
10. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
11. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
12. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subjects who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

**Subject Assessments:**

All subjects that provide informed consent / assent will enter a screening period up to 14 days prior to Day 0. During this time subjects will be evaluated to insure they meet the study entry criteria. Subjects will have vital signs, medical history review and laboratory samples to include hematology, chemistries and iron indices. Once it has been determined the subject qualifies for participation the subject will be scheduled to return to the clinic 1 day prior to Day 0 (Day -1) at which time additional blood samples will be taken (8am, 12pm and 8pm) to characterize the subjects iron profile.

Blood samples for PK/PD will also be assessed immediately prior to Ferric Carboxymaltose dosing on Day 0, at 1, 2, 6, 12, 24, 48 hours and at 72 hours.

Safety assessments, including vital signs and adverse events, will be assessed starting on Day 0 at the time of Ferric Carboxymaltose dosing through Day 35.

**Erythropoietin**
**Dosage:**

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

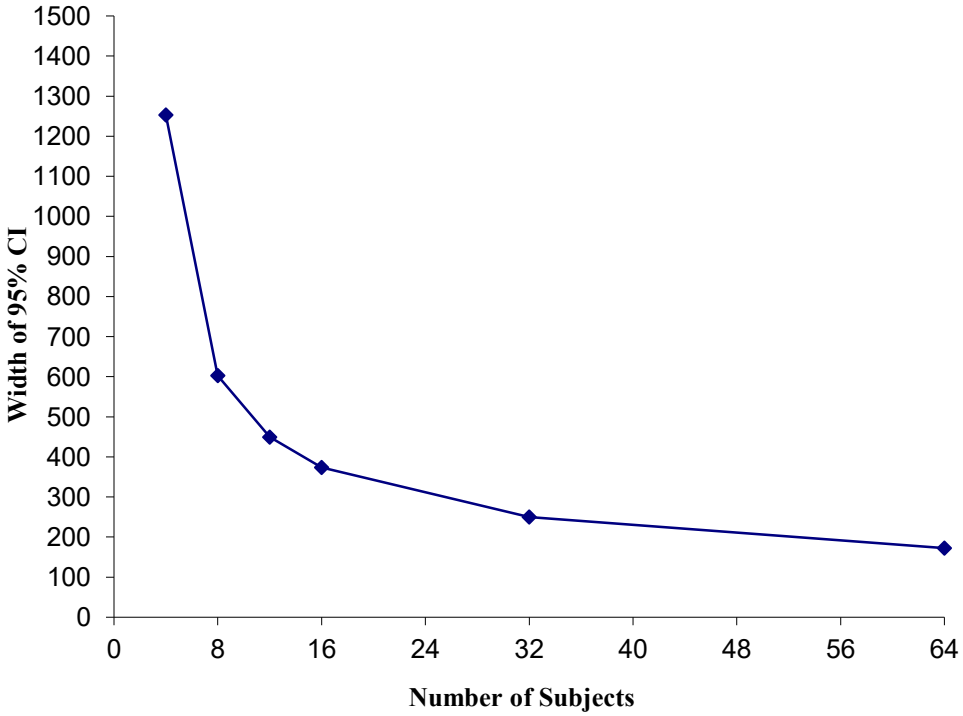
**Study Duration per subject:** up to 9 weeks

**Number of Subjects:** 32 subjects

**Sites:** Approximately 10

**Sample Size:**

Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients.




Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally distributed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system.

## CONTACT PERSON FOR THE STUDY

For study related questions please contact:

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| BP | Blood Pressure |
| BW | Body Weight |
| CI | confidence interval |
| CKD | Chronic Kidney Disease |
| conc. | concentration |
| CTCAE | Common Terminology Criteria for Adverse Event |
| dL | Deciliter |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| e.g. | for example |
| ESA | Erythropoiesis stimulating agent |
| FDA | Food and Drug Administration |
| Fe | Iron |
| g | Gram |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| Hct | Hematocrit |
| Hgb | Hemoglobin |
| HMW | high molecular weight |
| IBD | Inflammatory Bowel Diease |
| ICH | International Conference on Harmonisation |
| IDA | Iron Deficiency Anemia |
| i.e. | that is/ such that |
| IRB | Institutional Review Board |
| IV | Intravenous |
| IVP | Intravenous injection (push) |
| kg | Kilogram |
| L | Liter |
| LMW | low molecular weight |
| LOS | length of stay |
| MedDRA | Medical dictionary for regulatory activities |
| mg | Milligram |
| mL | Milliliter |
| ng | Nanogram |
| PET | positron emission tomography |
| p.o. | by mouth or orally |
| RES | Reticuloendothelial system |
| SAE | Serious adverse event |
| $t_{1/2}$ | Terminal half-life |
| t.i.d. | three times a day |
| TSAT | Transferrin Saturation |
| US | United States |
| vs | Versus |
| w/v | weight / volume |

# 1.0 INTRODUCTION

## 1.1 Treatment of Iron Deficiency Anemia

Iron deficiency anemia ("IDA") remains the most common nutritional deficiency in children in the United States. Rapid growth, insufficient dietary intake, and limited absorption of dietary iron combine to place children at increased risk for iron deficiency. Iron deficiency may contribute significantly to anemia due to malabsorption, gastrointestinal blood loss, or iatrogenically due to repeated blood samplings. As a result of severe digestive tract disorders, some children are unable to tolerate oral iron supplementation or are unresponsive to it.[1] Anemia may also decrease survival rates in patients (both adults and children) with chronic renal impairment where it is a commonly encountered problem[2;3] In addition, anemia is a commonly encountered manifestation of pediatric inflammatory bowel disease which is associated with a decrease in the quality of life and increased hospitalization.

Non-hematologic consequences of iron deficiency include poor weight gain, anorexia, irritability, decreased attention span, exercise intolerance and decreased physical activity. [4] However, IDA in infants and toddlers is associated with long-lasting diminished mental, motor, and behavioral functioning. Although the exact relationship between iron deficiency anemia and the developmental effects is not well understood, it appears that these effects do not occur until iron deficiency becomes severe and chronic enough to produce anemia. [5]

Options for correcting iron deficiency include both oral and parenteral formulations. As previously described, some children are unable to tolerate or are non-responsive to oral iron. Blood transfusion is an option to treat anemia and restore iron requirements, but the potential risk of blood-transmitted virus infection limits its use to severe and badly tolerated anemia. In view of the limitations associated with oral iron or blood transfusions, intravenous administration is an important option.

Multiple parenteral iron products are available. These vary in complex types which impacts the total amount of iron that may be administered in a single administration. Numerous other differences differentiate the products; however, all appear to effectively release iron post administration and restore the deficit of the patient. There are numerous studies with iron sucrose injection (Venofer®) that have been performed in the pediatric population [6-8]. Iron doses have varied in the studies with demonstrated efficacy and safety in doses up to 7mg iron/kg or 200mg given in time frames of 3 min, which was shown to be beneficial to both the child and health care facility[6].

Ferric Carboxymaltose has been characterized as a robust and strong type iron complex (Type 1) with a molecular mass of about 150,000 Daltons (Da). The solution is a dark brown color with a near neutral pH (5.0 to 7.0) and a physiological osmolarity permitting administration of higher single doses in short time periods. Although no interventional studies have been conducted with Ferric Carboxymaltose in the pediatric population to date, the product has been used in clinical practice in markets where it is currently approved for adults to aid correction of iron deficiency within the pediatric gastroenterological setting. A non-interventional/retrospective observational data collection has identified in 79 patient's aged 2 to 18 years with a mean age of 12.7 years. In

these subjects, Ferric Carboxymaltose showed efficacy with regard to hemoglobin, ferritin, and TSAT as well as safety and tolerability (manuscript in preparation).

Therefore, the proposed studies will assess higher single doses (i.e., 7.5 mg/kg and 15 mg/kg) than those used with currently available parenteral iron preparations in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population. The higher single doses permit fewer overall injections/infusions and may ultimately permit fewer visits to the treating facilities positively impacting both the child and family as well as health care system.

## 1.2 Ferric Carboxymaltose

### 1.2.1 Key features of Ferric Carboxymaltose

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, Ferric Carboxymaltose is mainly found in the liver (RES), 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 Ferric Carboxymaltose is metabolized by the glycolytic pathway.

### 1.2.2 Ferric Carboxymaltose versus Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various parenteral iron preparations available [(3)]. However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted their use. Ferric Carboxymaltose offers significant advantages compared to other available intravenous iron preparations.

Iron dextran, the first parenteral iron product available in the US, has been associated with an incidence of anaphylaxis/anaphylactoid reactions (i.e., dyspnea, wheezing, hypotension, urticaria, angioedema) as high as 1.7% [(6)]. Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran. The high incidence of anaphylaxis/anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Although some have suggested that high molecular weight (HMW) iron dextran is associated with a higher rate of life threatening adverse events and anaphylactic reactions in comparison to low molecular weight (LMW) iron dextran, the US Food and Drug Administration was unable to find a clear difference after an examination of post-marketing data, clinical trial data, death certificates, and emergency room diagnoses [(7)]. Iron dextran is limited to second line therapy for treatment of iron deficiency.

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. 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, Ferric Carboxymaltose 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[11] (data on file ). These characteristics of Ferric Carboxymaltose 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) 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 (see Ferumoxytol PI).

**Table 1.2.2.1 Administration of at least 1500 mg of Intravenous Iron with Currently Available Iron Preparations and Ferric Carboxymaltose**

| 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 | 300mg | 1.5 hours | 5 |
| Iron sucrose | No | 400 mg | 2.5 hours | 4 |
| ferumoxytol | No | 510 mg | < 1 minute | 3 |
| Ferric Carboxymaltose | 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 countries outside of the US; 750 mg maximum is the U.S. FDA approved dose

The larger Ferric Carboxymaltose and ferumoxytol doses result in less frequent administration of intravenous iron that should benefit, in particular, severely iron deficient and anemic populations. To be treated with currently available intravenous iron agents, the average inflammatory bowel disease, postpartum, heavy uterine bleeding and non-dialysis dependent patient would require an initial test dose, followed by 15 doses of iron dextran as labeled, each accompanied by personnel equipped and trained for resuscitation of anaphylaxis; 12 doses of ferric gluconate; or either 8 doses of iron sucrose (with 5 minute infusion time) or 5 / 4 doses of iron sucrose by prolonged (1.5 to 2.5 hours) intravenous infusion. Ferric gluconate and iron sucrose are not approved by the FDA for the treatment of IDA in non chronic kidney disease populations and iron dextran is only approved as second line therapy for treatment of iron deficiency. In contrast, most patients treated with Ferric Carboxymaltose would require 2 doses administered over 8 to15 minutes one week apart.

### 1.2.3 Ferric Carboxymaltose Human Experience

The Ferric Carboxymaltose development program demonstrated the safety and effectiveness of intravenous Ferric Carboxymaltose in the treatment of IDA. Clinical data are currently available from 20 Phase 2 and 3 studies including 5,799 patients, with IDA or IDA associated with CKD, who received Ferric Carboxymaltose.

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

Phase III studies demonstrated the effectiveness of Ferric Carboxymaltose in treating IDA secondary to inflammatory bowel disease, heavy uterine bleeding, chronic kidney disease (hemodialysis and non-hemodialysis) and the postpartum state. Clinically meaningful increases in hemoglobin, 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 chronic kidney disease. A head to head comparison of Ferric Carboxymaltose to Venofer (Iron sucrose) in over 2,500 subjects with non-dialysis dependent CKD and elevated risk of cardiovascular disease according to the Framingham criteria demonstrated that the recommended dose of Ferric Carboxymaltose, 750 mg x 2 (1500 mg total) had superior efficacy to the labeled dose of Iron sucrose (200 mg x 5 [1000 mg total]) with regard to hemoglobin elevation and had a similar cardiovascular (and overall) safety profile, based in part on an independently adjudicated composite cardiovascular safety endpoint [(8)] .

Important details of pre- and clinical safety and efficacy can be found in the Investigator's Brochure. Ferric carboxymaltose received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) approval on June 15, 2007 for the use of Ferric Carboxymaltose (EU Trade name: Ferinject) in 18 EU (European Union) countries and later in Switzerland. Ferric carboxymaltose was first approved as a prescription only medicine on July 6, 2007 in The Netherlands. Up until now, Ferric Carboxymaltose has received regulatory approval for marketing authorization in 58 countries worldwide: Argentina, Australia, Austria, Bangladesh, Belgium, Bolivia, Brazil, Bulgaria, Chile, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, Iceland, India, Iran, Ireland, Israel, Italy, Kazakhstan, Kuwait, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, New Zealand, Norway, Pakistan, Peru, Poland, Portugal, Romania, Russia, Singapore, Slovenia, Slovak Republic, South Korea, Spain, Sweden, Switzerland, The Netherlands, Turkey, Ukraine, and United Kingdom. Ferric Carboxymaltose received approved from the Food and Drug Administration (FDA) on July 25, 2013 for marketing in the United States.

## 2.0 MAIN TRIAL OBJECTIVE

The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Ferric Carboxymaltose for the pediatric population suffering from iron deficiency (ID) with anemia.

# 3.0 OVERALL STUDY DESIGN AND RATIONALE

## 3.1 Trial Design

This is a phase II, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Ferric Carboxymaltose dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Ferric Carboxymaltose.

Cohort 1: 16 subjects will be treated with Ferric Carboxymaltose at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Ferric Carboxymaltose at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

## 3.2 Rationale

### 3.2.1 Rationale for Trial Design

Ferric Carboxymaltose is a non-dextran IV iron recently approved by the United States Food and Drug Administration (FDA). This trial is designed to assess the single doses (i.e., 7.5 mg iron/kg and 15 mg iron/kg) in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population.

### 3.2.2 Rationale for open label design

The open-label, single arm trial design is considered appropriate because a control group is not required to estimate the PK/PD profile of Ferric Carboxymaltose. The risk from exposure to another form of IV iron is not offset by the minimal scientific benefit.

### 3.2.3. Schedule of Events

| Visit Day | Screening Period (Up to 14 Days) | Day -1 | Day 0 | 24 and 48 hours post dosing | 72 hours post dosing | Day 14 (week 2) | Day 28 (week 4) | Day 35 (week 5) |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Assess entry criteria | X | | X | | | | | |
| EDC | X | | X | | | | | X |
| Medical History | X | | X | | | | | |
| Physical Exam[1] | | | X | | | | | X |
| Vital Signs[6] | X | | X | | X | X | X | X |
| Height / Weight | | | X | | | | | |
| PK/PD Samples | | X[2] | X[3] | X[4] | X[4] | | | |
| Hematology, Chemistry and Iron Indices | X | | | | X | X | X | X |
| Serum pregnancy test | X | | | | | | | |
| Concomitant Medications | X | | X | | X | X | X | X |
| ESA Stability | X | | X | | X | X | X | X |
| Adverse Event Assessments[5] | | | X | X | X | X | X | X |
| Ferric Carboxymaltose | | | X | | | | | |

[1] Includes clinical assessment of skin, cardiovascular, pulmonary, abdominal, and central nervous system
[2] Blood samples drawn at 8am, 12pm and 8pm for subject iron profile
[3] Blood samples PK/PD should be taken prior to Ferric Carboxymaltose dosing and additional samples for PK/PD should be taken at 1, 2, 6 and 12 hours post dosing.
[4] Blood samples should be taken approximately the same time of day as the Day 0 samples were drawn
[5] Adverse event assessments starting at the time of Ferric Carboxymaltose dosing
[6] Sitting vital signs including blood pressure and heart rate should be collected immediately pre-dosing, immediately and 30 minutes post dosing. Body temperature will also be collected pre-dose only. Vital signs on non-dosing days include sitting heart rate and blood pressure only.

# 4.0 SUBJECT SELECTION

## 4.1 Number and Type of Subjects

Up to thirty two (32) subjects who have given written informed consent / assent along with parent or guardian's written informed consent with a diagnosis of iron deficiency anemia (IDA) who fulfill the inclusion criteria, do not meet any of the exclusion criteria will be registered to receive Ferric Carboxymaltose.

## 4.2 Screening Phase

Once a subject enters the screening phase, they will be assigned, via the Electronic Data Capture (EDC) system, a unique screening number. From the time of consent until the start of treatment of IV Ferric Carboxymaltose, the subject will not receive any form of iron outside of the study (intravenous or blood transfusion iron from 4 weeks prior to consent or oral iron including multivitamins with iron from time of consent).

If the subject does not qualify for study entry the subject should be entered into the EDC system as a screen failure. Subjects can be re-screened once, see section 6.2.

### 4.2.1 Entry Criteria

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving a erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial.

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Ferric Carboxymaltose.
2. Subject previously randomized and treated in this study or any other clinical study of Ferric Carboxymaltose (FCM, VIT-45).
3. Body mass index (BMI) ≤ 5$^{th}$ percentile for age (see APPENDIX 2)
4. Male or Female subject 1 year of age weighing < 12kg.
5. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
6. Chronic kidney disease subjects on hemodialysis.
7. Screening Ferritin level > 300 ng/mL.
8. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
9. Any active infection.

10. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
11. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
12. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subject who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

## 4.3 Subject Assignment and Registration Process

Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this 7 week study. Cohorts 1 and 2 will be enrolled and treated sequentially. Enrollment into Cohort 2 will not begin until all Cohort 1 subjects have completed 4 weeks of therapy and no safety issues with the administration of Ferric Carboxymaltose has been confirmed by the DSMB.

## 4.4 Withdrawal from Study

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

At the time of withdrawal, procedures for the Day 35 visit must be performed regardless of whether the subject has completed study drug treatment. In the event the subject has received any study drug; the subject should be contacted to assess adverse events 28 days post the last dose of Ferric Carboxymaltose, if possible.

In the event a subject withdraws without completing the full PK/PD sampling. Additional subjects may be enrolled to ensure adequate representations of the PK/PD parameters are available for analyses. Conditions for additional enrollment will be defined in more detail in the statistical analyses plan.

## 4.5 Intervention

Intervention is defined as follows:

- Increase in dose of erythropoietin for any reason (Day 0 thru Day 35).
- Blood transfusion.
- Use of IV iron outside of protocol.

- Use of oral iron outside the protocol.

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 subject should continue in the study as scheduled through Day 35.

## 5.0 STUDY DRUG

### 5.1 Formulation Packaging and Storage

All medication to be used in this study that has been supplied by Vifor Pharma Ltd. will have been prepared according to Good Manufacturing Practices (GMP).

Ferric Carboxymaltose (known in the EU as Ferinject®) will be supplied as 5% w/v (weight /volume) 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.

Study drug must be kept in a secure place at the investigational site, and stored at room temperature (see: USP). Ferric Carboxymaltose should not be frozen. **Vials may not be used for more than 1 dose or for more than 1 subject. All Ferric Carboxymaltose vials used and unused should be kept by the study staff.**

### 5.2 Drug Administration / Regimen

The Principal Investigator or designee will supervise administration of the study drug to subjects:

**Cohort 1**: 16 subjects will be treated with Ferric Carboxymaltose at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

**Cohort 2**: 16 subjects will be treated with Ferric Carboxymaltose at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

Ferric Carboxymaltose will be given on Day 0. It will be administered as either:

- An undiluted slow IV push at a rate of 100 mg/minute.
- Doses less than 100 mg should be given as a slow undiluted IV push within a minute.

## 5.3 IV Iron Precautions

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

- The subject 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 heart rate and blood pressure will be assessed pre-, immediately post, and 30 minutes post administration. If the subject 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 patients receiving IV iron therapies. Subjects 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 subjects 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 intravenous 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 Ferric Carboxymaltose. They will not allow Ferric Carboxymaltose 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 registered in the study, or to investigators not listed on the FDA 1572. When the study is completed, or if it is prematurely terminated, a final inventory of all clinical supplies must be compiled and the remainder of used and unused Ferric Carboxymaltose will be returned to Luitpold Pharmaceuticals, Inc. (or their designee). All data regarding Ferric Carboxymaltose must be recorded on the Drug Accountability Forms provided by the sponsor.

Investigators will keep adequate records of the administration and disposition of IV Ferric Carboxymaltose® used for patients selected for the trial.

## 5.5 Concomitant Medication

Concomitant medications along with their route of administration and duration must be recorded in the electronic case report form (eCRF) from 30 days prior to consent. **No additional iron preparations (IV iron from 4 weeks prior to consent or oral iron including multivitamins**

**with iron, from time of consent), will be allowed. No prophylactic medications may be administered prior to Ferric Carboxymaltose administration without prior approval from Luitpold Pharmaceuticals, Inc.**

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

## 6.0 STUDY PROCEDURES

### 6.1 Informed Consent

Prior to any study specific procedures, the investigator must explain to each subject 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 subject (who for this trial is 1 -17 years old) must assent, if appropriate and his/her legal guardian (who is above age of legal consent) voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The Code of Federal Regulations (CFR) is a codification of rules and regulations of the United States government. The subject's legal guardian will be given a copy of the signed consent form.

### 6.2 Screening (up to 14 days)

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

- Obtain screening number from EDC
- Medical history, including prior iron therapy use
- Vitals signs (including sitting heart rate and blood pressure)
- Hematology, Chemistries and iron indices
- Serum pregnancy test for female subjects of child bearing potential (negative results must be obtained prior to registering the subject for study drug dosing).
- Concomitant medications assessment
- ESA therapy stability ( if applicable)

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

## 6.3 Study Visits

### 6.3.1. Day (-1)

Once it's confirmed during the screening period that the subject continues meet the entry criteria all eligible subjects will return to the clinic on Day – 1, blood samples will be drawn at 8am, 12pm and 8pm to characterize the subject iron profile.

### 6.3.2 Day 0

On Day 0, prior Ferric Carboxymaltose dosing the following will occur:

- Re-verify the inclusion and exclusion criteria
- Update any relevant history
- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Height
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Log on to the EDC system and register subject for study drug dosing. The EDC system will assign the subject into Cohort 1 or 2 treatment group.

After assignment of the treatment group (Cohort 1 and 2) the following will occur:

- Blood samples for PK/PD before start of dose.
- Weight in kg without shoes
- Verify amount of single Ferric Carboxymaltose dose (7.5 or 15 mg/kg up to a maximum dose of 750 mg whichever is smaller).
- Document start and stop time of Ferric Carboxymaltose administration, the total dose administered.
- Obtain sitting heart rate and blood pressure immediately pre-dose, immediately post-dose, and 30 minutes post Ferric Carboxymaltose administration. Body temperature taken pre-dose
- Adverse event assessment (starting at beginning of Ferric Carboxymaltose injection).

Blood samples for PK/PD will be drawn at 1, 2, 6 and 12 hours post the Day 0 Ferric Carboxymaltose dose.

### 6.3.2. Days 1 and 2 (24 and 48 hour)

- Blood samples for PK/PD
- Adverse events assessment

### 6.3.3. 72 hour, and Days 14 and 28 (weeks 2 and 4)

- Blood samples for PK/PD (72 hour visit only)
- Vital signs
- Hematology, Chemistry and iron indices
- Adverse events assessment
- Concomitant medications assessment
- ESA stability/use ( if applicable)

### 6.3.4. Day 35 (week 5) End of Study

- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Vitals signs
- hematology, chemistries and iron indices
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Adverse events assessment
- Log onto EDC and enter subject as complete

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

### 6.3.5. Pharmacokinetics and Pharmacodynamics (PK/PD)

Blood samples will be collected for PK/PD assessment pre-dose and at 1, 2, 6, 12, 24, 48 and 72 hours post dose. Blood samples should be taken at approximately the same time of day as the initial pre-dose sample on Day 0.

Prior to Day 0, subjects will return to the clinic on Day -1 at which time blood samples will be drawn at 8am, 12pm and 8pm to characterize the subjects specific iron profile.

Total blood volume (regular hematology, chemistry, iron indices and PK/PD) collected per day and during the 35 Day study is provided below:

| | Screening | Day (-1) | Day 0 | 24hr | 48hr | 72hr | Day14 | Day 28 | Day 35 | **Total Blood Volume** |
|---|---|---|---|---|---|---|---|---|---|---|
| Hem/Chem/II (4.5ml) | 4.5ml | | | | | 4.5ml | 4.5ml | 4.5ml | 4.5ml | |
| PK/PD (2ml) | | 6ml | 10ml | 2ml | 2ml | 2ml | | | | |
| **TOTAL** | **4.5ml** | **6ml** | **10ml** | **2ml** | **2ml** | **6.5ml** | **4.5ml** | **4.5ml** | **4.5ml** | **44.5ml / approx. 9.03 tsps.*** |

***4.93 mL = 1 tsp.**

## 6.4 Central Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. All serum laboratory testing will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 35 laboratory, this laboratory may be obtained after notification of the Sponsor. The laboratory assessments will be determined as listed in Section 3.2.3.

| | |
|---|---|
| Hematology: | Hb, 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, bicarbonate and magnesium |
| Iron indices: | serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT) |
| Other: | Serum pregnancy test |

# 7.0 ASSESSMENT OF SAFETY

## 7.1 Adverse Events

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

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

To quantify the severity of adverse events, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version 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 Ferric Carboxymaltose through the completion of the study Day 35. AE's will be captured 28 days post the last dose of Ferric Carboxymaltose for subjects who early terminate from the trial. This can be completed via a phone call. All ongoing adverse events related to Ferric Carboxymaltose 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 Ferric Carboxymaltose 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*.

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

## 7.2 Reporting of Adverse Events

Adverse experiences will be elicited by nonspecific questions such as “Have you noticed any problems?” Subjects will be encouraged to report adverse events at their onset.
Any adverse experience spontaneously reported by, elicited from the subject 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 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:** All SAEs will be reported from the initial treatment with Ferric Carboxymaltose through the completion of the study Day 35. SAEs will be captured 28 days post the last dose of Ferric Carboxymaltose for subjects who early terminate from the trial. This can be completed via a phone call. 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 lead to prolongation of hospital stay should not be considered SAE’s. 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 (within 24 hours of learning of the event) 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 IRB / Ethics Committee per their reporting guidelines.

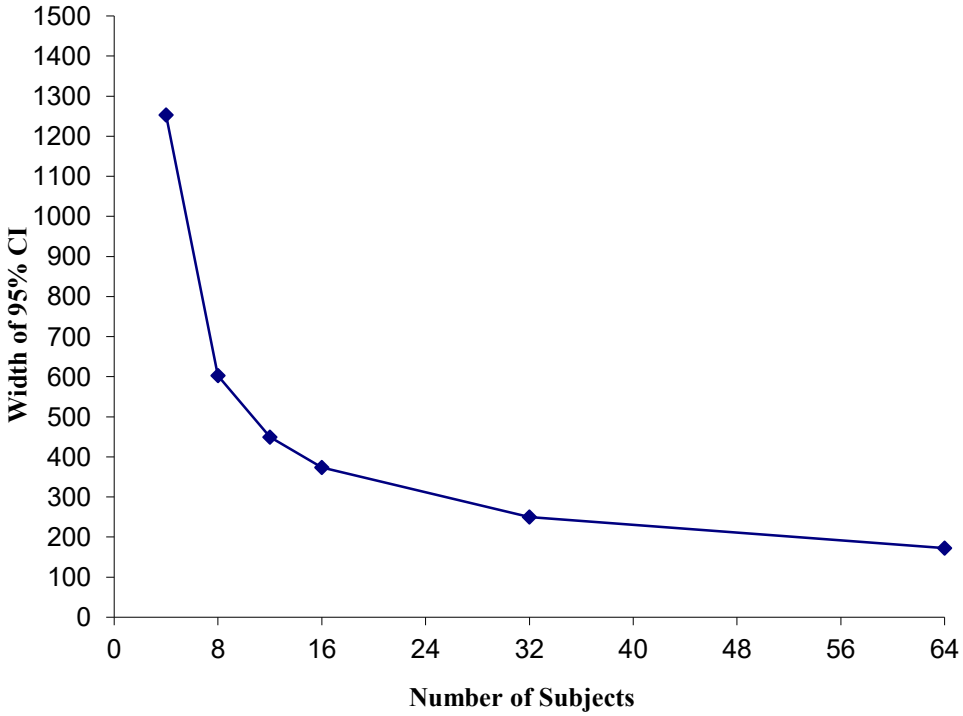
The responsible investigator must determine whether the degree of any untoward event warrants removal of any subject from the study. He/she should, in any case, institute appropriate diagnostic and/or therapeutic measures, and keep the subject under observation for as long as is medically indicated.

## 8.0 STATISTICS

No hypothesis testing will be performed for this study.

### 8.1 Sample Size

Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients.




Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally disturbed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system.

## 8.2 Analysis Populations

There will be 2 analysis populations:

- Safety population: Includes all subjects who receive Ferric Carboxymaltose.
- PK/PD population: Includes all subjects in the safety population who have evaluable iron profiles and no protocol violation that could affect the PK/PD of Ferric Carboxymaltose.

## 8.3 Demographic Characteristics

Demographic characteristics will be summarized for the Safety and PK/PD populations. The number and percentage of subject's who are registered, treated, prematurely discontinue, and complete the study will be summarized after the study's conclusion.

Subjects with clinically important protocol deviations will be identified for each analysis population, treatment group, and type of deviation. The clinical team will identify deviations and the deviations will be identified in the database.

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

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class (SOC) and preferred term for all subjects.

## 8.4 Endpoints and Definitions

### 8.4.1 Clinical Endpoints

Clinical endpoints include:

- Efficacy: change from baseline to each scheduled visit for hemoglobin, ferritin, and TSAT.
- Safety:
    - ✓ Proportion of subjects reporting treatment-emergent adverse events, overall and related, by SOC and preferred term
    - ✓ Subjects reporting treatment-emergent serious adverse events, overall and related, will be identified
    - ✓ Mean change from baseline to each scheduled visit for clinical laboratory values
    - ✓ Incidence of treatment-emergent potentially clinically significant (PCS) clinical laboratory values
    - ✓ Incidence of treatment-emergent PCS vital sign values.

## 8.5 Pharmacokinetics and Pharmacodynamics (PK/PD) Endpoints

The primary and secondary pharmacokinetic parameters will be determined for each subject as appropriate, based on serum concentration. The baseline parameters will be subtracted from all measured samples.

The primary parameters are the maximum serum concentration ($C_{max}$), the area under the serum concentration-time curve from time zero to the last sampling time (t) with a quantifiable concentration ($AUC_{0\text{-time last measured concentration}}$), the extrapolated area under the serum concentration- time curve from time zero to infinity ($AUC_{0\text{-infinity}}$), and the half-life ($T_{1/2}$). $C_{max}$ is calculated as a non-compartmental variable, which is a more conservative method than if it were calculated using a compartmental paradigm. $T_{1/2}$ incorporates the calculation of the rate elimination constant ($K_{el}$).

The secondary parameters are the mean residence time (MRT), the apparent serum clearance (Cl), and the apparent volume of distribution ($V_d$), which includes the initial volume of

distribution following the injection ($Vd_c$), the volume of distribution at the steady state ($Vd_{ss}$), and the volume of distribution at the final elimination ($Vd_{area}$).

Pharmacodynamic parameter will include serum ferritin, transferrin, transferrin saturation (TfS) UIBC, HGB, reticulocyte count and transferrin receptors.

The Pharmacokinetic and Pharmacodynamic parameters performed in this study for analysis will be outlined in a Statistical and Analytical Plan.

### 8.6 Statistical Analyses of Safety

The Medical Dictionary for Regulatory Activities (MedDRA) Terminology will be used to classify all adverse events with respect to system organ class and preferred term.
The number and proportion of subjects who report treatment-emergent adverse events will be summarized for each treatment group. A similar summary will be provided for all treatment emergent serious adverse events.

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 to study drug. Relationship to study drug will be categorized as related (possibly or probably related) and unrelated. Events with unknown severity or relationship will be counted as unknown.

Subjects 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 subject reports multiple preferred terms for a system organ class (SOC), the subject will be counted only once for that SOC.

Change in vital signs from baseline to each scheduled study visit will be summarized descriptively with the mean, median, standard deviation, minimum value, and maximum value. The number and percent of patients with potentially clinically significant vital signs will be summarized for each treatment group.

### 8.7 DSMB Analyses

A DSMB will review safety information for subjects in Cohort 1 before dosing begins for Cohort 2. A Charter will be developed outlining the DSMB processes.

## 9.0 ADMINISTRATIVE CONSIDERATIONS

### 9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including electronic copies of 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 subject must be maintained, that includes the signed Informed Consent form and copies of all study documentation related to that subject. 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 subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator Brochure, including potential risks and side effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (including amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subjects.
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 subjects into the study.

## 9.4 Advertisement for Subject Recruitment

All advertisements for subject recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisements may include but is not limited to newspaper, fliers, radio, television, etc. Any compensation to the subject 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 subject 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 subjects 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 (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 principal

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. 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 United States (US) Code of Federal Regulations on Protection of Human Subjects (21 CFR 50), IRB regulations (21 CFR 56), the 2000 Edinburgh, Scotland Revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312 and applicable ICH guidelines.

### 9.7.2 Institutional Review Board

The protocol and the Informed Consent / Assent 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 US Regulations (21 CFR 56). Investigators are responsible for the following:

- Obtain IRB approval of the protocol, Informed Consent / Assent and any advertisements to recruit subjects; 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 serious adverse events that occur or are reported to you by the Sponsor.

### 9.7.3 Informed Consent

Informed consent / Assent when appropriate must be obtained from each subject prior to study participation. The informed consent / assent will be provided to the subject in their native language. The consent/assent form must be signed by the subject and/or the subject's legally authorized representative. Each investigational site must provide the Sponsor (or designee) with a copy of the Informed Consent / Assent approved by that site's Institutional Review Board. The

original signed consent / assent form will be retained in the subject's study records, and a copy will be provided to the subject. The Clinical Monitor will assure that each Informed Consent / Assent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outlines the basic elements of informed consent and ICH guidelines. Translations of the informed consent / assent must be certified by a qualified translator and their use must be documented.

The Informed Consent / Assent documents the information the Investigator provides to the subject and the subject'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 / Assent must be signed and dated by each subject and/or legal representative before entering the study and prior to the performance of any study specific procedures.

### 9.7.4 Good Clinical Practice

The conduct of the study will conform to the recommendations for clinical studies in human subjects as set out in the current version of the Edinburgh, Scotland Revision of the "Declaration of Helsinki", the local legal requirements and the guidelines on "Good Clinical Practice", [21 CFR Part 312 and ICH guidelines].

## 9.8 Data Handling and Record Keeping

### 9.8.1 Electronic Case Report Form (eCRF)

- eCRFs will be provided for each subject on this study. The participants in this study will be identified only by initials and subject 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 eCRFs are to be reviewed by the Clinical Monitor at Luitpold Pharmaceuticals, Inc. (or designee). Source data will be reviewed by the Clinical Monitor 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 subjects 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, DSMB, investigator, or study 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 subjects, failure of the investigator to enroll subjects 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 subject 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, which 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.

## 10.0 GOVERNANCE COMMITTEE

### 10.1 Data and Safety Monitoring Board

The DSMB will be composed of approximately 3-5 senior academic individuals, including the DSMB Chair. They will have high-level expertise in pediatric iron deficiency anemia and/or statistics. A senior statistician assigned to the trial from the group performing data management services for this trial will oversee the provision of interim data reports for use by the DSMB. The data management group for this trial will transfer pre-agreed datasets to the DSMB. During the Open Session of the DSMB meetings, the Study Chair or Luitpold representatives may present updates on the trial status or the safety profile of Ferric Carboxymaltose, but will not be privy to discussions of the data conducted during the Closed Sessions and will not vote. Proceedings and

minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the patients and, to this end, will undertake reviews of the safety data. The DSMB will have access to an agreed subset of the study data as listed in the DSMB charter (updated as necessary during the trial) throughout the study duration. In addition, the DSMB will evaluate the data approximately (as outlined in the Charter) either by face to face meeting or teleconference. The DSMB will evaluate the safety from both cohorts 1 and 2 (7.5 or 15 mg/kg of Ferric Carboxymaltose). Only after all subjects in cohort 1 have completed through week 4 and the DSMB has evaluated the safety data as acceptable will registration into cohort 2 be granted. The DSMB will determine if it believes the trial should be terminated early because clear evidence of a significant safety concern exists.

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

## INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 50, 54, 56 and 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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## APPENDIX 1: FERRIC CARBOXYMALTOSE PACKAGE INSERT

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Injectafer safely and effectively. See full prescribing information for Injectafer.**

**INJECTAFER® (ferric carboxymaltose injection)**
**For intravenous use**
**Initial U.S. Approval: 20XX**

**----------INDICATIONS AND USAGE----------**

Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

**----------DOSAGE AND ADMINISTRATION----------**

For patients weighing 50kg (110lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750mg for a total cumulative dose of 1500mg of iron per course.

For patients weighing less than 50kg (110lb): Give Injectafer in two doses separated by at least 7 days and give each dose as 15 mg/kg body weight.

Injectafer treatment may be repeated if iron deficiency anemia reoccurs. (2)

**----------DOSAGE FORMS AND STRENGTHS----------**

750 mg iron / 15 mL single-use vial(3)

**----------CONTRAINDICATIONS----------**

Hypersensitivity to Injectafer or any of its inactive components. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- **Hypersensitivity reactions:** Observe for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of each administration. (5.1)
- **Hypertension:** Monitor patients closely for signs and symptoms of hypertension following each Injectafer administration. (5.2)

**----------ADVERSE REACTIONS----------**

The most common adverse reactions (≥2%) are nausea, hypertension, flushing, hypophosphatemia, and dizziness (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact American Regent at 1-800-734-9236 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**----------USE IN SPECIFIC POPULATIONS----------**

- Nursing Mothers: Exercise caution when administered to a nursing woman. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: July 2013**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Injectafer is indicated for the treatment of iron deficiency anemia in adult patients;

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

## 2 DOSAGE AND ADMINISTRATION

For patients weighing 50 kg (110 lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectafer in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

The dosage of Injectafer is expressed in mg of elemental iron. Each mL of Injectafer contains 50 mg of elemental iron. Injectafer treatment may be repeated if iron deficiency anemia reoccurs.

Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

When added to an infusion bag containing 0.9% Sodium Chloride Injection, USP, at concentrations ranging from 2 mg to 4 mg of iron per mL, Injectafer solution is physically and chemically stable for 72 hours when stored at room temperature. To maintain stability, do not dilute to concentrations less than 2 mg iron/mL.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Each vial of Injectafer is intended for single use only. Any unused drug remaining after injection must be discarded.

Avoid extravasation of Injectafer since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectafer administration at that site.

## 3 DOSAGE FORMS AND STRENGTHS

750 mg iron / 15 mL single-use vial

## 4 CONTRAINDICATIONS

Hypersensitivity to Injectafer or any of its components [see *Warnings and Precautions (5.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

**Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.** [see *Adverse Reactions (6.1 and 6.2)*]. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

### 5.2 Hypertension

In clinical studies, hypertension was reported in 3.8% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration [*see Dosage and Administration (2)*].

### 5.3 Laboratory Test Alterations

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

. Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
. Hypertension *[see Warnings and Precautions (5.2)]*
. Lab test alterations *[see Warnings and Precautions (5.3)]*

### 6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.
In two randomized clinical studies [Studies 1 and 2, *See Clinical Studies (14)*], a total of 1,775 patients were exposed to Injectafer 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥ 1% of treated patients are shown in the following table.

**Table 1. Adverse reactions reported in ≥ 1% of Study Patients in Clinical Trials 1 and 2**

| Term | Injectafer (N=1775) % | Pooled Comparators[a] (N=1783) % | Oral iron (N=253) % |
|---|---|---|---|
| Nausea | 7.2 | 1.8 | 1.2 |
| Hypertension | 3.8 | 1.9 | 0.4 |
| Flushing/Hot Flush | 3.6 | 0.2 | 0.0 |
| Blood Phosphorus Decrease | 2.1 | 0.1 | 0.0 |
| Dizziness | 2.0 | 1.2 | 0.0 |
| Vomiting | 1.7 | 0.5 | 0.4 |
| Injection Site Discoloration | 1.4 | 0.3 | 0.0 |
| Headache | 1.2 | 0.9 | 0.0 |
| Alanine Aminotransferase Increase | 1.1 | 0.2 | 0.0 |
| Dysgeusia | 1.1 | 2.1 | 0.0 |
| Hypotension | 1.0 | 1.9 | 0.0 |
| Constipation | 0.5 | 0.9 | 3.2 |

[a] Includes oral iron and all formulations of IV iron other than Injectafer

Other adverse reactions reported by ≥ 0.5% of treated patients include abdominal pain, diarrhea, gamma glutamyl transferase increased, injection site pain/irritation, rash, paraesthesia, sneezing. Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) have been observed in 27% (440/1638) patients in clinical trials.

### 6.2 Post-marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectafer: urticaria, dyspnea, pruritis, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a

subject who received 500 mg of Injectafer every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer.

## 7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Injectafer .

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

*Risk Summary*

Adequate and well controlled studies in pregnant women have not been conducted. However, animal reproduction studies have been conducted with ferric carboxymaltose. In these studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused fetal malformations and increased implantation loss at maternally toxic doses of approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area). The incidence of major malformations in human pregnancies has not been established for Injectafer. However, all pregnancies, regardless of exposure to any drug, has a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Animal Data*

Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Spontaneous abortions occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryofetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

### 8.3 Nursing Mothers

A study to determine iron concentrations in breast milk after administration of Injectafer (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectafer than in lactating women receiving oral ferrous sulfate.

### 8.4 Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

### 8.5 Geriatric Use
Of the 1775 subjects in clinical studies of Injectafer, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

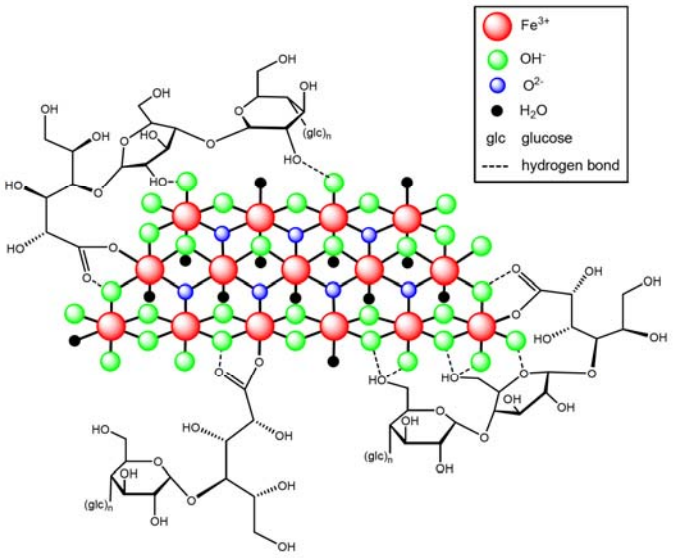
## 10 OVERDOSAGE
Excessive dosages of Injectafer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectafer 18,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability and asthenia . Hypophosphatemic osteomalacia was reported in a patient who received Injectafer 4000 mg over 4 months. Partial recovery followed discontinuation of Injectafer. [*see Post-marketing Experience (6.3)]*.

## 11 DESCRIPTION
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).

The chemical structure is presented below:




Injectafer (ferric carboxymaltose injection) is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Injectafer is available in 15 mL single-use vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0.

Vial closure is not made with natural rubber latex

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

### 12.2 Pharmacodynamics

Using positron emission tomography (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.

### 12.3 Pharmacokinetics

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 1.21 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ferric carboxymaltose.

Ferric carboxymaltose was not genotoxic in the following genetic toxicology studies: *in vitro* microbial mutagenesis (Ames) assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test at single intravenous doses up to 500 mg/kg.

In a combined male and female fertility study, ferric carboxymaltose was administered intravenously over one hour to male and female rats at iron doses of up to 30 mg/kg. Animals were dosed 3 times per week (on Days 0, 3, and 7). There was no effect on mating function, fertility or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

## 14 CLINICAL STUDIES

The safety and efficacy of Injectafer for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer was administered at a dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

### 14.1 Trial 1: Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

Trial 1 was a randomized, open-label, controlled clinical study in patients with iron deficiency anemia who had an unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2) during the 14 day oral iron run-in period. Inclusion criteria prior to randomization included hemoglobin (Hb) <12 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%. Cohort 1 subjects were randomized to Injectafer or oral iron for 14 more days. Cohort 2 subjects were randomized to Injectafer or another IV iron per standard of care [90% of subjects received iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

**Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | Cohort 1 | | Cohort 2 | |
|---|---|---|---|---|
| | Injectafer (N=244) | Oral Iron (N=251) | Injectafer (N=245) | IV SC[a] (N=237) |
| Baseline | 10.6 (1.0) | 10.6 (1.0) | 9.1 (1.6) | 9.0 (1.5) |
| Highest Value | 12.2 (1.1) | 11.4 (1.2) | 12.0 (1.2) | 11.2 (1.3) |
| Change (from baseline to highest value) | 1.6 (1.2) | 0.8 (0.8) | 2.9 (1.6) | 2.2 (1.3) |
| p-value | 0.001 | | 0.001 | |

SD=standard deviation; [a]: Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2±224.2 ng/mL in Cohort 1 and 218.2 ±211.4 ng/mL in Cohort 2), and transferrin saturation (13±16% in Cohort 1 and 20±15% in Cohort) were observed at Day 35 in Injectafer-treated patients.

**14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease**

Trial 2 was a randomized, open-label, controlled clinical study in patients with non-dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) ≤ 11.5 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%.Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 96); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

**Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | **Injectafer (N=1249)** | **Venofer (N=1244)** |
|---|---|---|
| Baseline | 10.3 (0.8) | 10.3 (0.8) |
| Highest Value | 11.4 (1.2) | 11.3 (1.1) |
| Change (from baseline to highest value) | 1.1 (1.0) | 0.9 (0.92) |
| Treatment Difference (95% CI) | 0.21 (0.13, 0.28) | |
| | | |

Increases from baseline in mean ferritin (734.7±337.8 ng/mL), and transferrin saturation (30±17%) were observed at Day 56 in Injectafer-treated patients.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

| | |
|---|---|
| NDC 0517-0650-01 | 750 mg iron/15 mL Single-Use Vial Individually boxed |
| NDC 0517-0650-02 | 750 mg iron/15 mL Single-Use Vial Packages of 2 |

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See the USP controlled room temperature]. Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*]

Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

AMERICAN
REGENT, INC.
SHIRLEY, NY  11967

IN0602
Rev. 7/13

**Patient Information**
**INJECTAFER (ferric carboxymaltose injection)**

Please read this information carefully before taking this medication. This summary does not tell you everything about INJECTAFER. Speak with your doctor or healthcare professional if there is something you do not understand or if you would like to learn more about INJECTAFER. Your doctor or healthcare professional is your best source of information about this medicine.

## What is INJECTAFER?

Iron is a mineral that the body needs to produce red blood cells. When the body does not get enough iron, it cannot produce the number of normal red blood cells needed to keep you in good health. This condition is called iron deficiency (iron shortage) or iron deficiency anemia.

INJECTAFER is used to treat iron deficiency anemia. Iron deficiency anemia may be caused by several medical conditions including heavy menstrual bleeding, pregnancy, childbirth, inflammatory bowel disease, other malabsorption diseases, bariatric surgery, or chronic kidney disease**.**

## General information about using INJECTAFER safely and effectively

Injectable iron is administered only by or under the supervision of your health care professional.

Serious or life threatening allergic reactions have been reported with intravenous iron products. Tell your health care professional if you have ever had any unusual or allergic reaction to any IV iron.

Patients should report to their healthcare professional any signs and symptoms of an allergic reaction to INJECTAFER, in particular rashes, shortness of breath and wheezing.

Iron is not easily eliminated from the body, and its build up may be lead to a condition called iron overload which may be harmful. Certain medical conditions such as liver disease may also make you more likely to develop iron overload. Ask your doctor or healthcare professional.

## Who should not take INJECTAFER?

You should not be given INJECTAFER if you have anemia that is not caused by iron deficiency, or if you have iron overload.

If you are pregnant or plan to become pregnant please notify your doctor or healthcare professional. They will decide whether it is safe for you to receive INJECTAFER.

## How should I take INJECTAFER?

INJECTAFER is administered intravenously (into your vein) by your doctor or health care professional in two doses.

**What should I avoid while taking INJECTAFER?**

You should not take iron supplements by mouth if you are receiving iron injections. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

**What are the possible side effects of INJECTAFER?**

The side effects of INJECTAFER are infrequent, usually mild and generally do not cause patients to stop treatment. The most common side effects are nausea, injection site reactions (including pain or bruising at the injection site), asymptomatic reductions in blood phosphorus, flushing, headache, hypertension, dizziness, and increased alanine aminotransferase. Potentially long lasting brown staining of skin near injection site may occur.

These are not all the possible side effects of INJECTAFER. For more information ask your doctor or healthcare professional.

Talk to your doctor if you think you have side effects from taking INJECTAFER.

## APPENDIX 2: WEIGHT CHARTS FOR BOYS AND GIRLS

**Boys (White) Weight Chart age 0-36 months** (http://www.halls.md/chart/boys-weight-w.htm)

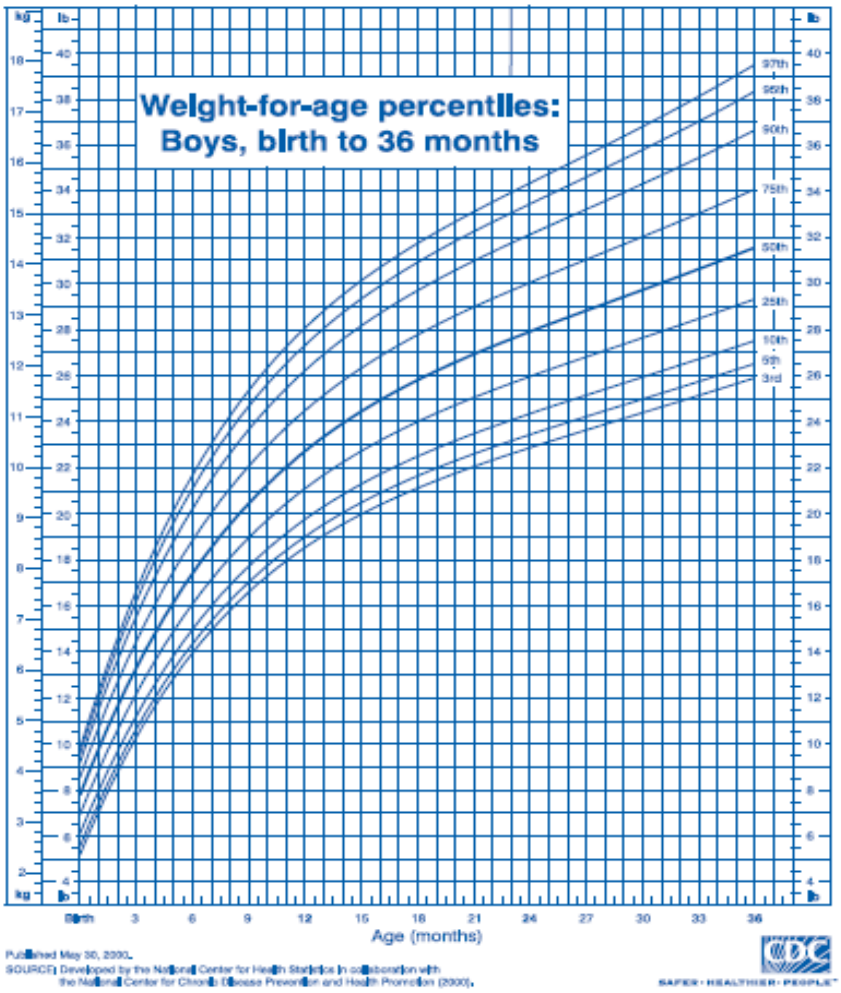
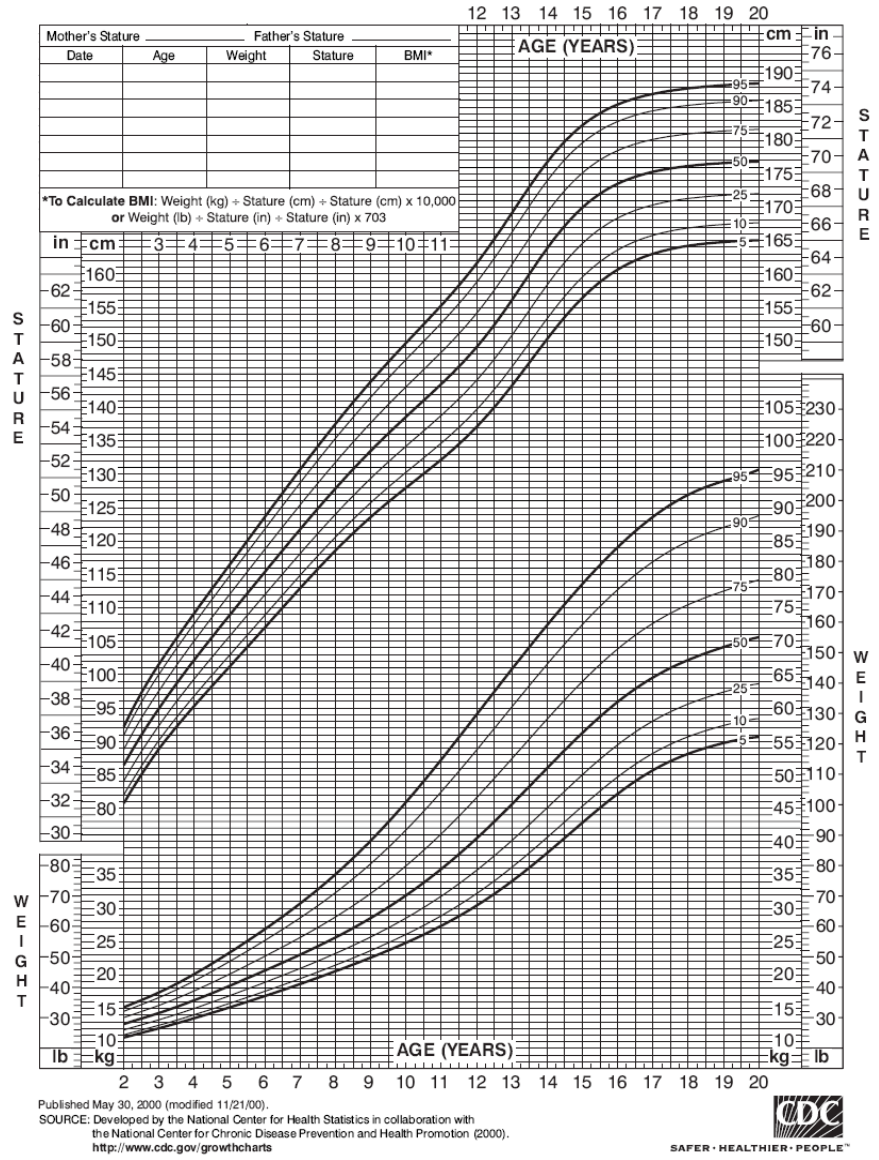



Figure 1. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Boys weight-for-age

## BOYS (WHITE) WEIGHT CHART AGE 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L021.PDF)



**Girls (White) Weight Chart age 0-36 months** (http://www.halls.md/on/girls-weight-w.htm)

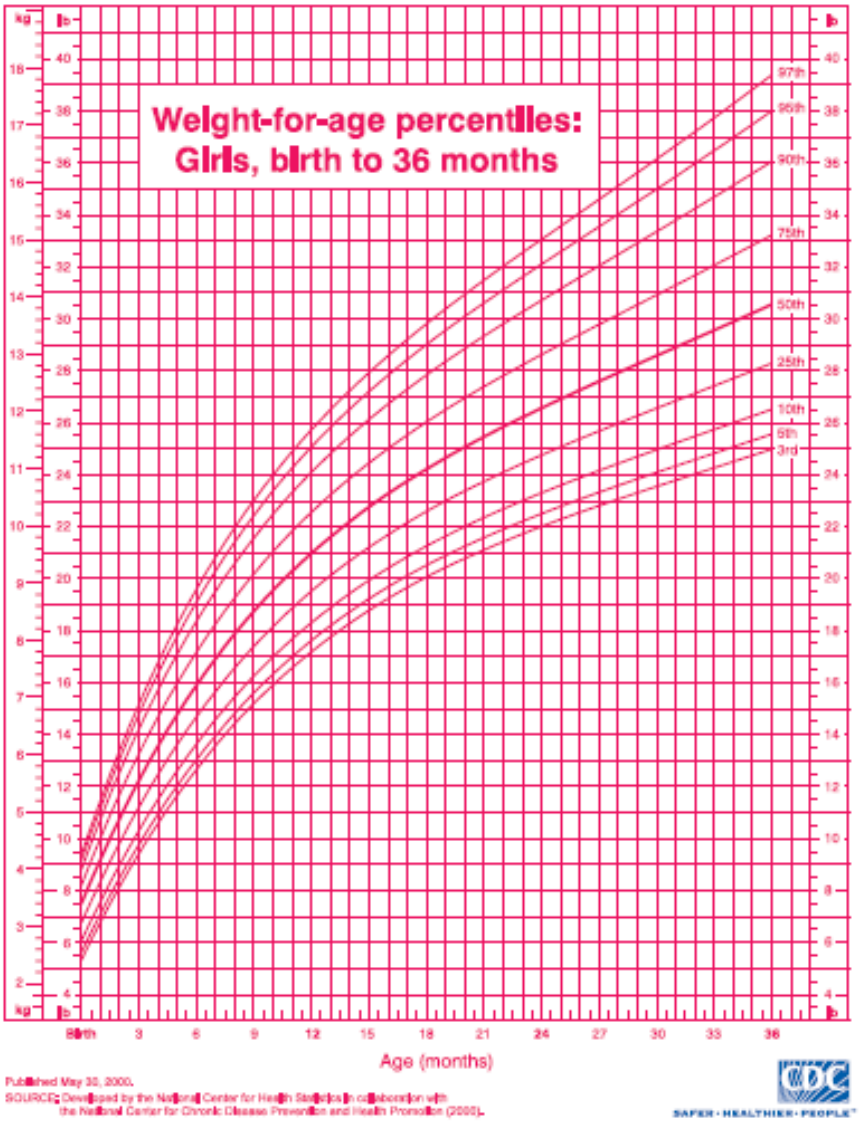
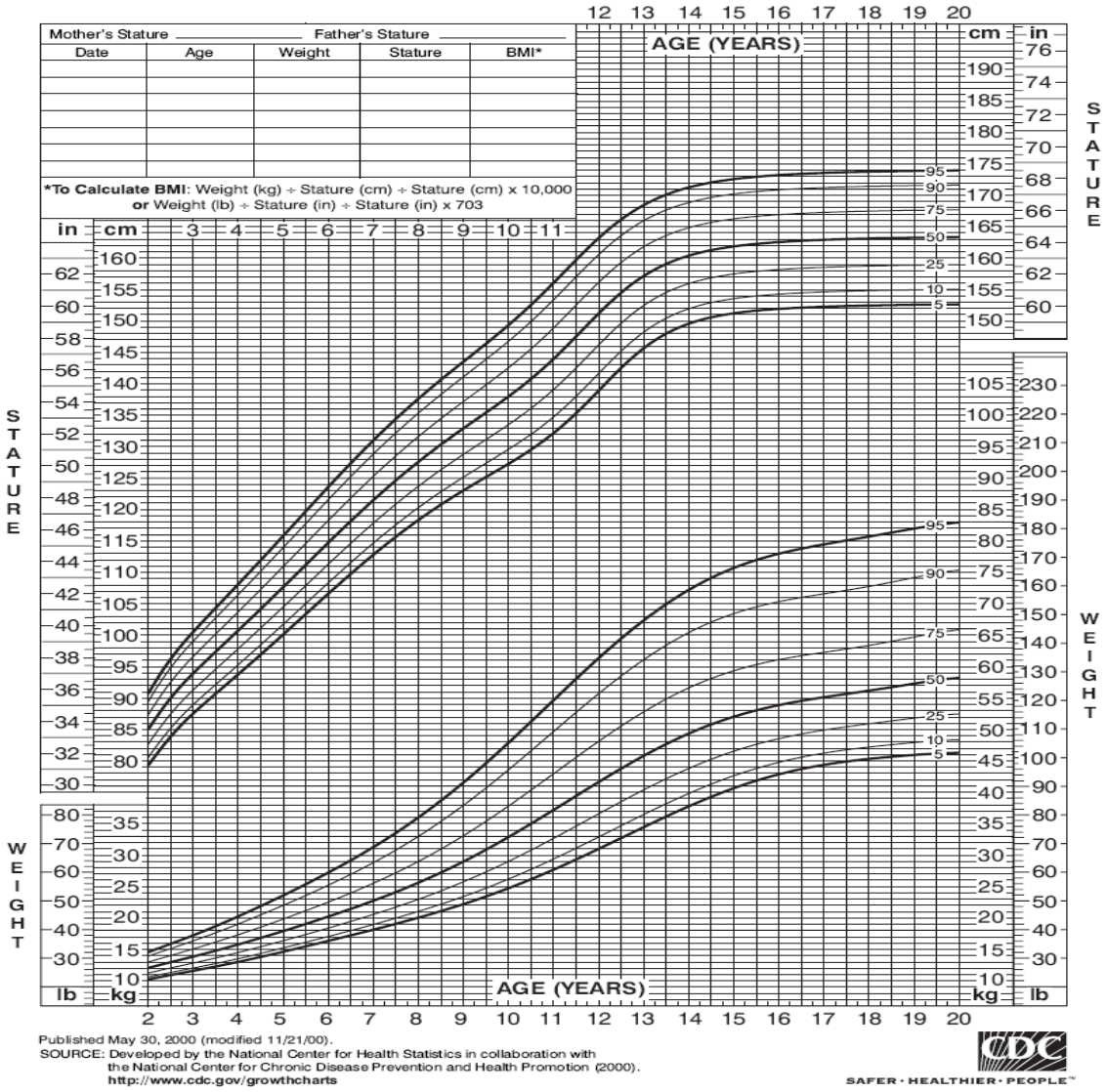



Figure 2. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Girls weight-for-age

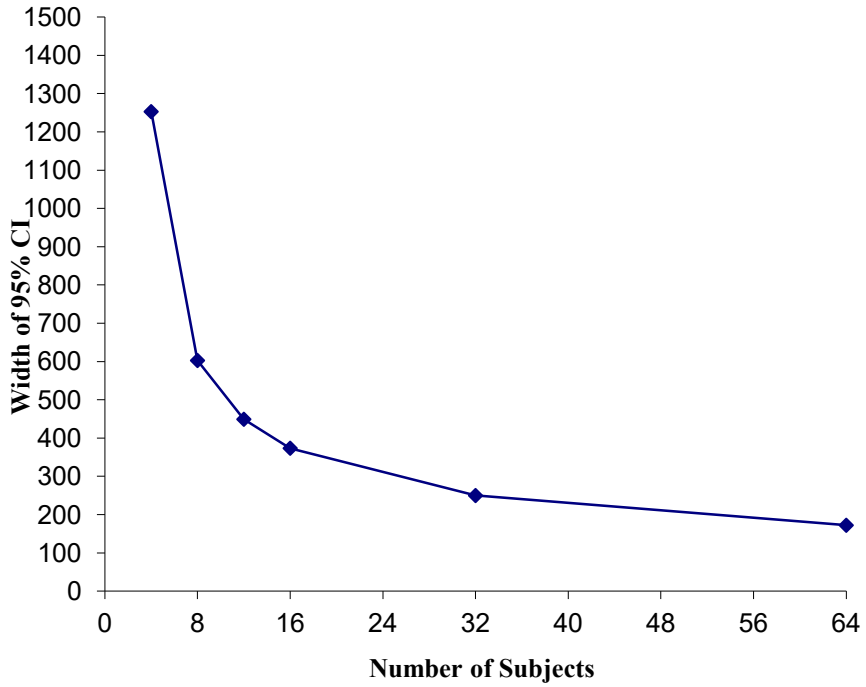
## GIRLS (WHITE) WEIGHT CHART AGES 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L022.PDF)



## APPENDIX 3: ADMENDMENT I CHANGES

| | |
|---|---|
| Title Page: | |
| Original Wording: | Protocol Date:<br>27 March 2014 |
| New Wording: | Protocol Date:<br>Amendment 1: 29 July 2014 |
| Study Synopsis and 8.1 Sample Size Rationale: | |
| New Wording: | Sample Size:<br><br>Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients. |

| | |
|---|---|
| |  <br><br>Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally disturbed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system. |
| Original Wording: | Exclusion Criteria:<br><br>3. Body mass index (BMI) ≤ 95$^{th}$ percentile for age (see APPENDIX 2) |
| New Wording: | 3. Body mass index (BMI) ≤ 5$^{th}$ percentile for age (see APPENDIX 2) |
| Original Wording: | Trial design – Phase III |
| New Wording: | Trial Design – Phase II |
| Additional Wording – Sections 7.1 | All laboratory values at the end of study/Day 35 that have been deemed clinical significant by the Investigator should be followed until they are back into normal range. |
| | |

## APPENDIX 4: ADMENDMENT II CHANGES

| | |
|---|---|
| Title Page: | |
| Original Wording: | Protocol Date: 27 March 2014<br>Amendment 1: 29 July 2014 |
| New Wording: | Protocol Date: 27 March 2014<br>Amendment 1: 29 July 2014<br>Amendment II: 08 October 2014 |
| Signature of Agreement For Protocol Original Wording: | Marc Tokars Date<br>Vice President of Clinical Operations<br>Luitpold Pharmaceuticals, Inc.<br><br>Marsha Simon Date<br>Sr. Manager-Regulatory Affairs<br>Luitpold Pharmaceuticals, Inc.<br><br>David Morris, PhD Date<br>Senior Director, Statistics<br>WebbWrites, LLC |
| Signature of Agreement For Protocol New Wording: | Sylvan Hurewitz, MD Date<br>Medical Director<br>Luitpold Pharmaceuticals, Inc.<br><br>Syed Quadri, MD Date<br>Medical Director, Pharmacovigilance<br>Luitpold Pharmaceuticals, Inc.<br><br>Marsha Simon Date<br>Sr. Manager-Regulatory Affairs<br>Luitpold Pharmaceuticals, Inc.<br><br>David Morris, PhD Date<br>Senior Director, Statistics<br>WebbWrites, LLC |

| | |
|---|---|
| New Exclusion Criteria Wording: | Exclusion Criteria # 4: Male or Female subject 1 year of age weighing < 12kg. |
| Exclusion Criteria Deletion | Deleted original criteria number 12. Significant blood loss (> 100 ml) within the last 3 months or any current bleeding disorders or anticipated need for surgery that may result in significant blood loss (> 100 ml). |
| Original Wording section 6.3.5 Blood Volume Table: | Total Blood Volume = 72mL/approx. 14.6 tsps |
| New Wording section 6.3.5 Blood Volume Table: | Total Blood Volume = 44.5mL/approx. 9.03 tsps |
| New Wording | Injectafer ® replaced by Ferric Carboxymaltose throughout Protocol |

**LUITPOLD PHARMACEUTICALS, INC.**

**PROTOCOL**

**No. 1VIT13036**

**IND #: 63,243**

# A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Ferric Carboxymaltose in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA)

SPONSOR

Luitpold Pharmaceuticals, Inc.
Clinical Research and Development
800 Adams Avenue
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**Protocol Date: 27 March 2014**

**Amendment I Date: 29 July 2014**

**Amendment II Date: 08 October 2014**

**Local Protocol Amendment I for Russia: 24 February 2015**

**SIGNATURES OF AGREEMENT FOR PROTOCOL**

Sylvan Hurewitz MD — 19 Mar 2015

Sylvan Hurewitz, MD
Medical Director
Luitpold Pharmaceuticals, Inc.

Date

19-Mar-2015

Syed Quadri, MD
Medical Director, Pharmacovigilance
Luitpold Pharmaceuticals, Inc.

Date

19 MAR 2015

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

Date

19 March 2015

David Morris, PhD
Senior Director, Statistics
WebbWrites, LLC

Date

## Study Synopsis

## Protocol No. 1VIT13036

**Title:** A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Ferric Carboxymaltose in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA).

**Drug:** Ferric Carboxymaltose

**Objectives:** The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Ferric Carboxymaltose for the pediatric population suffering from iron deficiency (ID) with anemia.

**Study Design:** This is a Phase II, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Ferric Carboxymaltose dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Ferric Carboxymaltose®.

**Treatment**

Cohort 1: 16 subjects will be treated with Ferric Carboxymaltose at 7.5 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Ferric Carboxymaltose at 15 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age (6 to 17 years of age in Russia only) with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving an erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Ferric Carboxymaltose.
2. Subject previously randomized and treated in this study or any other clinical study of Ferric Carboxymaltose (FCM or VIT-45).
3. Body mass index (BMI) ≤ 5$^{th}$ percentile for age (see APPENDIX 2)
4. Male or Female subject 1 year of age weighing < 12kg.
5. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
6. Chronic kidney disease subjects on hemodialysis.
7. Screening Ferritin level > 300ng/mL
8. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
9. Any active infection.
10. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
11. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
12. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subjects who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

**Subject Assessments:**

All subjects that provide informed consent / assent will enter a screening period up to 14 days prior to Day 0. During this time subjects will be evaluated to insure they meet the study entry criteria. Subjects will have vital signs, medical history review and laboratory samples to include hematology, chemistries and iron indices. Once it has been determined the subject qualifies for participation the subject will be scheduled to return to the clinic 1 day prior to Day 0 (Day -1) at which time additional blood samples will be taken (8am, 12pm and 8pm) to characterize the subjects iron profile.

Blood samples for PK/PD will also be assessed immediately prior to Ferric Carboxymaltose dosing on Day 0, at 1, 2, 6, 12, 24, 48 hours and at 72 hours.

Safety assessments, including vital signs and adverse events, will be assessed starting on Day 0 at the time of Ferric Carboxymaltose dosing through Day 35.

**Erythropoietin Dosage:**

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

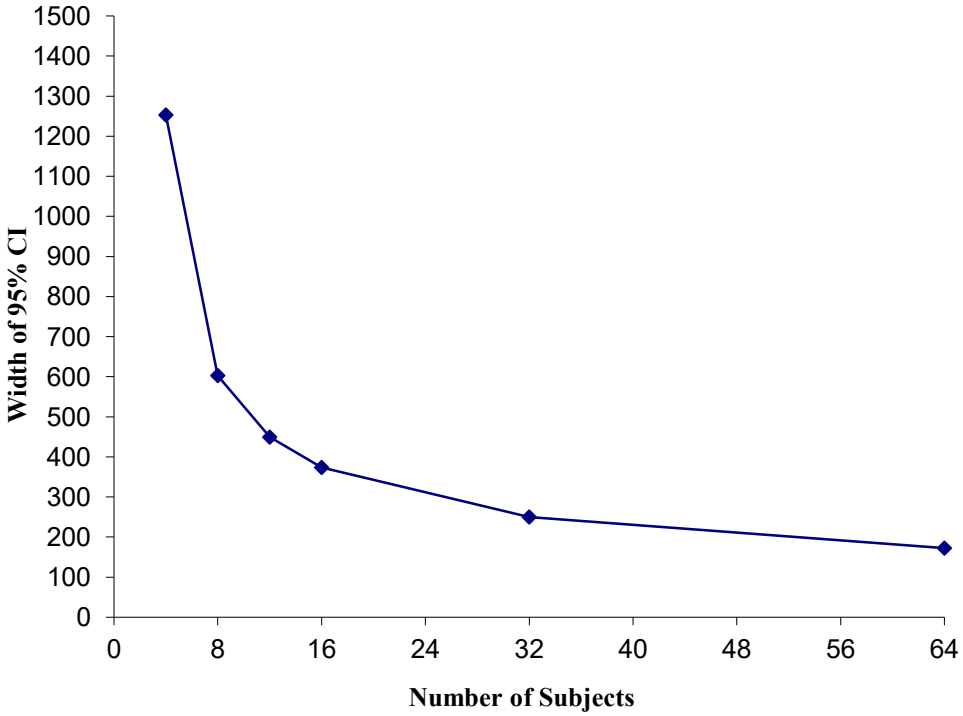
**Study Duration per subject:** up to 9 weeks

**Number of Subjects:** 32 subjects

**Sites:** Approximately 10

**Sample Size:**

Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients.




Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally distributed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system.

## CONTACT PERSON FOR THE STUDY

For study related questions please contact:

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Telephone: 610-650-4200
Fax: 610-650-7781

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| BP | Blood Pressure |
| BW | Body Weight |
| CI | confidence interval |
| CKD | Chronic Kidney Disease |
| conc. | concentration |
| CTCAE | Common Terminology Criteria for Adverse Event |
| dL | Deciliter |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| e.g. | for example |
| ESA | Erythropoiesis stimulating agent |
| FDA | Food and Drug Administration |
| Fe | Iron |
| g | Gram |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| Hct | Hematocrit |
| Hgb | Hemoglobin |
| HMW | high molecular weight |
| IBD | Inflammatory Bowel Diease |
| ICH | International Conference on Harmonisation |
| IDA | Iron Deficiency Anemia |
| i.e. | that is/ such that |
| IRB | Institutional Review Board |
| IV | Intravenous |
| IVP | Intravenous injection (push) |
| kg | Kilogram |
| L | Liter |
| LMW | low molecular weight |
| LOS | length of stay |
| MedDRA | Medical dictionary for regulatory activities |
| mg | Milligram |
| mL | Milliliter |
| ng | Nanogram |
| PET | positron emission tomography |
| p.o. | by mouth or orally |
| RES | Reticuloendothelial system |
| SAE | Serious adverse event |
| $t_{1/2}$ | Terminal half-life |
| t.i.d. | three times a day |
| TSAT | Transferrin Saturation |
| US | United States |
| vs | Versus |
| w/v | weight / volume |

# 1.0 INTRODUCTION

## 1.1 Treatment of Iron Deficiency Anemia

Iron deficiency anemia ("IDA") remains the most common nutritional deficiency in children in the United States. Rapid growth, insufficient dietary intake, and limited absorption of dietary iron combine to place children at increased risk for iron deficiency. Iron deficiency may contribute significantly to anemia due to malabsorption, gastrointestinal blood loss, or iatrogenically due to repeated blood samplings. As a result of severe digestive tract disorders, some children are unable to tolerate oral iron supplementation or are unresponsive to it.[1] Anemia may also decrease survival rates in patients (both adults and children) with chronic renal impairment where it is a commonly encountered problem[2;3] In addition, anemia is a commonly encountered manifestation of pediatric inflammatory bowel disease which is associated with a decrease in the quality of life and increased hospitalization.

Non-hematologic consequences of iron deficiency include poor weight gain, anorexia, irritability, decreased attention span, exercise intolerance and decreased physical activity. [4] However, IDA in infants and toddlers is associated with long-lasting diminished mental, motor, and behavioral functioning. Although the exact relationship between iron deficiency anemia and the developmental effects is not well understood, it appears that these effects do not occur until iron deficiency becomes severe and chronic enough to produce anemia. [5]

Options for correcting iron deficiency include both oral and parenteral formulations. As previously described, some children are unable to tolerate or are non-responsive to oral iron. Blood transfusion is an option to treat anemia and restore iron requirements, but the potential risk of blood-transmitted virus infection limits its use to severe and badly tolerated anemia. In view of the limitations associated with oral iron or blood transfusions, intravenous administration is an important option.

Multiple parenteral iron products are available. These vary in complex types which impacts the total amount of iron that may be administered in a single administration. Numerous other differences differentiate the products; however, all appear to effectively release iron post administration and restore the deficit of the patient. There are numerous studies with iron sucrose injection (Venofer®) that have been performed in the pediatric population [6-8]. Iron doses have varied in the studies with demonstrated efficacy and safety in doses up to 7mg iron/kg or 200mg given in time frames of 3 min, which was shown to be beneficial to both the child and health care facility[6].

Ferric Carboxymaltose has been characterized as a robust and strong type iron complex (Type 1) with a molecular mass of about 150,000 Daltons (Da). The solution is a dark brown color with a near neutral pH (5.0 to 7.0) and a physiological osmolarity permitting administration of higher single doses in short time periods. Although no interventional studies have been conducted with Ferric Carboxymaltose in the pediatric population to date, the product has been used in clinical practice in markets where it is currently approved for adults to aid correction of iron deficiency within the pediatric gastroenterological setting. A non-interventional/retrospective observational data collection has identified in 79 patient's aged 2 to 18 years with a mean age of 12.7 years. In

these subjects, Ferric Carboxymaltose showed efficacy with regard to hemoglobin, ferritin, and TSAT as well as safety and tolerability (manuscript in preparation).

Therefore, the proposed studies will assess higher single doses (i.e., 7.5 mg/kg and 15 mg/kg) than those used with currently available parenteral iron preparations in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population. The higher single doses permit fewer overall injections/infusions and may ultimately permit fewer visits to the treating facilities positively impacting both the child and family as well as health care system.

## 1.2 Ferric Carboxymaltose

### 1.2.1 Key features of Ferric Carboxymaltose

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, Ferric Carboxymaltose is mainly found in the liver (RES), 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 Ferric Carboxymaltose is metabolized by the glycolytic pathway.

### 1.2.2 Ferric Carboxymaltose versus Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various parenteral iron preparations available [(3)]. However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted their use. Ferric Carboxymaltose offers significant advantages compared to other available intravenous iron preparations.

Iron dextran, the first parenteral iron product available in the US, has been associated with an incidence of anaphylaxis/anaphylactoid reactions (i.e., dyspnea, wheezing, hypotension, urticaria, angioedema) as high as 1.7% [(6)]. Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran. The high incidence of anaphylaxis/anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Although some have suggested that high molecular weight (HMW) iron dextran is associated with a higher rate of life threatening adverse events and anaphylactic reactions in comparison to low molecular weight (LMW) iron dextran, the US Food and Drug Administration was unable to find a clear difference after an examination of post-marketing data, clinical trial data, death certificates, and emergency room diagnoses [(7)]. Iron dextran is limited to second line therapy for treatment of iron deficiency.

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. 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, Ferric Carboxymaltose 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[11] (data on file ). These characteristics of Ferric Carboxymaltose 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) 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 (see Ferumoxytol PI).

**Table 1.2.2.1 Administration of at least 1500 mg of Intravenous Iron with Currently Available Iron Preparations and Ferric Carboxymaltose**

| 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 | 300mg | 1.5 hours | 5 |
| Iron sucrose | No | 400 mg | 2.5 hours | 4 |
| ferumoxytol | No | 510 mg | < 1 minute | 3 |
| Ferric Carboxymaltose | 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 countries outside of the US; 750 mg maximum is the U.S. FDA approved dose

The larger Ferric Carboxymaltose and ferumoxytol doses result in less frequent administration of intravenous iron that should benefit, in particular, severely iron deficient and anemic populations. To be treated with currently available intravenous iron agents, the average inflammatory bowel disease, postpartum, heavy uterine bleeding and non-dialysis dependent patient would require an initial test dose, followed by 15 doses of iron dextran as labeled, each accompanied by personnel equipped and trained for resuscitation of anaphylaxis; 12 doses of ferric gluconate; or either 8 doses of iron sucrose (with 5 minute infusion time) or 5 / 4 doses of iron sucrose by prolonged (1.5 to 2.5 hours) intravenous infusion. Ferric gluconate and iron sucrose are not approved by the FDA for the treatment of IDA in non chronic kidney disease populations and iron dextran is only approved as second line therapy for treatment of iron deficiency. In contrast, most patients treated with Ferric Carboxymaltose would require 2 doses administered over 8 to15 minutes one week apart.

### 1.2.3 Ferric Carboxymaltose Human Experience

The Ferric Carboxymaltose development program demonstrated the safety and effectiveness of intravenous Ferric Carboxymaltose in the treatment of IDA. Clinical data are currently available from 20 Phase 2 and 3 studies including 5,799 patients, with IDA or IDA associated with CKD, who received Ferric Carboxymaltose.

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

Phase III studies demonstrated the effectiveness of Ferric Carboxymaltose in treating IDA secondary to inflammatory bowel disease, heavy uterine bleeding, chronic kidney disease (hemodialysis and non-hemodialysis) and the postpartum state. Clinically meaningful increases in hemoglobin, 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 chronic kidney disease. A head to head comparison of Ferric Carboxymaltose to Venofer (Iron sucrose) in over 2,500 subjects with non-dialysis dependent CKD and elevated risk of cardiovascular disease according to the Framingham criteria demonstrated that the recommended dose of Ferric Carboxymaltose, 750 mg x 2 (1500 mg total) had superior efficacy to the labeled dose of Iron sucrose (200 mg x 5 [1000 mg total]) with regard to hemoglobin elevation and had a similar cardiovascular (and overall) safety profile, based in part on an independently adjudicated composite cardiovascular safety endpoint [(8)] .

Important details of pre- and clinical safety and efficacy can be found in the Investigator's Brochure. Ferric carboxymaltose received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) approval on June 15, 2007 for the use of Ferric Carboxymaltose (EU Trade name: Ferinject) in 18 EU (European Union) countries and later in Switzerland. Ferric carboxymaltose was first approved as a prescription only medicine on July 6, 2007 in The Netherlands. Up until now, Ferric Carboxymaltose has received regulatory approval for marketing authorization in 58 countries worldwide: Argentina, Australia, Austria, Bangladesh, Belgium, Bolivia, Brazil, Bulgaria, Chile, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, Iceland, India, Iran, Ireland, Israel, Italy, Kazakhstan, Kuwait, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, New Zealand, Norway, Pakistan, Peru, Poland, Portugal, Romania, Russia, Singapore, Slovenia, Slovak Republic, South Korea, Spain, Sweden, Switzerland, The Netherlands, Turkey, Ukraine, and United Kingdom. Ferric Carboxymaltose received approved from the Food and Drug Administration (FDA) on July 25, 2013 for marketing in the United States.

## 2.0 MAIN TRIAL OBJECTIVE

The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Ferric Carboxymaltose for the pediatric population suffering from iron deficiency (ID) with anemia.

# 3.0 OVERALL STUDY DESIGN AND RATIONALE

## 3.1 Trial Design

This is a phase II, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Ferric Carboxymaltose dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Ferric Carboxymaltose.

Cohort 1: 16 subjects will be treated with Ferric Carboxymaltose at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Ferric Carboxymaltose at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

## 3.2 Rationale

### 3.2.1 Rationale for Trial Design

Ferric Carboxymaltose is a non-dextran IV iron recently approved by the United States Food and Drug Administration (FDA). This trial is designed to assess the single doses (i.e., 7.5 mg iron/kg and 15 mg iron/kg) in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population.

### 3.2.2 Rationale for open label design

The open-label, single arm trial design is considered appropriate because a control group is not required to estimate the PK/PD profile of Ferric Carboxymaltose. The risk from exposure to another form of IV iron is not offset by the minimal scientific benefit.

### 3.2.3. Schedule of Events

| Visit Day | Screening Period (Up to 14 Days) | Day -1 | Day 0 | 24 and 48 hours post dosing | 72 hours post dosing | Day 14 (week 2) | Day 28 (week 4) | Day 35 (week 5) |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Assess entry criteria | X | | X | | | | | |
| EDC | X | | X | | | | | X |
| Medical History | X | | X | | | | | |
| Physical Exam[1] | | | X | | | | | X |
| Vital Signs[6] | X | | X | | X | X | X | X |
| Height / Weight | | | X | | | | | |
| PK/PD Samples | | X[2] | X[3] | X[4] | X[4] | | | |
| Hematology, Chemistry and Iron Indices | X | | | | X | X | X | X |
| Serum pregnancy test | X | | | | | | | |
| Concomitant Medications | X | | X | | X | X | X | X |
| ESA Stability | X | | X | | X | X | X | X |
| Adverse Event Assessments[5] | | | X | X | X | X | X | X |
| Ferric Carboxymaltose | | | X | | | | | |

[1] Includes clinical assessment of skin, cardiovascular, pulmonary, abdominal, and central nervous system
[2] Blood samples drawn at 8am, 12pm and 8pm for subject iron profile
[3] Blood samples PK/PD should be taken prior to Ferric Carboxymaltose dosing and additional samples for PK/PD should be taken at 1, 2, 6 and 12 hours post dosing.
[4] Blood samples should be taken approximately the same time of day as the Day 0 samples were drawn
[5] Adverse event assessments starting at the time of Ferric Carboxymaltose dosing
[6] Sitting vital signs including blood pressure and heart rate should be collected immediately pre-dosing, immediately and 30 minutes post dosing. Body temperature will also be collected pre-dose only. Vital signs on non-dosing days include sitting heart rate and blood pressure only.

# 4.0 SUBJECT SELECTION

## 4.1 Number and Type of Subjects

Up to thirty two (32) subjects who have given written informed consent / assent along with parent or guardian's written informed consent with a diagnosis of iron deficiency anemia (IDA) who fulfill the inclusion criteria, do not meet any of the exclusion criteria will be registered to receive Ferric Carboxymaltose.

## 4.2 Screening Phase

Once a subject enters the screening phase, they will be assigned, via the Electronic Data Capture (EDC) system, a unique screening number. From the time of consent until the start of treatment of IV Ferric Carboxymaltose, the subject will not receive any form of iron outside of the study (intravenous or blood transfusion iron from 4 weeks prior to consent or oral iron including multivitamins with iron from time of consent).

If the subject does not qualify for study entry the subject should be entered into the EDC system as a screen failure. Subjects can be re-screened once, see section 6.2.

### 4.2.1 Entry Criteria

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age (6 to 17 years of age in Russia only) with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving a erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial.

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Ferric Carboxymaltose.
2. Subject previously randomized and treated in this study or any other clinical study of Ferric Carboxymaltose (FCM, VIT-45).
3. Body mass index (BMI) ≤ 5$^{th}$ percentile for age (see APPENDIX 2)
4. Male or Female subject 1 year of age weighing < 12kg.
5. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
6. Chronic kidney disease subjects on hemodialysis.
7. Screening Ferritin level > 300 ng/mL.
8. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
9. Any active infection.

10. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
11. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
12. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subject who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

## 4.3 Subject Assignment and Registration Process

Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this 7 week study. Cohorts 1 and 2 will be enrolled and treated sequentially. Enrollment into Cohort 2 will not begin until all Cohort 1 subjects have completed 4 weeks of therapy and no safety issues with the administration of Ferric Carboxymaltose has been confirmed by the DSMB.

## 4.4 Withdrawal from Study

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

At the time of withdrawal, procedures for the Day 35 visit must be performed regardless of whether the subject has completed study drug treatment. In the event the subject has received any study drug; the subject should be contacted to assess adverse events 28 days post the last dose of Ferric Carboxymaltose, if possible.

In the event a subject withdraws without completing the full PK/PD sampling. Additional subjects may be enrolled to ensure adequate representations of the PK/PD parameters are available for analyses. Conditions for additional enrollment will be defined in more detail in the statistical analyses plan.

## 4.5 Intervention

Intervention is defined as follows:

- Increase in dose of erythropoietin for any reason (Day 0 thru Day 35).
- Blood transfusion.
- Use of IV iron outside of protocol.

- Use of oral iron outside the protocol.

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 subject should continue in the study as scheduled through Day 35.

## 5.0 STUDY DRUG

### 5.1 Formulation Packaging and Storage

All medication to be used in this study that has been supplied by Vifor Pharma Ltd. will have been prepared according to Good Manufacturing Practices (GMP).

Ferric Carboxymaltose (known in the EU as Ferinject®) will be supplied as 5% w/v (weight /volume) 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.

Study drug must be kept in a secure place at the investigational site, and stored at room temperature (see: USP). Ferric Carboxymaltose should not be frozen. **Vials may not be used for more than 1 dose or for more than 1 subject. All Ferric Carboxymaltose vials used and unused should be kept by the study staff.**

### 5.2 Drug Administration / Regimen

The Principal Investigator or designee will supervise administration of the study drug to subjects:

**Cohort 1**: 16 subjects will be treated with Ferric Carboxymaltose at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

**Cohort 2**: 16 subjects will be treated with Ferric Carboxymaltose at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

Ferric Carboxymaltose will be given on Day 0. It will be administered as either:

- An undiluted slow IV push at a rate of 100 mg/minute.
- Doses less than 100 mg should be given as a slow undiluted IV push within a minute.

## 5.3 IV Iron Precautions

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

- The subject 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 heart rate and blood pressure will be assessed pre-, immediately post, and 30 minutes post administration. If the subject 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 patients receiving IV iron therapies. Subjects 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 subjects 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 intravenous 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 Ferric Carboxymaltose. They will not allow Ferric Carboxymaltose 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 registered in the study, or to investigators not listed on the FDA 1572. When the study is completed, or if it is prematurely terminated, a final inventory of all clinical supplies must be compiled and the remainder of used and unused Ferric Carboxymaltose will be returned to Luitpold Pharmaceuticals, Inc. (or their designee). All data regarding Ferric Carboxymaltose must be recorded on the Drug Accountability Forms provided by the sponsor.

Investigators will keep adequate records of the administration and disposition of IV Ferric Carboxymaltose® used for patients selected for the trial.

## 5.5 Concomitant Medication

Concomitant medications along with their route of administration and duration must be recorded in the electronic case report form (eCRF) from 30 days prior to consent. **No additional iron preparations (IV iron from 4 weeks prior to consent or oral iron including multivitamins**

**with iron, from time of consent), will be allowed. No prophylactic medications may be administered prior to Ferric Carboxymaltose administration without prior approval from Luitpold Pharmaceuticals, Inc.**

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

# 6.0 STUDY PROCEDURES

## 6.1 Informed Consent

Prior to any study specific procedures, the investigator must explain to each subject 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 subject (who for this trial is 1 -17 years old) must assent, if appropriate and his/her legal guardian (who is above age of legal consent) voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The Code of Federal Regulations (CFR) is a codification of rules and regulations of the United States government. The subject's legal guardian will be given a copy of the signed consent form.

## 6.2 Screening (up to 14 days)

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

- Obtain screening number from EDC
- Medical history, including prior iron therapy use
- Vitals signs (including sitting heart rate and blood pressure)
- Hematology, Chemistries and iron indices
- Serum pregnancy test for female subjects of child bearing potential (negative results must be obtained prior to registering the subject for study drug dosing).
- Concomitant medications assessment
- ESA therapy stability ( if applicable)

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

## 6.3 Study Visits

### 6.3.1. Day (-1)

Once it's confirmed during the screening period that the subject continues meet the entry criteria all eligible subjects will return to the clinic on Day – 1, blood samples will be drawn at 8am, 12pm and 8pm to characterize the subject iron profile.

### 6.3.2 Day 0

On Day 0, prior Ferric Carboxymaltose dosing the following will occur:

- Re-verify the inclusion and exclusion criteria
- Update any relevant history
- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Height
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Log on to the EDC system and register subject for study drug dosing.

After assignment of the treatment group (Cohort 1 and 2, subsequently) the following will occur:

- Blood samples for PK/PD before start of dose.
- Weight in kg without shoes
- Verify amount of single Ferric Carboxymaltose dose (7.5 or 15 mg/kg up to a maximum dose of 750 mg whichever is smaller).
- Document start and stop time of Ferric Carboxymaltose administration, the total dose administered.
- Obtain sitting heart rate and blood pressure immediately pre-dose, immediately post-dose, and 30 minutes post Ferric Carboxymaltose administration. Body temperature taken pre-dose
- Adverse event assessment (starting at beginning of Ferric Carboxymaltose injection).

Blood samples for PK/PD will be drawn at 1, 2, 6 and 12 hours post the Day 0 Ferric Carboxymaltose dose.

### 6.3.2. Days 1 and 2 (24 and 48 hour)

- Blood samples for PK/PD
- Adverse events assessment

### 6.3.3. 72 hour, and Days 14 and 28 (weeks 2 and 4)

- Blood samples for PK/PD (72 hour visit only)
- Vital signs
- Hematology, Chemistry and iron indices
- Adverse events assessment
- Concomitant medications assessment
- ESA stability/use ( if applicable)

### 6.3.4. Day 35 (week 5) End of Study

- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Vitals signs
- hematology, chemistries and iron indices
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Adverse events assessment
- Log onto EDC and enter subject as complete

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

### 6.3.5. Pharmacokinetics and Pharmacodynamics (PK/PD)

Blood samples will be collected for PK/PD assessment pre-dose and at 1, 2, 6, 12, 24, 48 and 72 hours post dose. Blood samples should be taken at approximately the same time of day as the initial pre-dose sample on Day 0.

Prior to Day 0, subjects will return to the clinic on Day -1 at which time blood samples will be drawn at 8am, 12pm and 8pm to characterize the subjects specific iron profile.

Total blood volume (regular hematology, chemistry, iron indices and PK/PD) collected per day and during the 35 Day study is provided below:

| | Screening | Day (-1) | Day 0 | 24hr | 48hr | 72hr | Day14 | Day 28 | Day 35 | **Total Blood Volume** |
|---|---|---|---|---|---|---|---|---|---|---|
| Hem/Chem/II (4.5ml) | 4.5ml | | | | | 4.5ml | 4.5ml | 4.5ml | 4.5ml | |
| PK/PD (2ml) | | 6ml | 10ml | 2ml | 2ml | 2ml | | | | |
| **TOTAL** | **4.5ml** | **6ml** | **10ml** | **2ml** | **2ml** | **6.5ml** | **4.5ml** | **4.5ml** | **4.5ml** | **44.5ml / approx. 9.03 tsps.*** |

***4.93 mL = 1 tsp.**

### 6.4 Central Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. All serum laboratory testing will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 35 laboratory, this laboratory may be obtained after notification of the Sponsor. The laboratory assessments will be determined as listed in Section 3.2.3.

| | |
|---|---|
| Hematology: | Hb, 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, bicarbonate and magnesium |
| Iron indices: | serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT) |
| Other: | Serum pregnancy test |

## 7.0 ASSESSMENT OF SAFETY

### 7.1 Adverse Events

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

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

To quantify the severity of adverse events, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version 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 Ferric Carboxymaltose through the completion of the study Day 35. AE's will be captured 28 days post the last dose of Ferric Carboxymaltose for subjects who early terminate from the trial. This can be completed via a phone call. All ongoing adverse events related to Ferric Carboxymaltose 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 Ferric Carboxymaltose 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*.

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

## 7.2 Reporting of Adverse Events

Adverse experiences will be elicited by nonspecific questions such as “Have you noticed any problems?” Subjects will be encouraged to report adverse events at their onset.
Any adverse experience spontaneously reported by, elicited from the subject 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 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:** All SAEs will be reported from the initial treatment with Ferric Carboxymaltose through the completion of the study Day 35. SAEs will be captured 28 days post the last dose of Ferric Carboxymaltose for subjects who early terminate from the trial. This can be completed via a phone call. 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 lead to prolongation of hospital stay should not be considered SAE’s. 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 (within 24 hours of learning of the event) 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 IRB / Ethics Committee per their reporting guidelines.

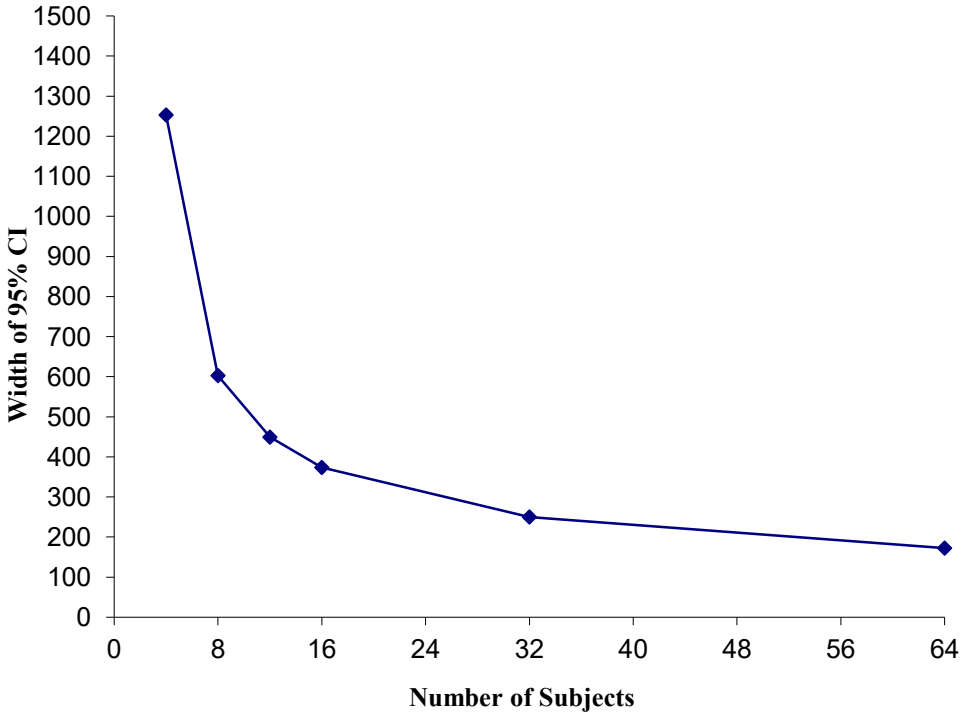
The responsible investigator must determine whether the degree of any untoward event warrants removal of any subject from the study. He/she should, in any case, institute appropriate diagnostic and/or therapeutic measures, and keep the subject under observation for as long as is medically indicated.

## 8.0 STATISTICS

No hypothesis testing will be performed for this study.

### 8.1 Sample Size

Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients.




Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally disturbed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system.

## 8.2 Analysis Populations

There will be 2 analysis populations:

- Safety population: Includes all subjects who receive Ferric Carboxymaltose.
- PK/PD population: Includes all subjects in the safety population who have evaluable iron profiles and no protocol violation that could affect the PK/PD of Ferric Carboxymaltose.

## 8.3 Demographic Characteristics

Demographic characteristics will be summarized for the Safety and PK/PD populations. The number and percentage of subject's who are registered, treated, prematurely discontinue, and complete the study will be summarized after the study's conclusion.

Subjects with clinically important protocol deviations will be identified for each analysis population, treatment group, and type of deviation. The clinical team will identify deviations and the deviations will be identified in the database.

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

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class (SOC) and preferred term for all subjects.

## 8.4 Endpoints and Definitions

### 8.4.1 Clinical Endpoints

Clinical endpoints include:

- Efficacy: change from baseline to each scheduled visit for hemoglobin, ferritin, and TSAT.
- Safety:
    - ✓ Proportion of subjects reporting treatment-emergent adverse events, overall and related, by SOC and preferred term
    - ✓ Subjects reporting treatment-emergent serious adverse events, overall and related, will be identified
    - ✓ Mean change from baseline to each scheduled visit for clinical laboratory values
    - ✓ Incidence of treatment-emergent potentially clinically significant (PCS) clinical laboratory values
    - ✓ Incidence of treatment-emergent PCS vital sign values.

## 8.5 Pharmacokinetics and Pharmacodynamics (PK/PD) Endpoints

The primary and secondary pharmacokinetic parameters will be determined for each subject as appropriate, based on serum concentration. The baseline parameters will be subtracted from all measured samples.

The primary parameters are the maximum serum concentration ($C_{max}$), the area under the serum concentration-time curve from time zero to the last sampling time (t) with a quantifiable concentration ($AUC_{0\text{-time last measured concentration}}$), the extrapolated area under the serum concentration- time curve from time zero to infinity ($AUC_{0\text{-infinity}}$), and the half-life ($T_{1/2}$). $C_{max}$ is calculated as a non-compartmental variable, which is a more conservative method than if it were calculated using a compartmental paradigm. $T_{1/2}$ incorporates the calculation of the rate elimination constant ($K_{el}$).

The secondary parameters are the mean residence time (MRT), the apparent serum clearance (Cl), and the apparent volume of distribution ($V_d$), which includes the initial volume of

distribution following the injection ($Vd_c$), the volume of distribution at the steady state ($Vd_{ss}$), and the volume of distribution at the final elimination ($Vd_{area}$).

Pharmacodynamic parameter will include serum ferritin, transferrin, transferrin saturation (TfS) UIBC, HGB, reticulocyte count and transferrin receptors.

The Pharmacokinetic and Pharmacodynamic parameters performed in this study for analysis will be outlined in a Statistical and Analytical Plan.

### 8.6 Statistical Analyses of Safety

The Medical Dictionary for Regulatory Activities (MedDRA) Terminology will be used to classify all adverse events with respect to system organ class and preferred term.
The number and proportion of subjects who report treatment-emergent adverse events will be summarized for each treatment group. A similar summary will be provided for all treatment emergent serious adverse events.

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 to study drug. Relationship to study drug will be categorized as related (possibly or probably related) and unrelated. Events with unknown severity or relationship will be counted as unknown.

Subjects 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 subject reports multiple preferred terms for a system organ class (SOC), the subject will be counted only once for that SOC.

Change in vital signs from baseline to each scheduled study visit will be summarized descriptively with the mean, median, standard deviation, minimum value, and maximum value. The number and percent of patients with potentially clinically significant vital signs will be summarized for each treatment group.

### 8.7 DSMB Analyses

A DSMB will review safety information for subjects in Cohort 1 before dosing begins for Cohort 2. A Charter will be developed outlining the DSMB processes.

## 9.0 ADMINISTRATIVE CONSIDERATIONS

### 9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including electronic copies of 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 subject must be maintained, that includes the signed Informed Consent form and copies of all study documentation related to that subject. 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 subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator Brochure, including potential risks and side effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (including amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subjects.
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 subjects into the study.

## 9.4 Advertisement for Subject Recruitment

All advertisements for subject recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisements may include but is not limited to newspaper, fliers, radio, television, etc. Any compensation to the subject 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 subject 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 subjects 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 (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 principal

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. 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 United States (US) Code of Federal Regulations on Protection of Human Subjects (21 CFR 50), IRB regulations (21 CFR 56), the most current version of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312 and applicable ICH guidelines.

### 9.7.2 Institutional Review Board

The protocol and the Informed Consent / Assent 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 US Regulations (21 CFR 56). Investigators are responsible for the following:

- Obtain IRB approval of the protocol, Informed Consent / Assent and any advertisements to recruit subjects; 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 serious adverse events that occur or are reported to you by the Sponsor.

### 9.7.3 Informed Consent

Informed consent / Assent when appropriate must be obtained from each subject prior to study participation. The informed consent / assent will be provided to the subject in their native language. The consent/assent form must be signed by the subject and/or the subject's legally authorized representative. Each investigational site must provide the Sponsor (or designee) with a copy of the Informed Consent / Assent approved by that site's Institutional Review Board. The

original signed consent / assent form will be retained in the subject's study records, and a copy will be provided to the subject. The Clinical Monitor will assure that each Informed Consent / Assent meets the requirements of Parts 50.20 and 50.25 of Title 21 of the CFR, which outlines the basic elements of informed consent and ICH guidelines. Translations of the informed consent / assent must be certified by a qualified translator and their use must be documented.

The Informed Consent / Assent documents the information the Investigator provides to the subject and the subject'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 / Assent must be signed and dated by each subject and/or legal representative before entering the study and prior to the performance of any study specific procedures.

### 9.7.4 Good Clinical Practice

The conduct of the study will conform to the recommendations for clinical studies in human subjects as set out in the current version of the Edinburgh, Scotland Revision of the "Declaration of Helsinki", the local legal requirements and the guidelines on "Good Clinical Practice", [21 CFR Part 312 and ICH guidelines].

## 9.8 Data Handling and Record Keeping

### 9.8.1 Electronic Case Report Form (eCRF)

- eCRFs will be provided for each subject on this study. The participants in this study will be identified only by initials and subject 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 eCRFs are to be reviewed by the Clinical Monitor at Luitpold Pharmaceuticals, Inc. (or designee). Source data will be reviewed by the Clinical Monitor 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 subjects 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, DSMB, investigator, or study 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 subjects, failure of the investigator to enroll subjects 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 subject 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, which 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.

## 10.0 GOVERNANCE COMMITTEE

### 10.1 Data and Safety Monitoring Board

The DSMB will be composed of approximately 3-5 senior academic individuals, including the DSMB Chair. They will have high-level expertise in pediatric iron deficiency anemia and/or statistics. A senior statistician assigned to the trial from the group performing data management services for this trial will oversee the provision of interim data reports for use by the DSMB. The data management group for this trial will transfer pre-agreed datasets to the DSMB. During the Open Session of the DSMB meetings, the Study Chair or Luitpold representatives may present updates on the trial status or the safety profile of Ferric Carboxymaltose, but will not be privy to discussions of the data conducted during the Closed Sessions and will not vote. Proceedings and

minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the patients and, to this end, will undertake reviews of the safety data. The DSMB will have access to an agreed subset of the study data as listed in the DSMB charter (updated as necessary during the trial) throughout the study duration. In addition, the DSMB will evaluate the data approximately (as outlined in the Charter) either by face to face meeting or teleconference. The DSMB will evaluate the safety from both cohorts 1 and 2 (7.5 or 15 mg/kg of Ferric Carboxymaltose). Only after all subjects in cohort 1 have completed through week 4 and the DSMB has evaluated the safety data as acceptable will registration into cohort 2 be granted. The DSMB will determine if it believes the trial should be terminated early because clear evidence of a significant safety concern exists.

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

## INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 50, 54, 56 and 312 and all applicable local, state, and federal regulations and ICH guidelines.

_____
Investigator's signature

_____
Date

_____
Investigator's Name (Please print)

## REFERENCES

1. Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment.Pharmacol.Ther.* 2006; 24: 1507-1523

2. Foley RN, Parfrey PS, Harnett JD *et al*. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int.* 1996; 49: 1379-1385

3. Staples AO, Greenbaum LA, Smith JM *et al*. Association between clinical risk factors and progression of chronic kidney disease in children. *Clin.J.Am.Soc.Nephrol.* 2010; 5: 2172-2179

4. Wharton BA. Iron deficiency in children: detection and prevention. *Br.J.Haematol.* 1999; 106: 270-280

5. Kazal LA, Jr. Prevention of iron deficiency in infants and toddlers. *Am.Fam.Physician* 2002; 66: 1217-1224

6. Michaud L, Guimber D, Mention K *et al*. Tolerance and efficacy of intravenous iron saccharate for iron deficiency anemia in children and adolescents receiving long-term parenteral nutrition. *Clin.Nutr.* 2002; 21: 403-407

7. Pinsk V, Levy J, Moser A, Yerushalmi B, Kapelushnik J. Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. *Isr.Med.Assoc.J.* 2008; 10: 335-338

8. Surico G, Muggeo P, Muggeo V *et al*. Parenteral iron supplementation for the treatment of iron deficiency anemia in children. *Ann.Hematol.* 2002; 81: 154-157

## APPENDIX 1: FERRIC CARBOXYMALTOSE PACKAGE INSERT

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Injectafer safely and effectively. See full prescribing information for Injectafer.**

**INJECTAFER® (ferric carboxymaltose injection)**
**For intravenous use**
**Initial U.S. Approval: 20XX**

**----------INDICATIONS AND USAGE----------**

Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

**----------DOSAGE AND ADMINISTRATION----------**

For patients weighing 50kg (110lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750mg for a total cumulative dose of 1500mg of iron per course.

For patients weighing less than 50kg (110lb): Give Injectafer in two doses separated by at least 7 days and give each dose as 15 mg/kg body weight.

Injectafer treatment may be repeated if iron deficiency anemia reoccurs. (2)

**----------DOSAGE FORMS AND STRENGTHS----------**

750 mg iron / 15 mL single-use vial(3)

**----------CONTRAINDICATIONS----------**

Hypersensitivity to Injectafer or any of its inactive components. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- **Hypersensitivity reactions:** Observe for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of each administration. (5.1)
- **Hypertension:** Monitor patients closely for signs and symptoms of hypertension following each Injectafer administration. (5.2)

**----------ADVERSE REACTIONS----------**

The most common adverse reactions (≥2%) are nausea, hypertension, flushing, hypophosphatemia, and dizziness (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact American Regent at 1-800-734-9236 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**----------USE IN SPECIFIC POPULATIONS----------**

- Nursing Mothers: Exercise caution when administered to a nursing woman. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: July 2013**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Injectafer is indicated for the treatment of iron deficiency anemia in adult patients;

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

## 2 DOSAGE AND ADMINISTRATION

For patients weighing 50 kg (110 lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectafer in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

The dosage of Injectafer is expressed in mg of elemental iron. Each mL of Injectafer contains 50 mg of elemental iron. Injectafer treatment may be repeated if iron deficiency anemia reoccurs.

Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

When added to an infusion bag containing 0.9% Sodium Chloride Injection, USP, at concentrations ranging from 2 mg to 4 mg of iron per mL, Injectafer solution is physically and chemically stable for 72 hours when stored at room temperature. To maintain stability, do not dilute to concentrations less than 2 mg iron/mL.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Each vial of Injectafer is intended for single use only. Any unused drug remaining after injection must be discarded.

Avoid extravasation of Injectafer since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectafer administration at that site.

## 3 DOSAGE FORMS AND STRENGTHS

750 mg iron / 15 mL single-use vial

## 4 CONTRAINDICATIONS

Hypersensitivity to Injectafer or any of its components [see *Warnings and Precautions (5.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

**Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.** [see *Adverse Reactions (6.1 and 6.2)*]. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

### 5.2 Hypertension

In clinical studies, hypertension was reported in 3.8% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration [*see Dosage and Administration (2)*].

### 5.3 Laboratory Test Alterations

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

. Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
. Hypertension *[see Warnings and Precautions (5.2)]*
. Lab test alterations *[see Warnings and Precautions (5.3)]*

### 6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.
In two randomized clinical studies [Studies 1 and 2, *See Clinical Studies (14)*], a total of 1,775 patients were exposed to Injectafer 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥ 1% of treated patients are shown in the following table.

**Table 1. Adverse reactions reported in ≥ 1% of Study Patients in Clinical Trials 1 and 2**

| Term | Injectafer (N=1775) % | Pooled Comparators[a] (N=1783) % | Oral iron (N=253) % |
|---|---|---|---|
| Nausea | 7.2 | 1.8 | 1.2 |
| Hypertension | 3.8 | 1.9 | 0.4 |
| Flushing/Hot Flush | 3.6 | 0.2 | 0.0 |
| Blood Phosphorus Decrease | 2.1 | 0.1 | 0.0 |
| Dizziness | 2.0 | 1.2 | 0.0 |
| Vomiting | 1.7 | 0.5 | 0.4 |
| Injection Site Discoloration | 1.4 | 0.3 | 0.0 |
| Headache | 1.2 | 0.9 | 0.0 |
| Alanine Aminotransferase Increase | 1.1 | 0.2 | 0.0 |
| Dysgeusia | 1.1 | 2.1 | 0.0 |
| Hypotension | 1.0 | 1.9 | 0.0 |
| Constipation | 0.5 | 0.9 | 3.2 |

[a] Includes oral iron and all formulations of IV iron other than Injectafer

Other adverse reactions reported by ≥ 0.5% of treated patients include abdominal pain, diarrhea, gamma glutamyl transferase increased, injection site pain/irritation, rash, paraesthesia, sneezing. Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) have been observed in 27% (440/1638) patients in clinical trials.

### 6.2 Post-marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectafer: urticaria, dyspnea, pruritis, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a

subject who received 500 mg of Injectafer every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer.

## 7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Injectafer .

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

*Risk Summary*

Adequate and well controlled studies in pregnant women have not been conducted. However, animal reproduction studies have been conducted with ferric carboxymaltose. In these studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused fetal malformations and increased implantation loss at maternally toxic doses of approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area). The incidence of major malformations in human pregnancies has not been established for Injectafer. However, all pregnancies, regardless of exposure to any drug, has a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Animal Data*

Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Spontaneous abortions occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryofetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

### 8.3 Nursing Mothers

A study to determine iron concentrations in breast milk after administration of Injectafer (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectafer than in lactating women receiving oral ferrous sulfate.

### 8.4 Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

### 8.5 Geriatric Use
Of the 1775 subjects in clinical studies of Injectafer, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

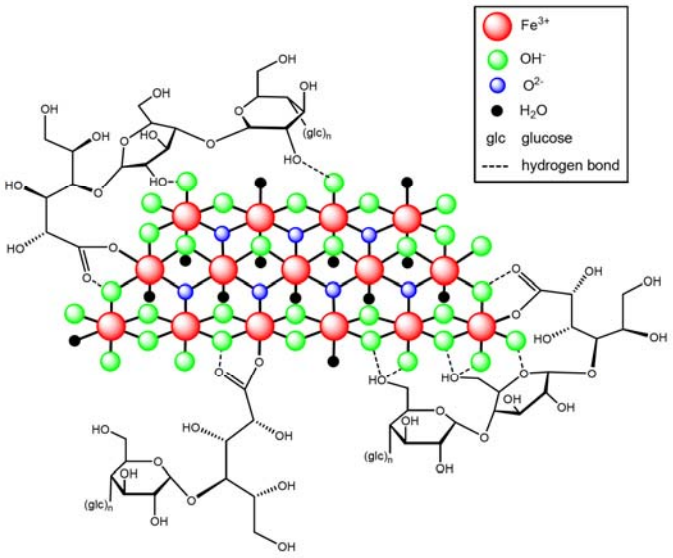
## 10 OVERDOSAGE
Excessive dosages of Injectafer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectafer 18,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability and asthenia . Hypophosphatemic osteomalacia was reported in a patient who received Injectafer 4000 mg over 4 months. Partial recovery followed discontinuation of Injectafer. [*see Post-marketing Experience (6.3)]*.

## 11 DESCRIPTION
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).

The chemical structure is presented below:




Injectafer (ferric carboxymaltose injection) is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Injectafer is available in 15 mL single-use vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0.

Vial closure is not made with natural rubber latex

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

### 12.2 Pharmacodynamics

Using positron emission tomography (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.

### 12.3 Pharmacokinetics

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 1.21 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ferric carboxymaltose.

Ferric carboxymaltose was not genotoxic in the following genetic toxicology studies: *in vitro* microbial mutagenesis (Ames) assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test at single intravenous doses up to 500 mg/kg.

In a combined male and female fertility study, ferric carboxymaltose was administered intravenously over one hour to male and female rats at iron doses of up to 30 mg/kg. Animals were dosed 3 times per week (on Days 0, 3, and 7). There was no effect on mating function, fertility or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

## 14 CLINICAL STUDIES

The safety and efficacy of Injectafer for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer was administered at a dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

### 14.1 Trial 1: Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

Trial 1 was a randomized, open-label, controlled clinical study in patients with iron deficiency anemia who had an unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2) during the 14 day oral iron run-in period. Inclusion criteria prior to randomization included hemoglobin (Hb) <12 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%. Cohort 1 subjects were randomized to Injectafer or oral iron for 14 more days. Cohort 2 subjects were randomized to Injectafer or another IV iron per standard of care [90% of subjects received iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

**Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | Cohort 1 | | Cohort 2 | |
|---|---|---|---|---|
| | Injectafer (N=244) | Oral Iron (N=251) | Injectafer (N=245) | IV SC[a] (N=237) |
| Baseline | 10.6 (1.0) | 10.6 (1.0) | 9.1 (1.6) | 9.0 (1.5) |
| Highest Value | 12.2 (1.1) | 11.4 (1.2) | 12.0 (1.2) | 11.2 (1.3) |
| Change (from baseline to highest value) | 1.6 (1.2) | 0.8 (0.8) | 2.9 (1.6) | 2.2 (1.3) |
| p-value | 0.001 | | 0.001 | |

SD=standard deviation; [a]: Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2±224.2 ng/mL in Cohort 1 and 218.2 ±211.4 ng/mL in Cohort 2), and transferrin saturation (13±16% in Cohort 1 and 20±15% in Cohort) were observed at Day 35 in Injectafer-treated patients.

**14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease**

Trial 2 was a randomized, open-label, controlled clinical study in patients with non-dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) ≤ 11.5 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%.Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 96); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

**Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | **Injectafer (N=1249)** | **Venofer (N=1244)** |
|---|---|---|
| Baseline | 10.3 (0.8) | 10.3 (0.8) |
| Highest Value | 11.4 (1.2) | 11.3 (1.1) |
| Change (from baseline to highest value) | 1.1 (1.0) | 0.9 (0.92) |
| Treatment Difference (95% CI) | 0.21 (0.13, 0.28) | |
| | | |

Increases from baseline in mean ferritin (734.7±337.8 ng/mL), and transferrin saturation (30±17%) were observed at Day 56 in Injectafer-treated patients.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

| | |
|---|---|
| NDC 0517-0650-01 | 750 mg iron/15 mL Single-Use Vial Individually boxed |
| NDC 0517-0650-02 | 750 mg iron/15 mL Single-Use Vial Packages of 2 |

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See the USP controlled room temperature]. Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*]

Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

AMERICAN
REGENT, INC.
SHIRLEY, NY  11967

IN0602
Rev. 7/13

**Patient Information**
**INJECTAFER (ferric carboxymaltose injection)**

Please read this information carefully before taking this medication. This summary does not tell you everything about INJECTAFER. Speak with your doctor or healthcare professional if there is something you do not understand or if you would like to learn more about INJECTAFER. Your doctor or healthcare professional is your best source of information about this medicine.

## What is INJECTAFER?

Iron is a mineral that the body needs to produce red blood cells. When the body does not get enough iron, it cannot produce the number of normal red blood cells needed to keep you in good health. This condition is called iron deficiency (iron shortage) or iron deficiency anemia.

INJECTAFER is used to treat iron deficiency anemia. Iron deficiency anemia may be caused by several medical conditions including heavy menstrual bleeding, pregnancy, childbirth, inflammatory bowel disease, other malabsorption diseases, bariatric surgery, or chronic kidney disease**.**

## General information about using INJECTAFER safely and effectively

Injectable iron is administered only by or under the supervision of your health care professional.

Serious or life threatening allergic reactions have been reported with intravenous iron products. Tell your health care professional if you have ever had any unusual or allergic reaction to any IV iron.

Patients should report to their healthcare professional any signs and symptoms of an allergic reaction to INJECTAFER, in particular rashes, shortness of breath and wheezing.

Iron is not easily eliminated from the body, and its build up may be lead to a condition called iron overload which may be harmful. Certain medical conditions such as liver disease may also make you more likely to develop iron overload. Ask your doctor or healthcare professional.

## Who should not take INJECTAFER?

You should not be given INJECTAFER if you have anemia that is not caused by iron deficiency, or if you have iron overload.

If you are pregnant or plan to become pregnant please notify your doctor or healthcare professional. They will decide whether it is safe for you to receive INJECTAFER.

## How should I take INJECTAFER?

INJECTAFER is administered intravenously (into your vein) by your doctor or health care professional in two doses.

**What should I avoid while taking INJECTAFER?**

You should not take iron supplements by mouth if you are receiving iron injections. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

**What are the possible side effects of INJECTAFER?**

The side effects of INJECTAFER are infrequent, usually mild and generally do not cause patients to stop treatment. The most common side effects are nausea, injection site reactions (including pain or bruising at the injection site), asymptomatic reductions in blood phosphorus, flushing, headache, hypertension, dizziness, and increased alanine aminotransferase. Potentially long lasting brown staining of skin near injection site may occur.

These are not all the possible side effects of INJECTAFER. For more information ask your doctor or healthcare professional.

Talk to your doctor if you think you have side effects from taking INJECTAFER.

## APPENDIX 2: WEIGHT CHARTS FOR BOYS AND GIRLS

**Boys (White) Weight Chart age 0-36 months** (http://www.halls.md/chart/boys-weight-w.htm)

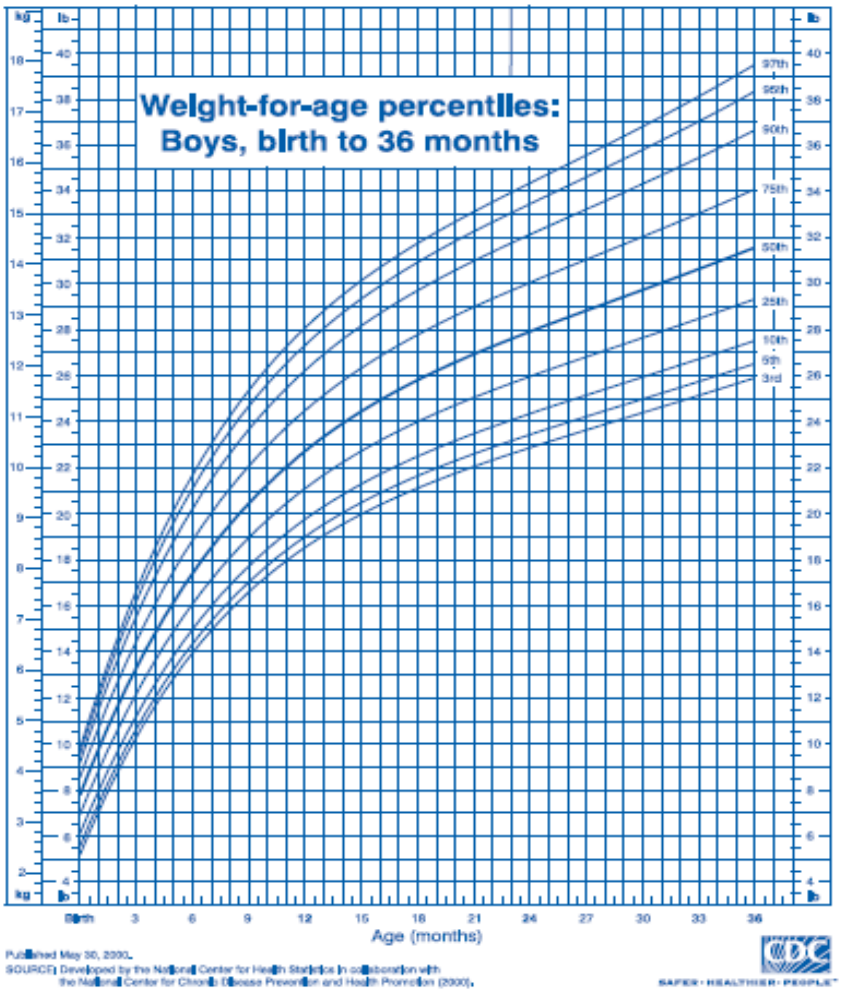
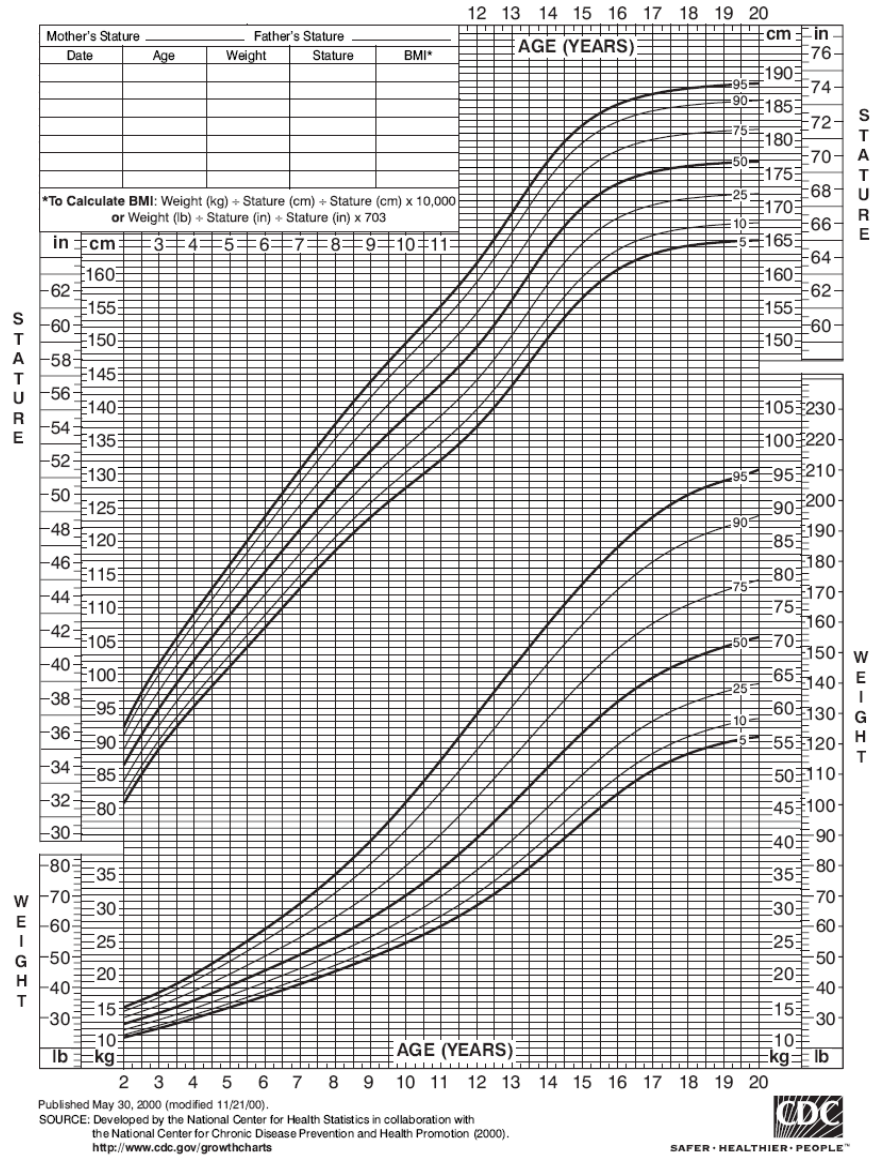



Figure 1. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Boys weight-for-age

## BOYS (WHITE) WEIGHT CHART AGE 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L021.PDF)



**Girls (White) Weight Chart age 0-36 months** (http://www.halls.md/on/girls-weight-w.htm)

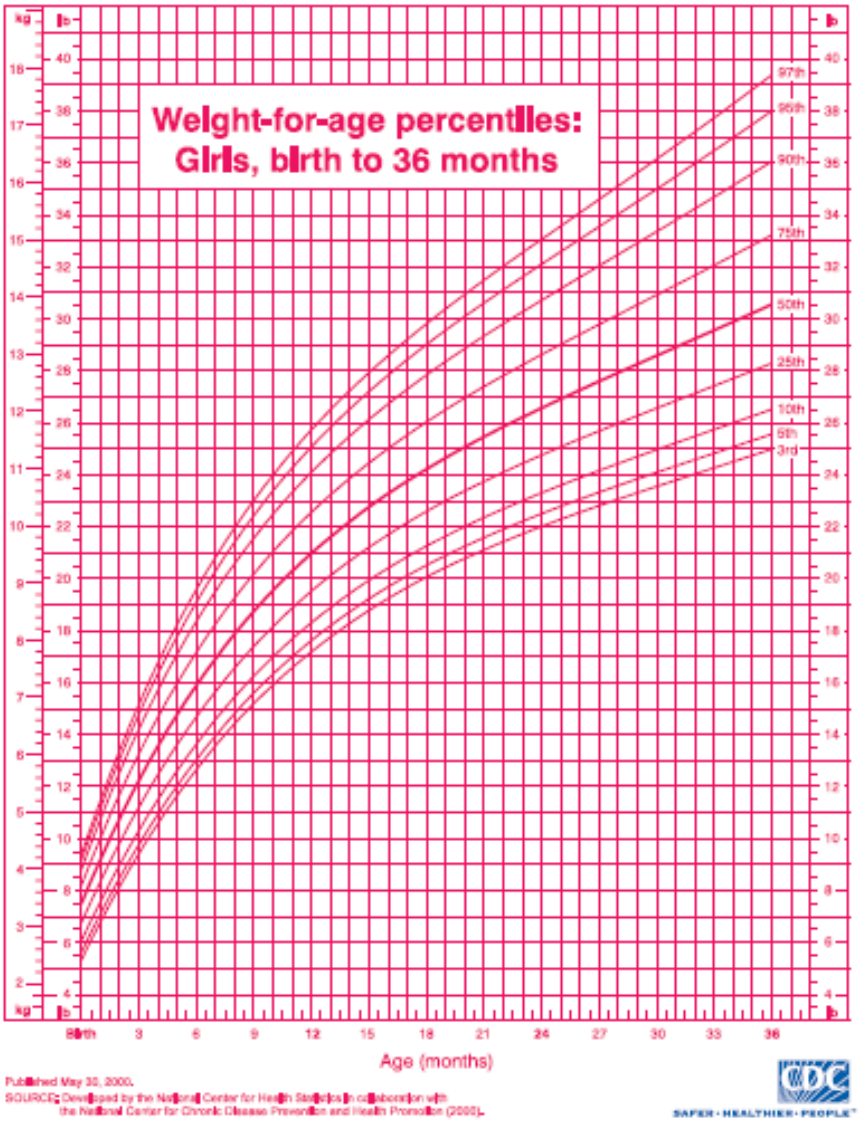
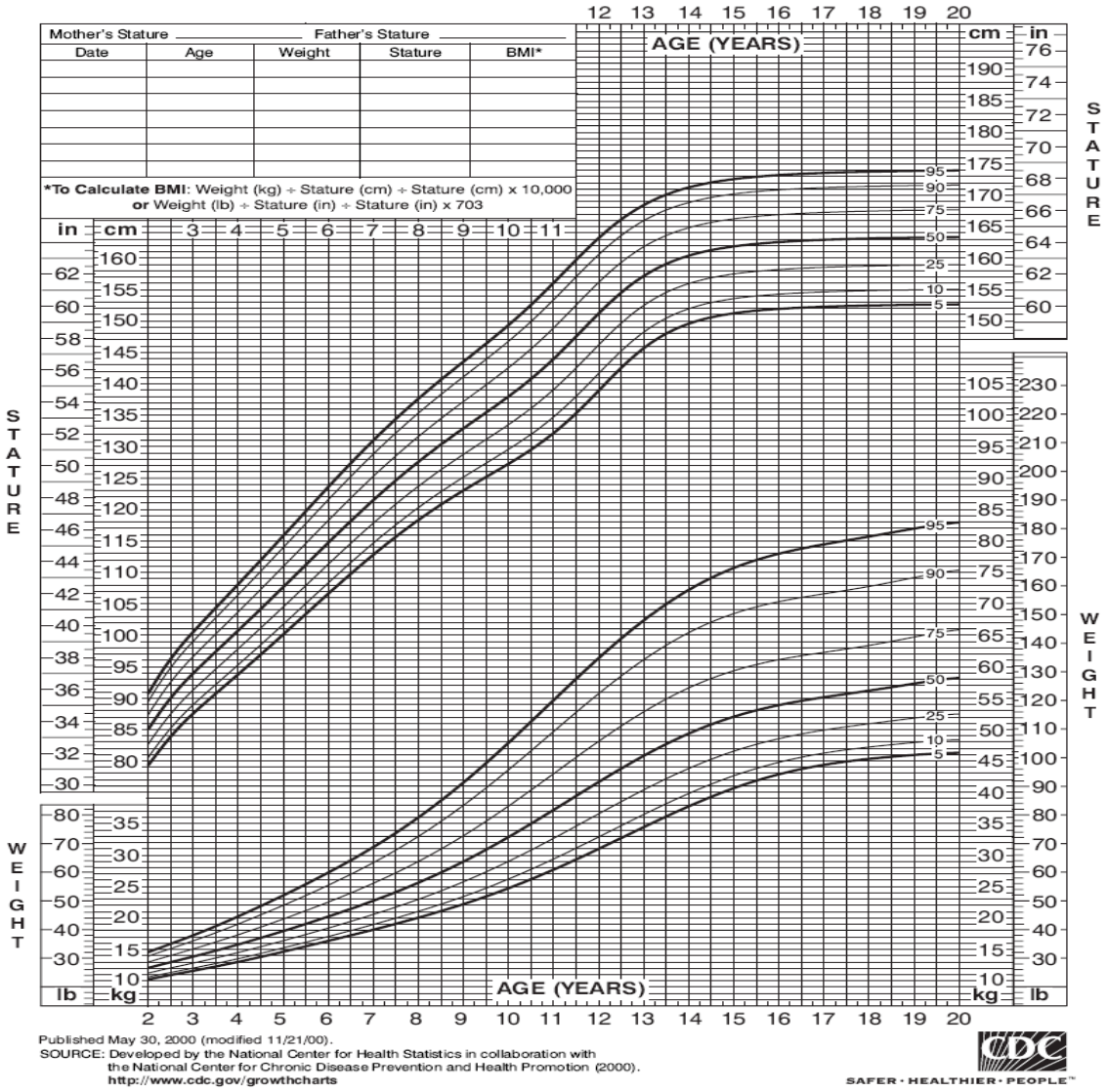



Figure 2. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Girls weight-for-age

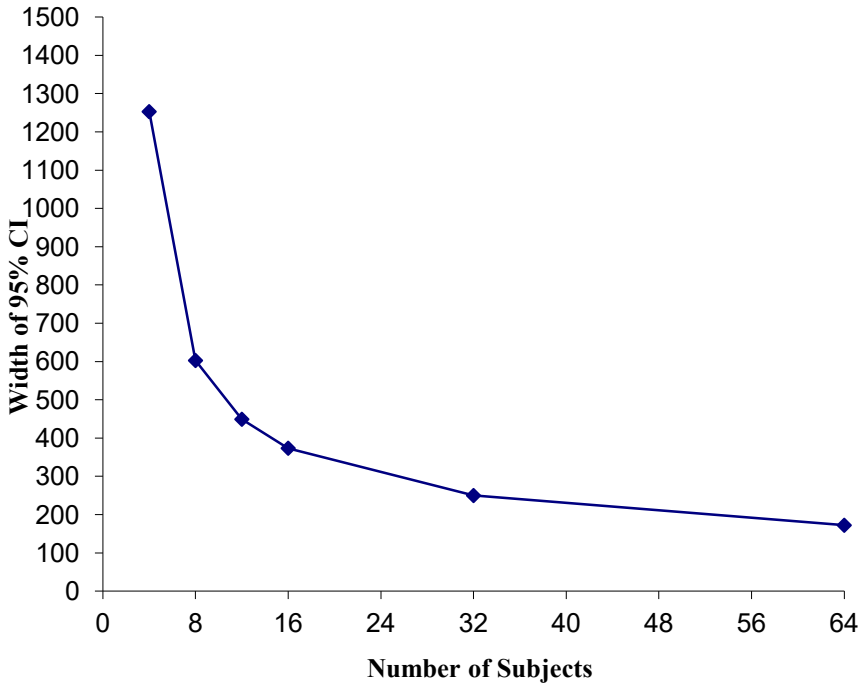
## GIRLS (WHITE) WEIGHT CHART AGES 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L022.PDF)



## APPENDIX 3: ADMENDMENT I CHANGES

| | |
|---|---|
| Title Page: | |
| Original Wording: | Protocol Date:<br>27 March 2014 |
| New Wording: | Protocol Date:<br>Amendment 1: 29 July 2014 |
| Study Synopsis and 8.1 Sample Size Rationale: | |
| New Wording: | Sample Size:<br><br>Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients. |

| | |
|---|---|
| |  <br><br>Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally disturbed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system. |
| Original Wording: | Exclusion Criteria:<br><br>3. Body mass index (BMI) ≤ 95$^{th}$ percentile for age (see APPENDIX 2) |
| New Wording: | 3. Body mass index (BMI) ≤ 5$^{th}$ percentile for age (see APPENDIX 2) |
| Original Wording: | Trial design – Phase III |
| New Wording: | Trial Design – Phase II |
| Additional Wording – Sections 7.1 | All laboratory values at the end of study/Day 35 that have been deemed clinical significant by the Investigator should be followed until they are back into normal range. |
| | |

## APPENDIX 4: ADMENDMENT II CHANGES

| | |
|---|---|
| Title Page: | |
| Original Wording: | Protocol Date: 27 March 2014<br>Amendment 1: 29 July 2014 |
| New Wording: | Protocol Date: 27 March 2014<br>Amendment 1: 29 July 2014<br>Amendment II: 08 October 2014 |
| Signature of Agreement For Protocol Original Wording: | Marc Tokars Date<br>Vice President of Clinical Operations<br>Luitpold Pharmaceuticals, Inc.<br><br>Marsha Simon Date<br>Sr. Manager-Regulatory Affairs<br>Luitpold Pharmaceuticals, Inc.<br><br>David Morris, PhD Date<br>Senior Director, Statistics<br>WebbWrites, LLC |
| Signature of Agreement For Protocol New Wording: | Sylvan Hurewitz, MD Date<br>Medical Director<br>Luitpold Pharmaceuticals, Inc.<br><br>Syed Quadri, MD Date<br>Medical Director, Pharmacovigilance<br>Luitpold Pharmaceuticals, Inc.<br><br>Marsha Simon Date<br>Sr. Manager-Regulatory Affairs<br>Luitpold Pharmaceuticals, Inc.<br><br>David Morris, PhD Date<br>Senior Director, Statistics<br>WebbWrites, LLC |

| | |
|---|---|
| New Exclusion Criteria Wording: | Exclusion Criteria # 4: Male or Female subject 1 year of age weighing < 12kg. |
| Exclusion Criteria Deletion | Deleted original criteria number 12. Significant blood loss (> 100 ml) within the last 3 months or any current bleeding disorders or anticipated need for surgery that may result in significant blood loss (> 100 ml). |
| Original Wording section 6.3.5 Blood Volume Table: | Total Blood Volume = 72mL/approx. 14.6 tsps |
| New Wording section 6.3.5 Blood Volume Table: | Total Blood Volume = 44.5mL/approx. 9.03 tsps |
| New Wording | Injectafer ® replaced by Ferric Carboxymaltose throughout Protocol |

## APPENDIX 5: Local Protocol Amendment I for Russia

| | |
|---|---|
| Title Page: | |
| Original Wording: | Protocol Date: 27 March 2014<br>Amendment 1: 29 July 2014<br>Amendment II: 08 October 2014 |
| New Wording: | Protocol Date: 27 March 2014<br>Amendment 1: 29 July 2014<br>Amendment II: 08 October 2014<br>Local Protocol Amendment I for Russia: 24 February 2015 |
| | |
| Inclusion Criteria: | Additional wording Inclusion criteria #1:<br>1. Male or female subjects 1 to 17 years of age (6 to 17 years of age in Russia only) with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee. |
| | |
| 6.3.2 Day 0 | • Log on to the EDC system and register subject for study drug dosing. The EDC system will assign the subject into Cohort 1 or 2 treatment group.<br><br>After assignment of the treatment group (Cohort 1 and 2) the following will occur: |
| | Updated wording:<br>• Log on to the EDC system and register subject for study drug dosing.<br><br>After assignment of the treatment group (Cohort 1 and 2, subsequently) the following will occur: |

**LUITPOLD PHARMACEUTICALS, INC.**

**PROTOCOL**

**No. 1VIT13036**

**IND #: 63,243**

# A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Injectafer® (Ferric Carboxymaltose) in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA)

SPONSOR

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

**Protocol Date: 27 March 2014**

**Amendment I Date: 29 July 2014**

**SIGNATURES OF AGREEMENT FOR PROTOCOL**

7/30/14

Marc Tokars
Vice President of Clinical Operations
Luitpold Pharmaceuticals, Inc.

Date

7/30/14

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

Date

30 July 2014

David Morris, PhD
Senior Director, Statistics
WebbWrites, LLC

Date

## Study Synopsis

## Protocol No. 1VIT13036

**Title:** A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Injectafer® (Ferric Carboxymaltose) in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA).

**Drugs:** Injectafer® **(**Ferric Carboxymaltose)

**Objectives:** The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Injectafer® for the pediatric population suffering from iron deficiency (ID) with anemia.

**Study Design:** This is a Phase II, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Injectafer® dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Injectafer®.

**Treatment**

Cohort 1: 16 subjects will be treated with Injectafer® at 7.5 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Injectafer® at 15 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving an erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Injectafer®.
2. Subject previously randomized and treated in this study or any other clinical study of Injectafer® (FCM or VIT-45).
3. Body mass index (BMI) $\leq 5^{th}$ percentile for age (see APPENDIX 2)
4. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
5. Chronic kidney disease subjects on hemodialysis.
6. Screening Ferritin level > 300ng/mL

7. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
8. Any active infection.
9. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
10. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
11. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.
12. Significant blood loss (> 100 ml) within the last 3 months or any current bleeding disorders or anticipated need for surgery that may result in significant blood loss (> 100 ml).
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subjects who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

**Subject Assessments:**

All subjects that provide informed consent / assent will enter a screening period up to 14 days prior to Day 0. During this time subjects will be evaluated to insure they meet the study entry criteria. Subjects will have vital signs, medical history review and laboratory samples to include hematology, chemistries and iron indices. Once it has been determine the subject qualifies for participation the subject will be scheduled to return to the clinic 1 day prior to Day 0 (Day -1) at which time additional blood samples will be taken (8am, 12pm and 8pm) to characterize the subjects iron profile.

Blood samples for PK/PD will also be assessed immediately prior to Injectafer® dosing on Day 0, at 1, 2, 6, 12, 24, 48 hours and at 72 hours.

Safety assessments, including vital signs and adverse events, will be assessed starting on Day 0 at the time of Injectafer® dosing through Day 35.

**Erythropoietin Dosage:**

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

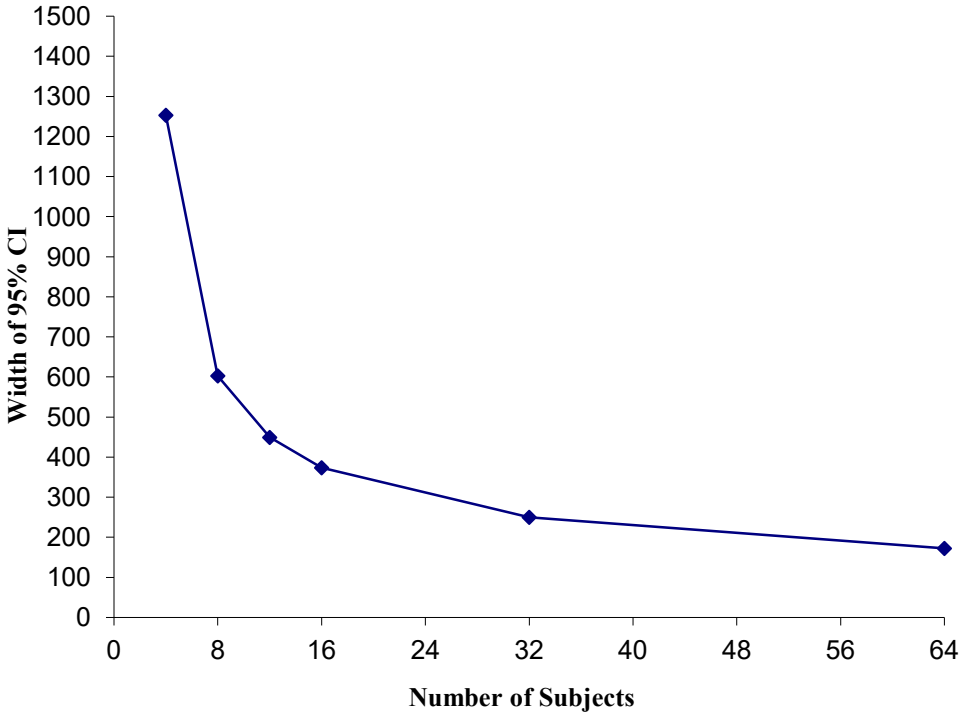
**Study Duration per subject:** up to 9 weeks

**Number of Subjects:** 32 subjects

**Sites:** Approximately 10

**Sample Size:**

Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients.




Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally disturbed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system.

## CONTACT PERSON FOR THE STUDY

For study related questions please contact:

Angelia D. Butcher
Senior Clinical Project Manager
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Norristown, PA 19403

Telephone: 610-650-4200
Fax: 610-650-7781

**TABLE OF CONTENTS**

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| BP | Blood Pressure |
| BW | Body Weight |
| CI | confidence interval |
| CKD | Chronic Kidney Disease |
| conc. | concentration |
| CTCAE | Common Terminology Criteria for Adverse Event |
| dL | Deciliter |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| e.g. | for example |
| ESA | Erythropoiesis stimulating agent |
| FDA | Food and Drug Administration |
| Fe | Iron |
| g | Gram |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| Hct | Hematocrit |
| Hgb | Hemoglobin |
| HMW | high molecular weight |
| IBD | Inflammatory Bowel Diease |
| ICH | International Conference on Harmonisation |
| IDA | Iron Deficiency Anemia |
| i.e. | that is/ such that |
| IRB | Institutional Review Board |
| IV | Intravenous |
| IVP | Intravenous injection (push) |
| kg | Kilogram |
| L | Liter |
| LMW | low molecular weight |
| LOS | length of stay |
| MedDRA | Medical dictionary for regulatory activities |
| mg | Milligram |
| mL | Milliliter |
| ng | Nanogram |
| PET | positron emission tomography |
| p.o. | by mouth or orally |
| RES | Reticuloendothelial system |
| SAE | Serious adverse event |
| $t_{1/2}$ | Terminal half-life |
| t.i.d. | three times a day |
| TSAT | Transferrin Saturation |
| US | United States |
| vs | Versus |
| w/v | weight / volume |

# 1.0 INTRODUCTION

## 1.1 Treatment of Iron Deficiency Anemia

Iron deficiency anemia ("IDA") remains the most common nutritional deficiency in children in the United States. Rapid growth, insufficient dietary intake, and limited absorption of dietary iron combine to place children at increased risk for iron deficiency. Iron deficiency may contribute significantly to anemia due to malabsorption, gastrointestinal blood loss, or iatrogenically due to repeated blood samplings. As a result of severe digestive tract disorders, some children are unable to tolerate oral iron supplementation or are unresponsive to it.[1] Anemia may also decrease survival rates in patients (both adults and children) with chronic renal impairment where it is a commonly encountered problem[2;3] In addition, anemia is a commonly encountered manifestation of pediatric inflammatory bowel disease which is associated with a decrease in the quality of life and increased hospitalization.

Non-hematologic consequences of iron deficiency include poor weight gain, anorexia, irritability, decreased attention span, exercise intolerance and decreased physical activity. [4] However, IDA in infants and toddlers is associated with long-lasting diminished mental, motor, and behavioral functioning. Although the exact relationship between iron deficiency anemia and the developmental effects is not well understood, it appears that these effects do not occur until iron deficiency becomes severe and chronic enough to produce anemia. [5]

Options for correcting iron deficiency include both oral and parenteral formulations. As previously described, some children are unable to tolerate or are non-responsive to oral iron. Blood transfusion is an option to treat anemia and restore iron requirements, but the potential risk of blood-transmitted virus infection limits its use to severe and badly tolerated anemia. In view of the limitations associated with oral iron or blood transfusions, intravenous administration is an important option.

Multiple parenteral iron products are available. These vary in complex types which impacts the total amount of iron that may be administered in a single administration. Numerous other differences differentiate the products; however, all appear to effectively release iron post administration and restore the deficit of the patient. There are numerous studies with iron sucrose injection (Venofer®) that have been performed in the pediatric population [6-8]. Iron doses have varied in the studies with demonstrated efficacy and safety in doses up to 7mg iron/kg or 200mg given in time frames of 3 min, which was shown to be beneficial to both the child and health care facility[6].

Injectafer® has been characterized as a robust and strong type iron complex (Type 1) with a molecular mass of about 150,000 Daltons (Da). The solution is a dark brown color with a near neutral pH (5.0 to 7.0) and a physiological osmolarity permitting administration of higher single doses in short time periods. Although no interventional studies have been conducted with Injectafer® in the pediatric population to date, the product has been used in clinical practice in markets where it is currently approved for adults to aid correction of iron deficiency within the pediatric gastroenterological setting. A non-interventional/retrospective observational data collection has identified in 79 patient's aged 2 to 18 years with a mean age of 12.7 years. In these subjects, Injectafer® showed efficacy with regard to hemoglobin, ferritin, and TSAT as well as safety and tolerability (manuscript in preparation).

Therefore, the proposed studies will assess higher single doses (i.e., 7.5 mg/kg and 15 mg/kg) than those used with currently available parenteral iron preparations in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population. The higher single doses permit fewer

overall injections/infusions and may ultimately permit fewer visits to the treating facilities positively impacting both the child and family as well as health care system.

## 1.2 Injectafer

### 1.2.1 Key features of Injectafer

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 (RES), 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.

### 1.2.2 Injectafer versus Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various parenteral iron preparations available [(3)]. However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted their use. Injectafer offers significant advantages compared to other available intravenous iron preparations.

Iron dextran, the first parenteral iron product available in the US, has been associated with an incidence of anaphylaxis/anaphylactoid reactions (i.e., dyspnea, wheezing, hypotension, urticaria, angioedema) as high as 1.7% [(6)]. Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran. The high incidence of anaphylaxis/anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Although some have suggested that high molecular weight (HMW) iron dextran is associated with a higher rate of life threatening adverse events and anaphylactic reactions in comparison to low molecular weight (LMW) iron dextran, the US Food and Drug Administration was unable to find a clear difference after an examination of post-marketing data, clinical trial data, death certificates, and emergency room diagnoses [(7)]. Iron dextran is limited to second line therapy for treatment of iron deficiency.

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. 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, 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[11] (data on file ). 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 1.2.2.1).** Another recently approved IV iron is ferumoxytol (AMAG) 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 (see Ferumoxytol PI).

**Table 1.2.2.1 Administration of at least 1500 mg of Intravenous Iron with Currently Available Iron Preparations and Injectafer**

| 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 | 300mg | 1.5 hours | 5 |
| 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 countries outside of the US; 750 mg maximum is the U.S. FDA approved dose

The larger Injectafer and ferumoxytol doses result in less frequent administration of intravenous iron that should benefit, in particular, severely iron deficient and anemic populations. To be treated with currently available intravenous iron agents, the average inflammatory bowel disease, postpartum, heavy uterine bleeding and non-dialysis dependent patient would require an initial test dose, followed by 15 doses of iron dextran as labeled, each accompanied by personnel equipped and trained for resuscitation of anaphylaxis; 12 doses of ferric gluconate; or either 8 doses of iron sucrose (with 5 minute infusion time) or 5 / 4 doses of iron sucrose by prolonged (1.5 to 2.5 hours) intravenous infusion. Ferric gluconate and iron sucrose are not approved by the FDA for the treatment of IDA in non chronic kidney disease populations and iron dextran is only approved as second line therapy for treatment of iron deficiency. In contrast, most patients treated with Injectafer would require 2 doses administered over 8 to15 minutes one week apart.

### 1.2.3 Injectafer Human Experience

The Injectafer development program demonstrated the safety and effectiveness of intravenous Injectafer in the treatment of IDA. Clinical data are currently available from 20 Phase 2 and 3 studies including 5,799 patients, with IDA or IDA associated with CKD, who received Injectafer.
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 ($t_{½}$) was calculated to 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.

Phase III studies demonstrated the effectiveness of Injectafer in treating IDA secondary to inflammatory bowel disease, heavy uterine bleeding, chronic kidney disease (hemodialysis and non-hemodialysis) and the postpartum state. Clinically meaningful increases in hemoglobin, 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 chronic kidney disease. A head to head comparison of Injectafer (Ferric carboxymaltose) to Venofer (Iron sucrose) in over 2,500 subjects with non-dialysis dependent CKD and elevated risk of cardiovascular disease according to the Framingham criteria demonstrated that the recommended dose of Injectafer, 750 mg x 2 (1500 mg total) had superior efficacy to the labeled dose of Iron sucrose (200 mg x 5 [1000 mg total]) with regard to hemoglobin elevation and had a similar cardiovascular (and overall) safety profile, based in part on an independently adjudicated composite cardiovascular safety endpoint [(8)] .

Important details of pre- and clinical safety and efficacy can be found in the Investigator's Brochure. Ferric carboxymaltose received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) approval on June 15, 2007 for the use of Injectafer (EU Trade name: Ferinject) in 18 EU (European Union) countries and later in Switzerland. Ferric carboxymaltose was first approved as a prescription only medicine on July 6, 2007 in The Netherlands. Up until now, Injectafer has received regulatory approval for marketing authorization in 58 countries worldwide: Argentina, Australia, Austria, Bangladesh, Belgium, Bolivia, Brazil, Bulgaria, Chile, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, Iceland, India, Iran, Ireland, Israel, Italy, Kazakhstan, Kuwait, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, New Zealand, Norway, Pakistan, Peru, Poland, Portugal, Romania, Russia, Singapore, Slovenia, Slovak Republic, South Korea, Spain, Sweden, Switzerland, The Netherlands, Turkey, Ukraine, and United Kingdom. Injectafer® received approved from the Food and Drug Administration (FDA) on July 25, 2013 for marketing in the United States.

## 2.0 MAIN TRIAL OBJECTIVE

The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Injectafer® for the pediatric population suffering from iron deficiency (ID) with anemia.

## 3.0 OVERALL STUDY DESIGN AND RATIONALE

### 3.1 Trial Design

This is a phase II, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Injectafer® dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Injectafer®.

Cohort 1: 16 subjects will be treated with Injectafer® at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Injectafer® at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

### 3.2 Rationale

#### 3.2.1 Rationale for Trial Design

Injectafer is a non-dextran IV iron recently approved by the United States Food and Drug Administration (FDA). This trial is designed to assess the single doses (i.e., 7.5 mg iron/kg and 15 mg iron/kg) in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population.

### 3.2.2 Rationale for open label design

The open-label, single arm trial design is considered appropriate because a control group is not required to estimate the PK/PD profile of Injectafer®. The risk from exposure to another form of IV iron is not offset by the minimal scientific benefit.

### 3.2.3. Schedule of Events

| Visit Day | Screening Period (Up to 14 Days) | Day -1 | Day 0 | 24 and 48 hours post dosing | 72 hours post dosing | Day 14 (week 2) | Day 28 (week 4) | Day 35 (week 5) |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Assess entry criteria | X | | X | | | | | |
| EDC | X | | X | | | | | X |
| Medical History | X | | X | | | | | |
| Physical Exam[1] | | | X | | | | | X |
| Vital Signs[6] | X | | X | | X | X | X | X |
| Height / Weight | | | X | | | | | |
| PK/PD Samples | | X[2] | X[3] | X[4] | X[4] | | | |
| Hematology, Chemistry and Iron Indices | X | | | | X | X | X | X |
| Serum pregnancy test | X | | | | | | | |
| Concomitant Medications | X | | X | | X | X | X | X |
| ESA Stability | X | | X | | X | X | X | X |
| Adverse Event Assessments[5] | | | X | X | X | X | X | X |
| Injectafer® Dosing[6] | | | X | | | | | |

[1] Includes clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system
[2] Blood samples drawn at 8am, 12pm and 8pm for subject iron profile
[3] Blood samples PK/PD should be taken prior to Injectafer® dosing and additional samples for PK/PD should be taken at 1, 2, 6 and 12 hours post dosing.
[4] Blood samples should be taken approximately the same time of day as the Day 0 samples were drawn
[5] Adverse event assessments starting at the time of Injectafer® dosing
[6] Sitting vital signs including blood pressure and heart rate should be collected immediately pre-dosing, immediately and 30 minutes post dosing. Body temperature will also be collected pre-dose only. Vital signs on non-dosing days include sitting heart rate and blood pressure only.

# 4.0 SUBJECT SELECTION

## 4.1 Number and Type of Subjects

Up to thirty two (32) subjects who have given written informed consent / assent along with parent or guardian's written informed consent with a diagnosis of iron deficiency anemia (IDA) who fulfill the inclusion criteria, do not meet any of the exclusion criteria will be registered to receive Injectafer®.

## 4.2 Screening Phase

Once a subject enters the screening phase, they will be assigned, via the Electronic Data Capture (EDC) system, a unique screening number. From the time of consent until the start of treatment of IV Injectafer®, the subject will not receive any form of iron outside of the study (intravenous or blood transfusion iron from 4 weeks prior to consent or oral iron including multivitamins with iron from time of consent).

If the subject does not qualify for study entry the subject should be entered into the EDC system as a screen failure. Subjects can be re-screened once, see section 6.2.

### 4.2.1 Entry Criteria

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving a erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial.

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Injectafer®.
2. Subject previously randomized and treated in this study or any other clinical study of Injectafer® (FCM, VIT-45).
3. Body mass index (BMI) $\leq 5^{th}$ percentile for age (see APPENDIX 2)
4. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
5. Chronic kidney disease subjects on hemodialysis.
6. Screening Ferritin level > 300 ng/mL.
7. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
8. Any active infection.
9. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
10. Known positive HIV-1/HIV-2 antibodies (anti-HIV).

11. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.
12. Significant blood loss (> 100 ml) within the last 3 months or any current bleeding disorders or anticipated need for surgery that may result in significant blood loss (> 100 ml).
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subject who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

### 4.3 Subject Assignment and Registration Process

Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this 7 week study. Cohorts 1 and 2 will be enrolled and treated sequentially. Enrollment into Cohort 2 will not begin until all Cohort 1 subjects have completed 4 weeks of therapy and no safety issues with the administration of Injectafer® has been confirmed by the DSMB.

### 4.4 Withdrawal from Study

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

At the time of withdrawal, procedures for the Day 35 visit must be performed regardless of whether the subject has completed study drug treatment. In the event the subject has received any study drug; the subject should be contacted to assess adverse events 28 days post the last dose of Injectafer®, if possible.

In the event a subject withdraws without completing the full PK/PD sampling. Additional subjects may be enrolled to ensure adequate representations of the PK/PD parameters are available for analyses. Conditions for additional enrollment will be defined in more detail in the statistical analyses plan.

### 4.5 Intervention

Intervention is defined as follows:

- Increase in dose of erythropoietin for any reason (Day 0 thru Day 35).
- Blood transfusion.
- Use of IV iron outside of protocol.
- Use of oral iron outside the protocol.

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 subject should continue in the study as scheduled through Day 35.

# 5.0 STUDY DRUG

## 5.1 Formulation Packaging and Storage

All medication to be used in this study that has been supplied by Vifor Pharma Ltd. will have been prepared according to Good Manufacturing Practices (GMP).

Injectafer® (known in the EU as Ferinject®) will be supplied as 5% w/v (weight /volume) 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.

Study drug must be kept in a secure place at the investigational site, and stored at room temperature (see: USP). Injectafer® should not be frozen. **Vials may not be used for more than 1 dose or for more than 1 subject.**

**All Injectafer® vials used and unused should be kept by the study staff and returned to Vifor Pharma Ltd., after drug accountability has been completed by the monitor.**

## 5.2 Drug Administration / Regimen

The Principal Investigator or designee will supervise administration of the study drug to subjects:

**Cohort 1**: 16 subjects will be treated with Injectafer® at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

**Cohort 2**: 16 subjects will be treated with Injectafer® at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

Injectafer® will be given on Day 0. It will be administered as either:

- An undiluted slow IV push at a rate of 100 mg/minute.
- Doses less than 100 mg should be given as a slow undiluted IV push within a minute.

## 5.3 IV Iron Precautions

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

- The subject 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 heart rate and blood pressure will be assessed pre-, immediately post, and 30 minutes post administration. If the subject 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 patients receiving IV iron therapies. Subjects 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 subjects 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 intravenous 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 Injectafer®. They will not allow Injectafer® 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 registered in the study, or to investigators not listed on the FDA 1572. When the study is completed, or if it is prematurely terminated, a final inventory of all clinical supplies must be compiled and the remainder of used and unused Injectafer® will be returned to Luitpold Pharmaceuticals, Inc. (or their designee). All data regarding Injectafer® must be recorded on the Drug Accountability Forms provided by the sponsor.

Investigators will keep adequate records of the administration and disposition of IV Injectafer® used for patients selected for the trial.

## 5.5 Concomitant Medication

Concomitant medications along with their route of administration and duration must be recorded in the electronic case report form (eCRF) from 30 days prior to consent. **No additional iron preparations (IV iron from 4 weeks prior to consent or oral iron including multivitamins with iron, from time of consent), will be allowed. No prophylactic medications may be administered prior to Injectafer® administration without prior approval from Luitpold Pharmaceuticals, Inc.**

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

# 6.0 STUDY PROCEDURES

## 6.1 Informed Consent

Prior to any study specific procedures, the investigator must explain to each subject 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 subject (who for this trial is 1 -17 years old) must assent, if appropriate and his/her legal guardian (who is above age of legal consent) voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The Code of Federal Regulations (CFR) is a codification of

rules and regulations of the United States government. The subject's legal guardian will be given a copy of the signed consent form.

## 6.2 Screening (up to 14 days)

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

- Obtain screening number from EDC
- Medical history, including prior iron therapy use
- Vitals signs (including sitting heart rate and blood pressure)
- Hematology, Chemistries and iron indices
- Serum pregnancy test for female subjects of child bearing potential (negative results must be obtained prior to registering the subject for study drug dosing).
- Concomitant medications assessment
- ESA therapy stability ( if applicable)

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

## 6.3 Study Visits

### 6.3.1. Day (-1)

Once it's confirmed during the screening period that the subject continues meet the entry criteria all eligible subjects will return to the clinic on Day – 1, blood samples will be drawn at 8am, 12pm and 8pm to characterize the subject iron profile.

### 6.3.2 Day 0

On Day 0, prior Injectafer® dosing the following will occur:

- Re-verify the inclusion and exclusion criteria
- Update any relevant history
- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Height
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Log on to the EDC system and register subject for study drug dosing. The EDC system will assign the subject into Cohort 1 or 2 treatment group.

After assignment of the treatment group (Cohort 1 and 2) the following will occur:

- Blood samples for PK/PD before start of dose.
- Weight in kg without shoes

- Verify amount of single Injectafer® dose (7.5 or 15 mg/kg up to a maximum dose of 750 mg whichever is smaller).
- Document start and stop time of Injectafer® administration, the total dose administered and if diluted.
- Obtain sitting heart rate and blood pressure immediately pre-dose, immediately post-dose, and 30 minutes post Injectafer® administration. Body temperature taken pre-dose
- Adverse event assessment (starting at beginning of Injectafer® injection).

Blood samples for PK/PD will be drawn at 1, 2, 6 and 12 hours post the Day 0 Injectafer® dose.

### 6.3.2. Days 1 and 2 (24 and 48 hour)

- Blood samples for PK/PD
- Adverse events assessment

### 6.3.3. 72 hour, and Days 14 and 28 (weeks 2 and 4)

- Blood samples for PK/PD (72 hour visit only)
- Vital signs
- Hematology, chemistries and iron indices
- Adverse events assessment
- Concomitant medications assessment
- ESA stability/use ( if applicable)

### 6.3.4. Day 35 (week 5) End of Study

- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Vitals signs
- hematology, chemistries and iron indices
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Adverse events assessment
- Log onto EDC and enter subject as complete

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

### 6.3.5. Pharmacokinetics and Pharmacodynamics (PK/PD)

Blood samples will be collected for PK/PD assessment pre-dose and at 1, 2, 6, 12, 24, 48 and 72 hours post dose. Blood samples should be taken at approximately the same time of day as the initial pre-dose sample on Day 0.

Prior to Day 0, subjects will return to the clinic on Day -1 at which time blood samples will be drawn at 8am, 12pm and 8pm to characterize the subjects specific iron profile.

Total blood volume (regular hematology, chemistry, iron indices and PK/PD) collected per day and during the 35 Day study is provided below:

| | Screening | Day (-1) | Day 0 | 24hr | 48hr | 72hr | Day14 | Day 28 | Day 35 | **Total Blood Volume** |
|---|---|---|---|---|---|---|---|---|---|---|
| Hem/Chem/II (10ml) | 10ml | | | | | 10ml | 10ml | 10ml | 10ml | |
| PK/PD (2ml) | | 6ml | 10ml | 2ml | 2ml | 2ml | | | | |
| **TOTAL** | **10ml** | **6ml** | **10ml** | **2ml** | **2ml** | **12ml** | **10ml** | **10ml** | **10ml** | **72ml / approx. 14.6 tsps.*** |

***4.93 mL = 1 tsp.**

## 6.4 Central Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. All serum laboratory testing will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 35 laboratory, this laboratory may be obtained after notification of the Sponsor. The laboratory assessments will be determined as listed in Section 3.2.3.

| | |
|---|---|
| Hematology: | Hb, 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, bicarbonate and magnesium |
| Iron indices: | serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT) |
| Other: | Serum pregnancy test |

# 7.0 ASSESSMENT OF SAFETY

## 7.1 Adverse Events

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

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

To quantify the severity of adverse events, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version 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 Injectafer® through the completion of the study Day 35. AE's will be captured 28 days post the last dose of Injectafer® for subjects who early terminate from the trial. This can be completed via a phone call. All ongoing adverse events related to Injectafer® 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 Injectafer® 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*.

* For the purposes of this trial, "study drug" is defined as: **Injectafer®** (known in the EU as **Ferinject®**)

## 7.2 Reporting of Adverse Events

Adverse experiences will be elicited by nonspecific questions such as “Have you noticed any problems?” Subjects will be encouraged to report adverse events at their onset.
Any adverse experience spontaneously reported by, elicited from the subject 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 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:** All SAEs will be reported from the initial treatment with Injectafer® through the completion of the study Day 35. SAEs will be captured 28 days post the last dose of Injectafer® for subjects who early terminate from the trial. This can be completed via a phone call. 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 lead to prolongation of hospital stay should not be considered SAE’s. 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 (within 24 hours of learning of the event) 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 IRB / Ethics Committee per their reporting guidelines.

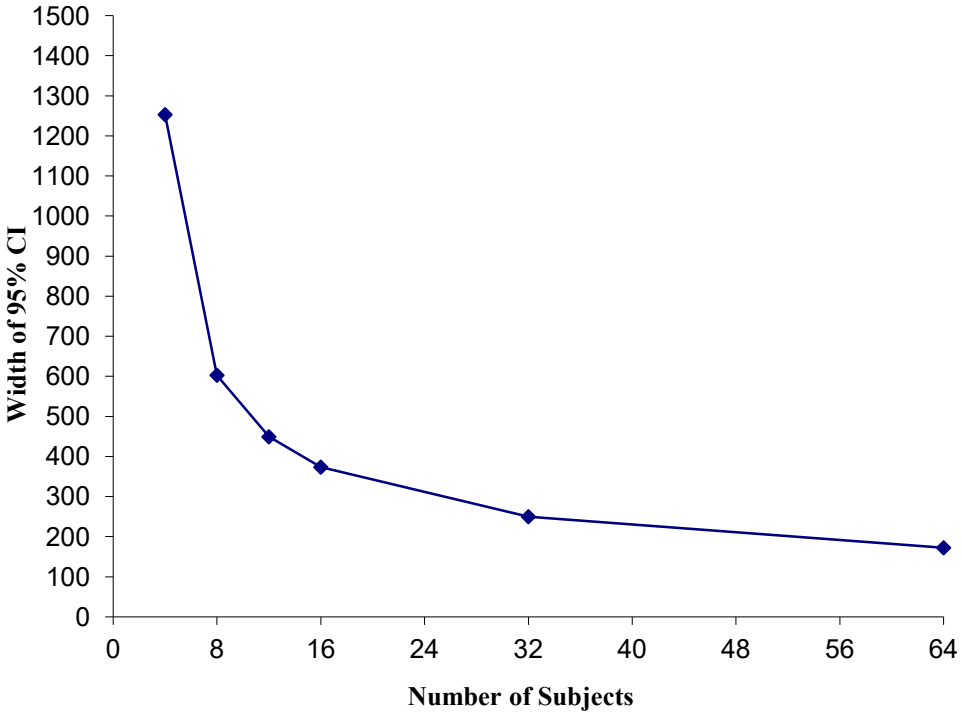
The responsible investigator must determine whether the degree of any untoward event warrants removal of any subject from the study. He/she should, in any case, institute appropriate diagnostic and/or therapeutic measures, and keep the subject under observation for as long as is medically indicated.

## 8.0 STATISTICS

No hypothesis testing will be performed for this study.

### 8.1 Sample Size

Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients.




Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally disturbed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system.

## 8.2 Analysis Populations

There will be 2 analysis populations:

- Safety population: Includes all subjects who receive Injectafer®.
- PK/PD population: Includes all subjects in the safety population who have evaluable iron profiles and no protocol violation that could affect the PK/PD of Injectafer®.

## 8.3 Demographic Characteristics

Demographic characteristics will be summarized for the Safety and PK/PD populations. The number and percentage of subject's who are registered, treated, prematurely discontinue, and complete the study will be summarized after the study's conclusion.

Subjects with clinically important protocol deviations will be identified for each analysis population, treatment group, and type of deviation. The clinical team will identify deviations and the deviations will be identified in the database.

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

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class (SOC) and preferred term for all subjects.

## 8.4 Endpoints and Definitions

### 8.4.1 Clinical Endpoints

Clinical endpoints include:

- Efficacy: change from baseline to each scheduled visit for hemoglobin, ferritin, and TSAT.
- Safety:
    - ✓ Proportion of subjects reporting treatment-emergent adverse events, overall and related, by SOC and preferred term
    - ✓ Subjects reporting treatment-emergent serious adverse events, overall and related, will be identified
    - ✓ Mean change from baseline to each scheduled visit for clinical laboratory values
    - ✓ Incidence of treatment-emergent potentially clinically significant (PCS) clinical laboratory values
    - ✓ Incidence of treatment-emergent PCS vital sign values.

## 8.5 Pharmacokinetics and Pharmacodynamics (PK/PD) Endpoints

The primary and secondary pharmacokinetic parameters will be determined for each subject as appropriate, based on serum concentration. The baseline parameters will be subtracted from all measured samples.

The primary parameters are the maximum serum concentration ($C_{max}$), the area under the serum concentration-time curve from time zero to the last sampling time (t) with a quantifiable concentration ($AUC_{0\text{-time last measured concentration}}$), the extrapolated area under the serum concentration- time curve from time zero to infinity ($AUC_{0\text{-infinity}}$), and the half-life ($T_{1/2}$). $C_{max}$ is calculated as a non-compartmental variable, which is a more conservative method than if it were calculated using a compartmental paradigm. $T_{1/2}$ incorporates the calculation of the rate elimination constant ($K_{el}$).

The secondary parameters are the mean residence time (MRT), the apparent serum clearance (Cl), and the apparent volume of distribution ($V_d$), which includes the initial volume of distribution following the injection ($Vd_c$), the volume of distribution at the steady state ($Vd_{ss}$), and the volume of distribution at the final elimination ($Vd_{area}$).

Pharmacodynamic parameter will include serum ferritin, transferrin, transferrin saturation (TfS) UIBC, HGB, reticulocyte count and transferrin receptors.

The Pharmacokinetic and Pharmacodynamic parameters performed in this study for analysis will be outlined in a Statistical and Analytical Plan.

## 8.6 Statistical Analyses of Safety

The Medical Dictionary for Regulatory Activities (MedDRA) Terminology will be used to classify all adverse events with respect to system organ class and preferred term.
The number and proportion of subjects who report treatment-emergent adverse events will be summarized for each treatment group. A similar summary will be provided for all treatment emergent serious adverse events.

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 to study drug. Relationship to study drug will be categorized as related (possibly or probably related) and unrelated. Events with unknown severity or relationship will be counted as unknown.

Subjects 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 subject reports multiple preferred terms for a system organ class (SOC), the subject will be counted only once for that SOC.

Change in vital signs from baseline to each scheduled study visit will be summarized descriptively with the mean, median, standard deviation, minimum value, and maximum value. The number and percent of patients with potentially clinically significant vital signs will be summarized for each treatment group.

## 8.7 DSMB Analyses

A DSMB will review safety information for subjects in Cohort 1 before dosing begins for Cohort 2. A Charter will be developed outlining the DSMB processes.

# 9.0 ADMINISTRATIVE CONSIDERATIONS

## 9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including electronic copies of 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 Pharmaceutical 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 subject must be maintained, that includes the signed Informed Consent form and copies of all study documentation related to that subject. 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 subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator Brochure, including potential risks and side effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (including amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subjects.
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 subjects into the study.

### 9.4 Advertisement for Subject Recruitment

All advertisements for subject recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisements may include but is not limited to newspaper, fliers, radio, television, etc. Any compensation to the subject 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 subject 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 subjects 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 (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 principal 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. 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 United States (US) Code of Federal Regulations on Protection of Human Subjects (21 CFR 50), IRB regulations (21 CFR 56), the 2000 Edinburgh, Scotland Revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312 and applicable ICH guidelines.

### 9.7.2 Institutional Review Board

The protocol and the Informed Consent / Assent 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 US Regulations (21 CFR 56). Investigators are responsible for the following:

- Obtain IRB approval of the protocol, Informed Consent / Assent and any advertisements to recruit subjects; 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 serious adverse events that occur or are reported to you by the Sponsor.

### 9.7.3 Informed Consent

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

basic elements of informed consent and ICH guidelines. Translations of the informed consent / assent must be certified by a qualified translator and their use must be documented.

The Informed Consent / Assent documents the information the Investigator provides to the subject and the subject'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 / Assent must be signed and dated by each subject and/or legal representative before entering the study and prior to the performance of any study specific procedures.

### 9.7.4 Good Clinical Practice

The conduct of the study will conform to the recommendations for clinical studies in human subjects as set out in the current version of the Edinburgh, Scotland Revision of the "Declaration of Helsinki", the local legal requirements and the guidelines on "Good Clinical Practice", [21 CFR Part 312 and ICH guidelines].

## 9.8 Data Handling and Record Keeping

### 9.8.1 Electronic Case Report Form (eCRF)

- eCRFs will be provided for each subject on this study. The participants in this study will be identified only by initials and subject 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 eCRFs are to be reviewed by the Clinical Monitor at Luitpold Pharmaceuticals, Inc. (or designee). Source data will be reviewed by the Clinical Monitor 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 subjects 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, DSMB, investigator, or study 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 subjects, failure of the investigator to enroll subjects 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 subject 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, which 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.

## 10.0 GOVERNANCE COMMITTEE

### 10.1 Data and Safety Monitoring Board

The DSMB will be composed of approximately 3-5 senior academic individuals, including the DSMB Chair. They will have high-level expertise in pediatric iron deficiency anemia and/or statistics. A senior statistician assigned to the trial from the group performing data management services for this trial will oversee the provision of interim data reports for use by the DSMB. The data management group for this trial will transfer pre-agreed datasets to the DSMB. During the Open Session of the DSMB meetings, the Study Chair or Luitpold representatives may present updates on the trial status or the safety profile of Injectafer®, but will not be privy to discussions of the data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the patients and, to this end, will undertake reviews of the safety data. The DSMB will have access to an agreed subset of the study data as listed in the DSMB charter (updated as necessary during the trial) throughout the study duration. In addition, the DSMB will evaluate the data approximately (as outlined in the Charter) either by face to face meeting or teleconference. The DSMB

will evaluate the safety from both cohorts 1 and 2 (7.5 or 15 mg/kg of Injectafer®). Only after all subjects in cohort 1 have completed through week 4 and the DSMB has evaluated the safety data as acceptable will registration into cohort 2 be granted. The DSMB will determine if it believes the trial should be terminated early because clear evidence of a significant safety concern exists.

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

## INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 50, 54, 56 and 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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2. Foley RN, Parfrey PS, Harnett JD *et al*. Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int.* 1996; 49: 1379-1385

3. Staples AO, Greenbaum LA, Smith JM *et al*. Association between clinical risk factors and progression of chronic kidney disease in children. *Clin.J.Am.Soc.Nephrol.* 2010; 5: 2172-2179

4. Wharton BA. Iron deficiency in children: detection and prevention. *Br.J.Haematol.* 1999; 106: 270-280

5. Kazal LA, Jr. Prevention of iron deficiency in infants and toddlers. *Am.Fam.Physician* 2002; 66: 1217-1224

6. Michaud L, Guimber D, Mention K *et al*. Tolerance and efficacy of intravenous iron saccharate for iron deficiency anemia in children and adolescents receiving long-term parenteral nutrition. *Clin.Nutr.* 2002; 21: 403-407

7. Pinsk V, Levy J, Moser A, Yerushalmi B, Kapelushnik J. Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. *Isr.Med.Assoc.J.* 2008; 10: 335-338

8. Surico G, Muggeo P, Muggeo V *et al*. Parenteral iron supplementation for the treatment of iron deficiency anemia in children. *Ann.Hematol.* 2002; 81: 154-157

# APPENDIX 1: INJECTAFER® PACKAGE INSERT

HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use Injectafer safely and effectively. See full prescribing information for Injectafer.**

**INJECTAFER® (ferric carboxymaltose injection)**
**For intravenous use**
**Initial U.S. Approval: 20XX**

----------INDICATIONS AND USAGE----------

Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

----------DOSAGE AND ADMINISTRATION----------

For patients weighing 50kg (110lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750mg for a total cumulative dose of 1500mg of iron per course.

For patients weighing less than 50kg (110lb): Give Injectafer in two doses separated by at least 7 days and give each dose as 15 mg/kg body weight.

Injectafer treatment may be repeated if iron deficiency anemia reoccurs. (2)

----------DOSAGE FORMS AND STRENGTHS----------

750 mg iron / 15 mL single-use vial(3)

----------CONTRAINDICATIONS----------

Hypersensitivity to Injectafer or any of its inactive components. (4)

----------WARNINGS AND PRECAUTIONS----------

- **Hypersensitivity reactions:** Observe for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of each administration. (5.1)
- **Hypertension:** Monitor patients closely for signs and symptoms of hypertension following each Injectafer administration. (5.2)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥2%) are nausea, hypertension, flushing, hypophosphatemia, and dizziness (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact American Regent at 1-800-734-9236 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Exercise caution when administered to a nursing woman. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: July 2013**

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FULL PRESCRIBING INFORMATION: CONTENTS*



* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Injectafer is indicated for the treatment of iron deficiency anemia in adult patients;

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

## 2 DOSAGE AND ADMINISTRATION

For patients weighing 50 kg (110 lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectafer in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

The dosage of Injectafer is expressed in mg of elemental iron. Each mL of Injectafer contains 50 mg of elemental iron. Injectafer treatment may be repeated if iron deficiency anemia reoccurs.

Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

When added to an infusion bag containing 0.9% Sodium Chloride Injection, USP, at concentrations ranging from 2 mg to 4 mg of iron per mL, Injectafer solution is physically and chemically stable for 72 hours when stored at room temperature. To maintain stability, do not dilute to concentrations less than 2 mg iron/mL.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Each vial of Injectafer is intended for single use only. Any unused drug remaining after injection must be discarded.

Avoid extravasation of Injectafer since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectafer administration at that site.

## 3 DOSAGE FORMS AND STRENGTHS

750 mg iron / 15 mL single-use vial

## 4 CONTRAINDICATIONS

Hypersensitivity to Injectafer or any of its components [see *Warnings and Precautions (5.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

**Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.** [see *Adverse Reactions (6.1 and 6.2)*].

In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

### 5.2 Hypertension

In clinical studies, hypertension was reported in 3.8% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration [*see Dosage and Administration (2)*].

### 5.3 Laboratory Test Alterations

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

. Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
. Hypertension *[see Warnings and Precautions (5.2)]*
. Lab test alterations *[see Warnings and Precautions (5.3)]*

### 6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.
In two randomized clinical studies [Studies 1 and 2, *See Clinical Studies (14)*], a total of 1,775 patients were exposed to Injectafer 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥ 1% of treated patients are shown in the following table.

**Table 1. Adverse reactions reported in ≥ 1% of Study Patients in Clinical Trials 1 and 2**

| Term | Injectafer (N=1775) % | Pooled Comparators[a] (N=1783) % | Oral iron (N=253) % |
|---|---|---|---|
| Nausea | 7.2 | 1.8 | 1.2 |
| Hypertension | 3.8 | 1.9 | 0.4 |
| Flushing/Hot Flush | 3.6 | 0.2 | 0.0 |
| Blood Phosphorus Decrease | 2.1 | 0.1 | 0.0 |
| Dizziness | 2.0 | 1.2 | 0.0 |
| Vomiting | 1.7 | 0.5 | 0.4 |
| Injection Site Discoloration | 1.4 | 0.3 | 0.0 |
| Headache | 1.2 | 0.9 | 0.0 |
| Alanine Aminotransferase Increase | 1.1 | 0.2 | 0.0 |
| Dysgeusia | 1.1 | 2.1 | 0.0 |
| Hypotension | 1.0 | 1.9 | 0.0 |
| Constipation | 0.5 | 0.9 | 3.2 |

[a] Includes oral iron and all formulations of IV iron other than Injectafer

Other adverse reactions reported by ≥ 0.5% of treated patients include abdominal pain, diarrhea, gamma glutamyl transferase increased, injection site pain/irritation, rash, paraesthesia, sneezing. Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) have been observed in 27% (440/1638) patients in clinical trials.

### 6.2 Post-marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectafer: urticaria, dyspnea, pruritis, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a

subject who received 500 mg of Injectafer every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer.

## 7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Injectafer .

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

*Risk Summary*

Adequate and well controlled studies in pregnant women have not been conducted. However, animal reproduction studies have been conducted with ferric carboxymaltose. In these studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused fetal malformations and increased implantation loss at maternally toxic doses of approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area). The incidence of major malformations in human pregnancies has not been established for Injectafer. However, all pregnancies, regardless of exposure to any drug, has a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Animal Data*

Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Spontaneous abortions occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryofetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

### 8.3 Nursing Mothers

A study to determine iron concentrations in breast milk after administration of Injectafer (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectafer than in lactating women receiving oral ferrous sulfate.

### 8.4 Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

### 8.5 Geriatric Use
Of the 1775 subjects in clinical studies of Injectafer, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

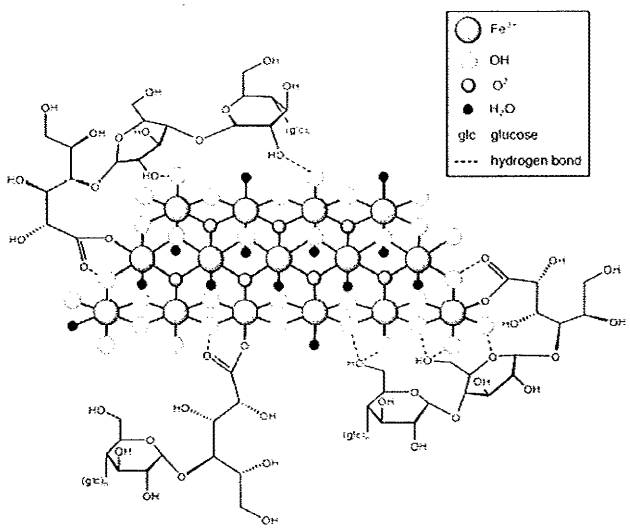
## 10 OVERDOSAGE
Excessive dosages of Injectafer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectafer 18,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability and asthenia . Hypophosphatemic osteomalacia was reported in a patient who received Injectafer 4000 mg over 4 months. Partial recovery followed discontinuation of Injectafer. [*see Post-marketing Experience (6.3)]*.

## 11 DESCRIPTION
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).

The chemical structure is presented below:




Injectafer (ferric carboxymaltose injection) is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Injectafer is available in 15 mL single-use vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0.

Vial closure is not made with natural rubber latex

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

### 12.2 Pharmacodynamics

Using positron emission tomography (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.

### 12.3 Pharmacokinetics

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 1.21 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ferric carboxymaltose.

Ferric carboxymaltose was not genotoxic in the following genetic toxicology studies: *in vitro* microbial mutagenesis (Ames) assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test at single intravenous doses up to 500 mg/kg.

In a combined male and female fertility study, ferric carboxymaltose was administered intravenously over one hour to male and female rats at iron doses of up to 30 mg/kg. Animals were dosed 3 times per week (on Days 0, 3, and 7). There was no effect on mating function, fertility or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

## 14 CLINICAL STUDIES

The safety and efficacy of Injectafer for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer was administered at a dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

### 14.1 Trial 1: Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

Trial 1 was a randomized, open-label, controlled clinical study in patients with iron deficiency anemia who had an unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2) during the 14 day oral iron run-in period. Inclusion criteria prior to randomization included hemoglobin (Hb) <12 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%. Cohort 1 subjects were randomized to Injectafer or oral iron for 14 more days. Cohort 2 subjects were randomized to Injectafer or another IV iron per standard of care [90% of subjects received iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

**Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | Cohort 1 | | Cohort 2 | |
|---|---|---|---|---|
| | Injectafer (N=244) | Oral Iron (N=251) | Injectafer (N=245) | IV SC[a] (N=237) |
| Baseline | 10.6 (1.0) | 10.6 (1.0) | 9.1 (1.6) | 9.0 (1.5) |
| Highest Value | 12.2 (1.1) | 11.4 (1.2) | 12.0 (1.2) | 11.2 (1.3) |
| Change (from baseline to highest value) | 1.6 (1.2) | 0.8 (0.8) | 2.9 (1.6) | 2.2 (1.3) |
| p-value | 0.001 | | 0.001 | |

SD=standard deviation; [a]: Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2±224.2 ng/mL in Cohort 1 and 218.2 ±211.4 ng/mL in Cohort 2), and transferrin saturation (13±16% in Cohort 1 and 20±15% in Cohort) were observed at Day 35 in Injectafer-treated patients.

**14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease**

Trial 2 was a randomized, open-label, controlled clinical study in patients with non-dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) ≤ 11.5 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%.Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 96); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

**Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | **Injectafer (N=1249)** | **Venofer (N=1244)** |
|---|---|---|
| Baseline | 10.3 (0.8) | 10.3 (0.8) |
| Highest Value | 11.4 (1.2) | 11.3 (1.1) |
| Change (from baseline to highest value) | 1.1 (1.0) | 0.9 (0.92) |
| Treatment Difference (95% CI) | 0.21 (0.13, 0.28) | |
| | | |

Increases from baseline in mean ferritin (734.7±337.8 ng/mL), and transferrin saturation (30±17%) were observed at Day 56 in Injectafer-treated patients.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

| | | |
|---|---|---|
| NDC 0517-0650-01 | 750 mg iron/15 mL Single-Use Vial | Individually boxed |
| NDC 0517-0650-02 | 750 mg iron/15 mL Single-Use Vial | Packages of 2 |

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See the USP controlled room temperature]. Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*]

Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

AMERICAN
REGENT, INC.
SHIRLEY, NY 11967

IN0602
Rev. 7/13

**Patient Information**
**INJECTAFER (ferric carboxymaltose injection)**

Please read this information carefully before taking this medication. This summary does not tell you everything about INJECTAFER. Speak with your doctor or healthcare professional if there is something you do not understand or if you would like to learn more about INJECTAFER. Your doctor or healthcare professional is your best source of information about this medicine.

**What is INJECTAFER?**

Iron is a mineral that the body needs to produce red blood cells. When the body does not get enough iron, it cannot produce the number of normal red blood cells needed to keep you in good health. This condition is called iron deficiency (iron shortage) or iron deficiency anemia.

INJECTAFER is used to treat iron deficiency anemia. Iron deficiency anemia may be caused by several medical conditions including heavy menstrual bleeding, pregnancy, childbirth, inflammatory bowel disease, other malabsorption diseases, bariatric surgery, or chronic kidney disease.

**General information about using INJECTAFER safely and effectively**

Injectable iron is administered only by or under the supervision of your health care professional.

Serious or life threatening allergic reactions have been reported with intravenous iron products. Tell your health care professional if you have ever had any unusual or allergic reaction to any IV iron.

Patients should report to their healthcare professional any signs and symptoms of an allergic reaction to INJECTAFER, in particular rashes, shortness of breath and wheezing.

Iron is not easily eliminated from the body, and its build up may be lead to a condition called iron overload which may be harmful. Certain medical conditions such as liver disease may also make you more likely to develop iron overload. Ask your doctor or healthcare professional.

**Who should not take INJECTAFER?**

You should not be given INJECTAFER if you have anemia that is not caused by iron deficiency, or if you have iron overload.

If you are pregnant or plan to become pregnant please notify your doctor or healthcare professional. They will decide whether it is safe for you to receive INJECTAFER.

**How should I take INJECTAFER?**

INJECTAFER is administered intravenously (into your vein) by your doctor or health care professional in two doses.

**What should I avoid while taking INJECTAFER?**

You should not take iron supplements by mouth if you are receiving iron injections. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

**What are the possible side effects of INJECTAFER?**

The side effects of INJECTAFER are infrequent, usually mild and generally do not cause patients to stop treatment. The most common side effects are nausea, injection site reactions (including pain or bruising at the injection site), asymptomatic reductions in blood phosphorus, flushing, headache, hypertension, dizziness, and increased alanine aminotransferase. Potentially long lasting brown staining of skin near injection site may occur.

These are not all the possible side effects of INJECTAFER. For more information ask your doctor or healthcare professional.

Talk to your doctor if you think you have side effects from taking INJECTAFER.

## APPENDIX 2: WEIGHT CHARTS FOR BOYS AND GIRLS

**Boys (White) Weight Chart age 0-36 months** (http://www.halls.md/chart/boys-weight-w.htm)

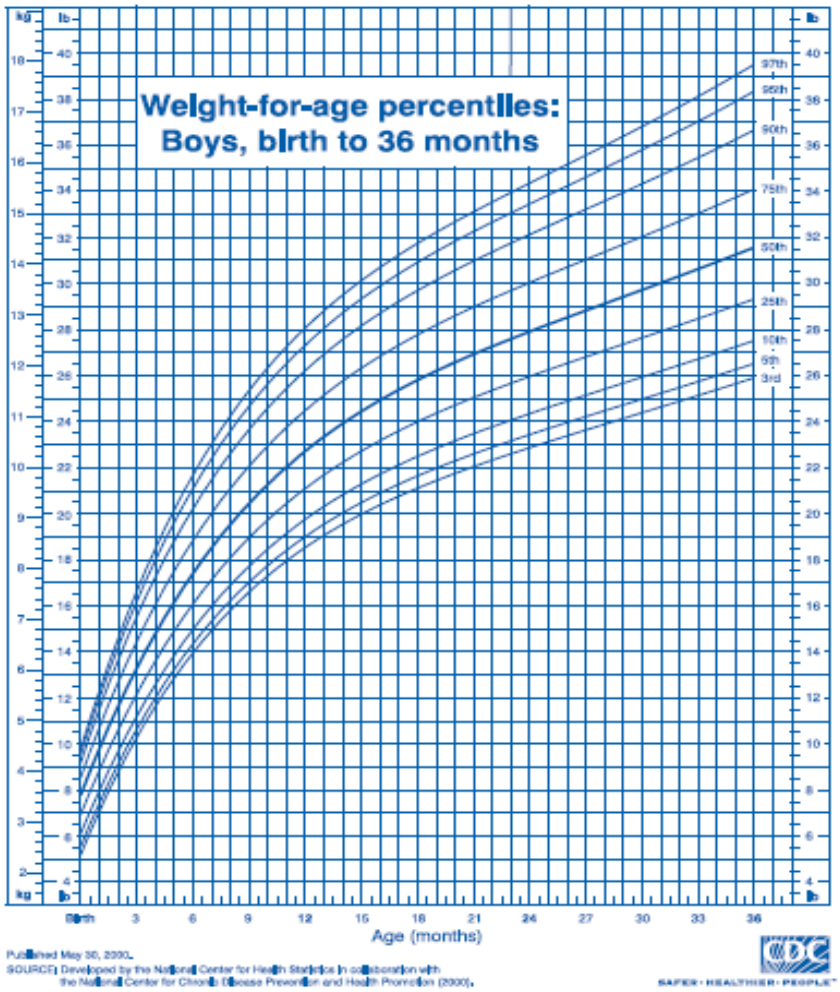
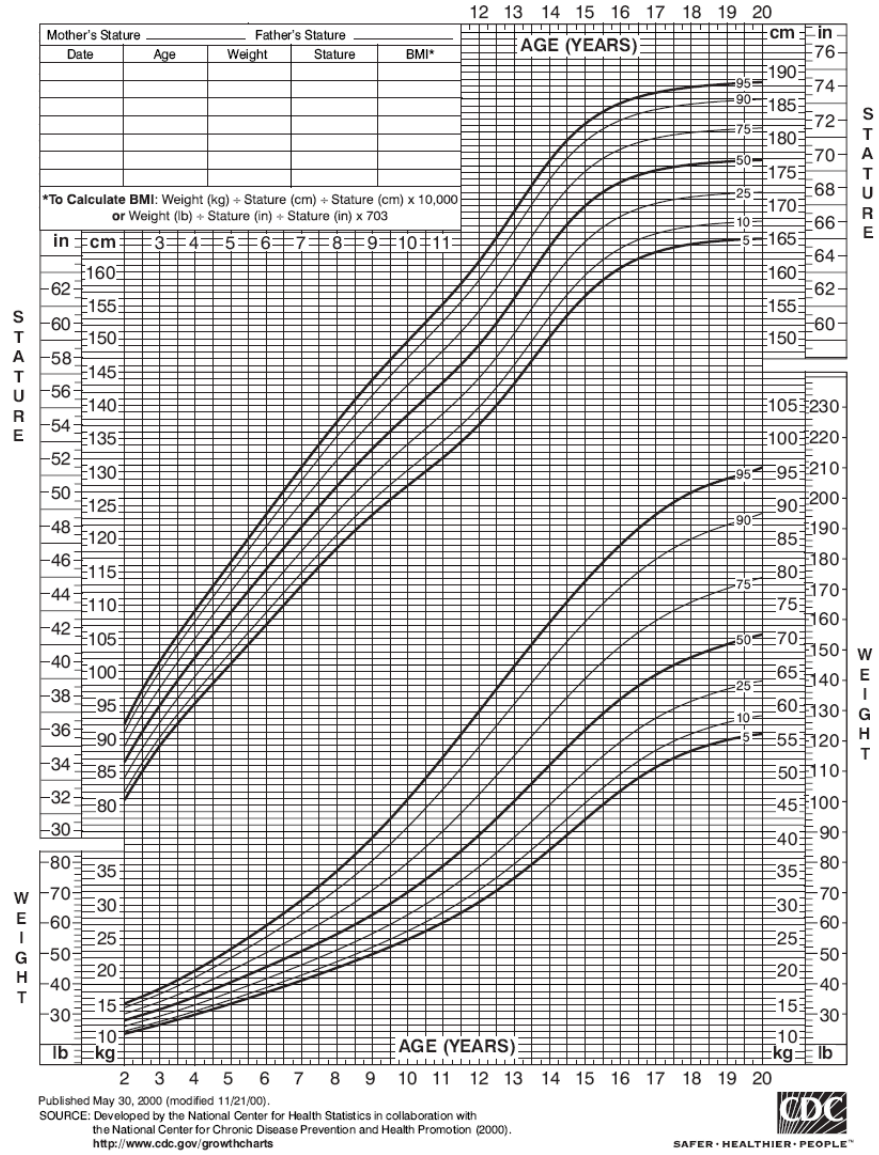



Figure 1. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Boys weight-for-age

# BOYS (WHITE) WEIGHT CHART AGE 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L021.PDF)



**Girls (White) Weight Chart age 0-36 months** (http://www.halls.md/on/girls-weight-w.htm)

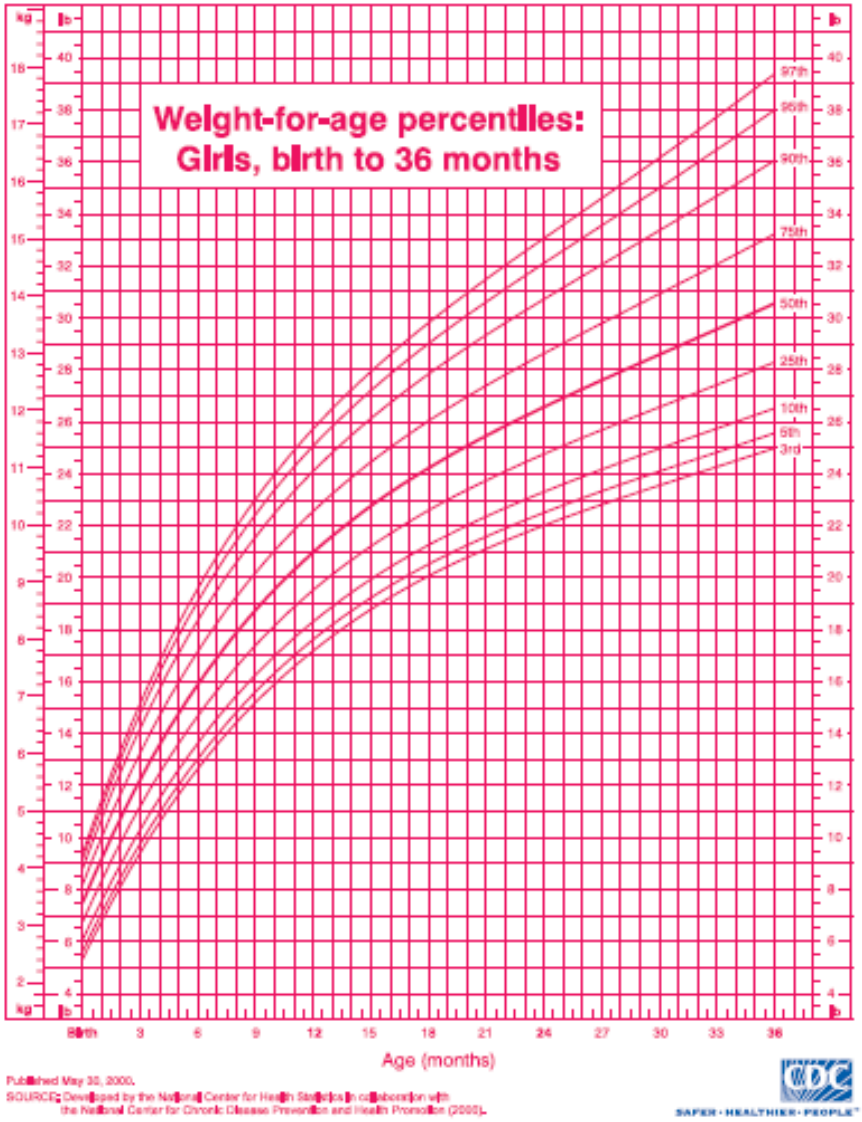
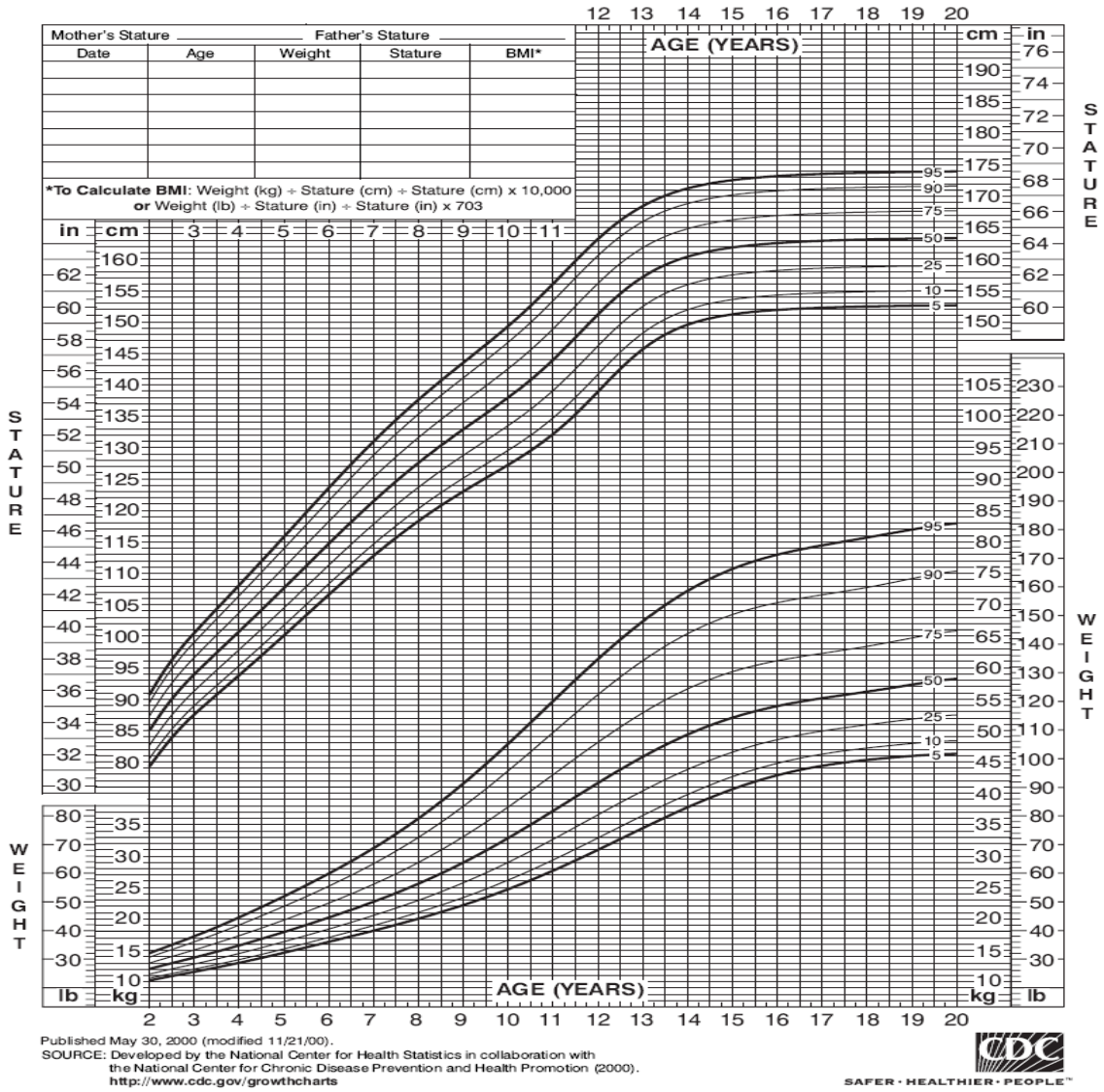



Figure 2. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Girls weight-for-age

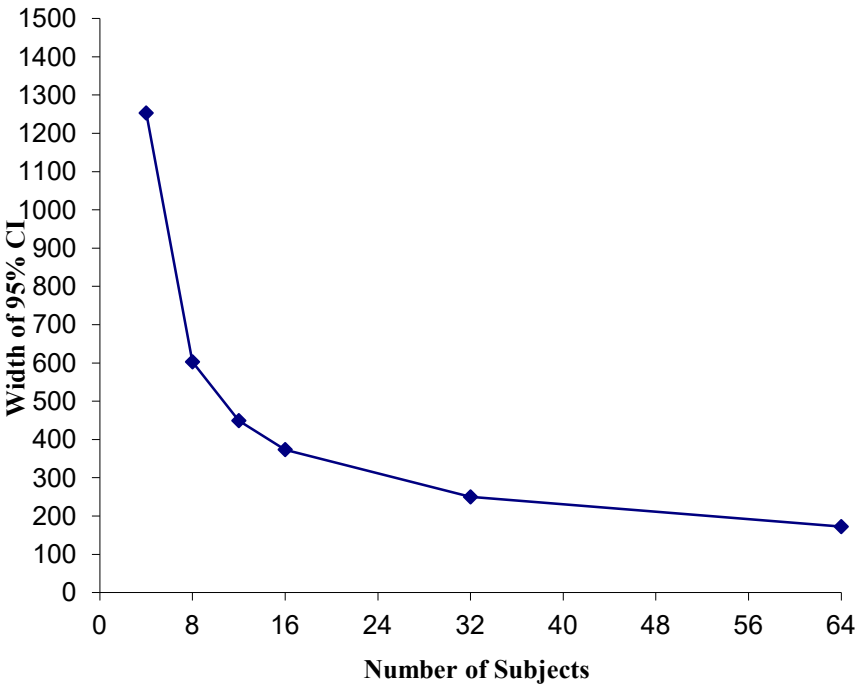
## GIRLS (WHITE) WEIGHT CHART AGES 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L022.PDF)



# APPENDIX 3: ADMENDMENT I CHANGES

| | |
|---|---|
| Title Page: | |
| Original Wording: | Protocol Date:<br>27 March 2014 |
| New Wording: | Protocol Date:<br>Amendment 1: 29 July 2014 |
| Study Synopsis and 8.1 Sample Size Rationale: | |
| New Wording: | Sample Size:<br><br>Determination of sample size for this single-arm, pediatric, pharmacokinetic study is a compromise between obtaining sufficiently precise estimates of pharmacokinetic parameters and the ethics of including a large number of pediatric patients in an experiment. The precision of estimation can be quantified as the width of the 95% confidence interval for $AUC_{0-72}$ from this single-arm study (i.e., smaller width indicates better precision). Based on Study VIT-IV-CL-002 in adults, the standard deviation for total serum iron $AUC_{0-72}$ following a 500 mg intravenous dose is approximately 300 µg◦hour/mL. The width of a 95% confidence interval, using a standard deviation of 300 µg◦hour/mL, is presented below for selected sample sizes. As seen in the figure, 16 patients appears to be a reasonable compromise between precision and number of exposed pediatric patients. |

| | |
|---|---|
| |  <br><br>Approximately 32 subjects will be enrolled in this study, 16 subjects in cohort I and 16 subjects in cohort II. Within each cohort of 16 subjects will be equally disturbed by age, which will include 8 subject's 1 – 6 years of age and 8 subjects > 6 – 17 year of age. Subject enrollment and ages will be tracked and monitored via interactive web response (IWR) system. |
| Original Wording: | Exclusion Criteria:<br><br>3. Body mass index (BMI) ≤ 95$^{th}$ percentile for age (see APPENDIX 2) |
| New Wording: | 3. Body mass index (BMI) ≤ 5$^{th}$ percentile for age (see APPENDIX 2) |
| Original Wording: | Trial design – Phase III |
| New Wording: | Trial Design – Phase II |
| Additional Wording – Sections 7.1 | All laboratory values at the end of study/Day 35 that have been deemed clinical significant by the Investigator should be followed until they are back into normal range. |
| | |

**LUITPOLD PHARMACEUTICALS, INC.**

# PROTOCOL

**No. 1VIT13036**

**IND #: 63,243**

# A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Injectafer® (Ferric Carboxymaltose) in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA)

SPONSOR

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

**Protocol Date: 27 March 2014**

**SIGNATURES OF AGREEMENT FOR PROTOCOL**

4/3/14.

Ariel Abreu, MD
Medical Director, Pharmacovigilance
Luitpold Pharmaceuticals, Inc.

Date

4/3/2014

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

Date

03 Apr. 2014

David Morris, PhD
Senior Director, Statistics
WebbWrites, LLC

Date

## Study Synopsis

## Protocol No. 1VIT13036

**Title:** A Multi-center, Open-label, Single Arm Study to Characterize the Pharmacokinetics and Pharmacodynamics Profile of Intravenous Injectafer® (Ferric Carboxymaltose) in Pediatric Subjects 1 – 17 years old with Iron Deficiency Anemia (IDA).

**Drugs:** Injectafer® **(**Ferric Carboxymaltose)

**Objectives:** The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Injectafer® for the pediatric population suffering from iron deficiency (ID) with anemia.

**Study Design:** This is a Phase III, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Injectafer® dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Injectafer®.

**Treatment**

Cohort 1: 16 subjects will be treated with Injectafer® at 7.5 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Injectafer® at 15 mg/kg to a maximum single dose of 750 mg iron, whichever is smaller.

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving an erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Injectafer®.
2. Subject previously randomized and treated in this study or any other clinical study of Injectafer® (FCM or VIT-45).
3. Body mass index (BMI) $\leq 95^{th}$ percentile for age (see APPENDIX 2)
4. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
5. Chronic kidney disease subjects on hemodialysis.
6. Screening Ferritin level > 300ng/mL

7. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
8. Any active infection.
9. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
10. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
11. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.
12. Significant blood loss (> 100 ml) within the last 3 months or any current bleeding disorders or anticipated need for surgery that may result in significant blood loss (> 100 ml).
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subjects who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

**Subject Assessments:**

All subjects that provide informed consent / assent will enter a screening period up to 14 days prior to Day 0. During this time subjects will be evaluated to insure they meet the study entry criteria. Subjects will have vital signs, medical history review and laboratory samples to include hematology, chemistries and iron indices. Once it has been determine the subject qualifies for participation the subject will be scheduled to return to the clinic 1 day prior to Day 0 (Day -1) at which time additional blood samples will be taken (8am, 12pm and 8pm) to characterize the subjects iron profile.

Blood samples for PK/PD will also be assessed immediately prior to Injectafer® dosing on Day 0, at 1, 2, 6, 12, 24, 48 hours and at 72 hours.

Safety assessments, including vital signs and adverse events, will be assessed starting on Day 0 at the time of Injectafer® dosing through Day 35.

**Erythropoietin Dosage:**

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

**Study Duration per subject:** up to 9 weeks

**Number of Subjects:** 32 subjects

**Sites:** Approximately 10

## CONTACT PERSON FOR THE STUDY

For study related questions please contact:

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| BP | Blood Pressure |
| BW | Body Weight |
| CI | confidence interval |
| CKD | Chronic Kidney Disease |
| conc. | concentration |
| CTCAE | Common Terminology Criteria for Adverse Event |
| dL | Deciliter |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| e.g. | for example |
| ESA | Erythropoiesis stimulating agent |
| FDA | Food and Drug Administration |
| Fe | Iron |
| g | Gram |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| Hct | Hematocrit |
| Hgb | Hemoglobin |
| HMW | high molecular weight |
| IBD | Inflammatory Bowel Diease |
| ICH | International Conference on Harmonisation |
| IDA | Iron Deficiency Anemia |
| i.e. | that is/ such that |
| IRB | Institutional Review Board |
| IV | Intravenous |
| IVP | Intravenous injection (push) |
| kg | Kilogram |
| L | Liter |
| LMW | low molecular weight |
| LOS | length of stay |
| MedDRA | Medical dictionary for regulatory activities |
| mg | Milligram |
| mL | Milliliter |
| ng | Nanogram |
| PET | positron emission tomography |
| p.o. | by mouth or orally |
| RES | Reticuloendothelial system |
| SAE | Serious adverse event |
| $t_{1/2}$ | Terminal half-life |
| t.i.d. | three times a day |
| TSAT | Transferrin Saturation |
| US | United States |
| vs | Versus |
| w/v | weight / volume |

# 1.0 INTRODUCTION

## 1.1 Treatment of Iron Deficiency Anemia

Iron deficiency anemia ("IDA") remains the most common nutritional deficiency in children in the United States. Rapid growth, insufficient dietary intake, and limited absorption of dietary iron combine to place children at increased risk for iron deficiency. Iron deficiency may contribute significantly to anemia due to malabsorption, gastrointestinal blood loss, or iatrogenically due to repeated blood samplings. As a result of severe digestive tract disorders, some children are unable to tolerate oral iron supplementation or are unresponsive to it.[1] Anemia may also decrease survival rates in patients (both adults and children) with chronic renal impairment where it is a commonly encountered problem[2;3] In addition, anemia is a commonly encountered manifestation of pediatric inflammatory bowel disease which is associated with a decrease in the quality of life and increased hospitalization.

Non-hematologic consequences of iron deficiency include poor weight gain, anorexia, irritability, decreased attention span, exercise intolerance and decreased physical activity. [4] However, IDA in infants and toddlers is associated with long-lasting diminished mental, motor, and behavioral functioning. Although the exact relationship between iron deficiency anemia and the developmental effects is not well understood, it appears that these effects do not occur until iron deficiency becomes severe and chronic enough to produce anemia. [5]

Options for correcting iron deficiency include both oral and parenteral formulations. As previously described, some children are unable to tolerate or are non-responsive to oral iron. Blood transfusion is an option to treat anemia and restore iron requirements, but the potential risk of blood-transmitted virus infection limits its use to severe and badly tolerated anemia. In view of the limitations associated with oral iron or blood transfusions, intravenous administration is an important option.

Multiple parenteral iron products are available. These vary in complex types which impacts the total amount of iron that may be administered in a single administration. Numerous other differences differentiate the products; however, all appear to effectively release iron post administration and restore the deficit of the patient. There are numerous studies with iron sucrose injection (Venofer®) that have been performed in the pediatric population [6-8]. Iron doses have varied in the studies with demonstrated efficacy and safety in doses up to 7mg iron/kg or 200mg given in time frames of 3 min, which was shown to be beneficial to both the child and health care facility[6].

Injectafer® has been characterized as a robust and strong type iron complex (Type 1) with a molecular mass of about 150,000 Daltons (Da). The solution is a dark brown color with a near neutral pH (5.0 to 7.0) and a physiological osmolarity permitting administration of higher single doses in short time periods. Although no interventional studies have been conducted with Injectafer® in the pediatric population to date, the product has been used in clinical practice in markets where it is currently approved for adults to aid correction of iron deficiency within the pediatric gastroenterological setting. A non-interventional/retrospective observational data collection has identified in 79 patient's aged 2 to 18 years with a mean age of 12.7 years. In these subjects, Injectafer® showed efficacy with regard to hemoglobin, ferritin, and TSAT as well as safety and tolerability (manuscript in preparation).

Therefore, the proposed studies will assess higher single doses (i.e., 7.5 mg/kg and 15 mg/kg) than those used with currently available parenteral iron preparations in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population. The higher single doses permit fewer

overall injections/infusions and may ultimately permit fewer visits to the treating facilities positively impacting both the child and family as well as health care system.

## 1.2 Injectafer

### 1.2.1 Key features of Injectafer

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 (RES), 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.

### 1.2.2 Injectafer versus Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various parenteral iron preparations available [(3)]. However, prior to the approval of non-dextran formulations, the risk of systemic adverse reactions restricted their use. Injectafer offers significant advantages compared to other available intravenous iron preparations.

Iron dextran, the first parenteral iron product available in the US, has been associated with an incidence of anaphylaxis/anaphylactoid reactions (i.e., dyspnea, wheezing, hypotension, urticaria, angioedema) as high as 1.7% [(6)]. Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran. The high incidence of anaphylaxis/anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Although some have suggested that high molecular weight (HMW) iron dextran is associated with a higher rate of life threatening adverse events and anaphylactic reactions in comparison to low molecular weight (LMW) iron dextran, the US Food and Drug Administration was unable to find a clear difference after an examination of post-marketing data, clinical trial data, death certificates, and emergency room diagnoses [(7)]. Iron dextran is limited to second line therapy for treatment of iron deficiency.

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. 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, 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[11] (data on file ). 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 1.2.2.1).** Another recently approved IV iron is ferumoxytol (AMAG) 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 (see Ferumoxytol PI).

**Table 1.2.2.1 Administration of at least 1500 mg of Intravenous Iron with Currently Available Iron Preparations and Injectafer**

| 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 | 300mg | 1.5 hours | 5 |
| 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 countries outside of the US; 750 mg maximum is the U.S. FDA approved dose

The larger Injectafer and ferumoxytol doses result in less frequent administration of intravenous iron that should benefit, in particular, severely iron deficient and anemic populations. To be treated with currently available intravenous iron agents, the average inflammatory bowel disease, postpartum, heavy uterine bleeding and non-dialysis dependent patient would require an initial test dose, followed by 15 doses of iron dextran as labeled, each accompanied by personnel equipped and trained for resuscitation of anaphylaxis; 12 doses of ferric gluconate; or either 8 doses of iron sucrose (with 5 minute infusion time) or 5 / 4 doses of iron sucrose by prolonged (1.5 to 2.5 hours) intravenous infusion. Ferric gluconate and iron sucrose are not approved by the FDA for the treatment of IDA in non chronic kidney disease populations and iron dextran is only approved as second line therapy for treatment of iron deficiency. In contrast, most patients treated with Injectafer would require 2 doses administered over 8 to15 minutes one week apart.

### 1.2.3 Injectafer Human Experience

The Injectafer development program demonstrated the safety and effectiveness of intravenous Injectafer in the treatment of IDA. Clinical data are currently available from 20 Phase 2 and 3 studies including 5,799 patients, with IDA or IDA associated with CKD, who received Injectafer.
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 ($t_{½}$) was calculated to 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.

Phase III studies demonstrated the effectiveness of Injectafer in treating IDA secondary to inflammatory bowel disease, heavy uterine bleeding, chronic kidney disease (hemodialysis and non-hemodialysis) and the postpartum state. Clinically meaningful increases in hemoglobin, 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 chronic kidney disease. A head to head comparison of Injectafer (Ferric carboxymaltose) to Venofer (Iron sucrose) in over 2,500 subjects with non-dialysis dependent CKD and elevated risk of cardiovascular disease according to the Framingham criteria demonstrated that the recommended dose of Injectafer, 750 mg x 2 (1500 mg total) had superior efficacy to the labeled dose of Iron sucrose (200 mg x 5 [1000 mg total]) with regard to hemoglobin elevation and had a similar cardiovascular (and overall) safety profile, based in part on an independently adjudicated composite cardiovascular safety endpoint [(8)] .

Important details of pre- and clinical safety and efficacy can be found in the Investigator's Brochure. Ferric carboxymaltose received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) approval on June 15, 2007 for the use of Injectafer (EU Trade name: Ferinject) in 18 EU (European Union) countries and later in Switzerland. Ferric carboxymaltose was first approved as a prescription only medicine on July 6, 2007 in The Netherlands. Up until now, Injectafer has received regulatory approval for marketing authorization in 58 countries worldwide: Argentina, Australia, Austria, Bangladesh, Belgium, Bolivia, Brazil, Bulgaria, Chile, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, Iceland, India, Iran, Ireland, Israel, Italy, Kazakhstan, Kuwait, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malta, Mexico, New Zealand, Norway, Pakistan, Peru, Poland, Portugal, Romania, Russia, Singapore, Slovenia, Slovak Republic, South Korea, Spain, Sweden, Switzerland, The Netherlands, Turkey, Ukraine, and United Kingdom. Injectafer® received approved from the Food and Drug Administration (FDA) on July 25, 2013 for marketing in the United States.

## 2.0 MAIN TRIAL OBJECTIVE

The primary objectives of this study are to characterize the pharmacokinetics and determine appropriate dosing and safety of Injectafer® for the pediatric population suffering from iron deficiency (ID) with anemia.

## 3.0 OVERALL STUDY DESIGN AND RATIONALE

### 3.1 Trial Design

This is a phase III, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics (PK/PD) profile of Injectafer® dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of Injectafer®.

Cohort 1: 16 subjects will be treated with Injectafer® at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

Cohort 2: 16 subjects will be treated with Injectafer® at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

### 3.2 Rationale

#### 3.2.1 Rationale for Trial Design

Injectafer is a non-dextran IV iron recently approved by the United States Food and Drug Administration (FDA). This trial is designed to assess the single doses (i.e., 7.5 mg iron/kg and 15 mg iron/kg) in iron deficient children with anemia to characterize the pharmacokinetics and pharmacodynamics in this younger population.

### 3.2.2 Rationale for open label design

The open-label, single arm trial design is considered appropriate because a control group is not required to estimate the PK/PD profile of Injectafer®. The risk from exposure to another form of IV iron is not offset by the minimal scientific benefit.

### 3.2.3. Schedule of Events

| Visit Day | Screening Period (Up to 14 Days) | Day -1 | Day 0 | 24 and 48 hours post dosing | 72 hours post dosing | Day 14 (week 2) | Day 28 (week 4) | Day 35 (week 5) |
|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | |
| Assess entry criteria | X | | X | | | | | |
| EDC | X | | X | | | | | X |
| Medical History | X | | X | | | | | |
| Physical Exam[1] | | | X | | | | | X |
| Vital Signs[6] | X | | X | | X | X | X | X |
| Height / Weight | | | X | | | | | |
| PK/PD Samples | | X[2] | X[3] | X[4] | X[4] | | | |
| Hematology, Chemistry and Iron Indices | X | | | | X | X | X | X |
| Serum pregnancy test | X | | | | | | | |
| Concomitant Medications | X | | X | | X | X | X | X |
| ESA Stability | X | | X | | X | X | X | X |
| Adverse Event Assessments[5] | | | X | X | X | X | X | X |
| Injectafer® Dosing[6] | | | X | | | | | |

[1] Includes clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system
[2] Blood samples drawn at 8am, 12pm and 8pm for subject iron profile
[3] Blood samples PK/PD should be taken prior to Injectafer® dosing and additional samples for PK/PD should be taken at 1, 2, 6 and 12 hours post dosing.
[4] Blood samples should be taken approximately the same time of day as the Day 0 samples were drawn
[5] Adverse event assessments starting at the time of Injectafer® dosing
[6] Sitting vital signs including blood pressure and heart rate should be collected immediately pre-dosing, immediately and 30 minutes post dosing. Body temperature will also be collected pre-dose only. Vital signs on non-dosing days include sitting heart rate and blood pressure only.

# 4.0 SUBJECT SELECTION

## 4.1 Number and Type of Subjects

Up to thirty two (32) subjects who have given written informed consent / assent along with parent or guardian's written informed consent with a diagnosis of iron deficiency anemia (IDA) who fulfill the inclusion criteria, do not meet any of the exclusion criteria will be registered to receive Injectafer®.

## 4.2 Screening Phase

Once a subject enters the screening phase, they will be assigned, via the Electronic Data Capture (EDC) system, a unique screening number. From the time of consent until the start of treatment of IV Injectafer®, the subject will not receive any form of iron outside of the study (intravenous or blood transfusion iron from 4 weeks prior to consent or oral iron including multivitamins with iron from time of consent).

If the subject does not qualify for study entry the subject should be entered into the EDC system as a screen failure. Subjects can be re-screened once, see section 6.2.

### 4.2.1 Entry Criteria

**Inclusion Criteria:**

1. Male or female subjects 1 to 17 years of age with assent to participation and his/her parent or guardian is willing and able to sign the informed consent approved by the Independent Review Board / Ethics Committee.
2. Screening TSAT < 20%
3. Screening Hemoglobin < 11 g/dL
4. For subjects who are receiving a erythropoietin stimulating agent (ESA): stable ESA therapy (+/- 20% of current dose) for > 8 weeks prior to the qualifying screening visit and no ESA dosing or product changes anticipated for the length of the trial.

**Exclusion Criteria:**

1. Known hypersensitivity reaction to any component of Injectafer®.
2. Subject previously randomized and treated in this study or any other clinical study of Injectafer® (FCM, VIT-45).
3. Body mass index (BMI) $\leq 95^{th}$ percentile for age (see APPENDIX 2)
4. History of acquired iron overload, hemochromatosis or other iron accumulation disorders.
5. Chronic kidney disease subjects on hemodialysis.
6. Screening Ferritin level > 300 ng/mL.
7. Subjects with significant severe diseases of the liver, hemopoietic system, cardiovascular system, psychiatric disorder or other conditions which on the opinion of the investigator may place a subject at added risk.
8. Any active infection.
9. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
10. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
11. Anemia due to reasons other than iron deficiency (i.e. hemoglobinopathy). Subjects treated with vitamin B12 or folic acid deficiency are permitted.

12. Significant blood loss (> 100 ml) within the last 3 months or any current bleeding disorders or anticipated need for surgery that may result in significant blood loss (> 100 ml).
13. Intravenous iron and /or blood transfusion in the 4 weeks prior to screening.
14. Immunosuppressive therapy that may lead to anemia (i.e. cyclophosphamide, azathioprine, mycophenolate mofetil). Note steroid therapy is permitted.
15. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
16. Alcohol or drug abuse within the past six months.
17. Female subject who are pregnant or lactating, or sexually active female who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.
18. Subject is unable to comply with study assessments.

### 4.3 Subject Assignment and Registration Process

Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this 7 week study. Cohorts 1 and 2 will be enrolled and treated sequentially. Enrollment into Cohort 2 will not begin until all Cohort 1 subjects have completed 4 weeks of therapy and no safety issues with the administration of Injectafer® has been confirmed by the DSMB.

### 4.4 Withdrawal from Study

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

At the time of withdrawal, procedures for the Day 35 visit must be performed regardless of whether the subject has completed study drug treatment. In the event the subject has received any study drug; the subject should be contacted to assess adverse events 28 days post the last dose of Injectafer®, if possible.

In the event a subject withdraws without completing the full PK/PD sampling. Additional subjects may be enrolled to ensure adequate representations of the PK/PD parameters are available for analyses. Conditions for additional enrollment will be defined in more detail in the statistical analyses plan.

### 4.5 Intervention

Intervention is defined as follows:

- Increase in dose of erythropoietin for any reason (Day 0 thru Day 35).
- Blood transfusion.
- Use of IV iron outside of protocol.
- Use of oral iron outside the protocol.

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 subject should continue in the study as scheduled through Day 35.

# 5.0 STUDY DRUG

## 5.1 Formulation Packaging and Storage

All medication to be used in this study that has been supplied by Vifor Pharma Ltd. will have been prepared according to Good Manufacturing Practices (GMP).

Injectafer® (known in the EU as Ferinject®) will be supplied as 5% w/v (weight /volume) 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.

Study drug must be kept in a secure place at the investigational site, and stored at room temperature (see: USP). Injectafer® should not be frozen. **Vials may not be used for more than 1 dose or for more than 1 subject.**

**All Injectafer® vials used and unused should be kept by the study staff and returned to Vifor Pharma Ltd., after drug accountability has been completed by the monitor.**

## 5.2 Drug Administration / Regimen

The Principal Investigator or designee will supervise administration of the study drug to subjects:

**Cohort 1**: 16 subjects will be treated with Injectafer® at 7.5 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

***Cohort 2 will initiate enrollment only after all subjects in Cohort 1 have completed 4 weeks of therapy and a DSMB approves continuation.***

**Cohort 2**: 16 subjects will be treated with Injectafer® at 15 mg/kg with a maximum single dose of 750 mg, whichever is smaller.

Injectafer® will be given on Day 0. It will be administered as either:

- An undiluted slow IV push at a rate of 100 mg/minute.
- Doses less than 100 mg should be given as a slow undiluted IV push within a minute.

## 5.3 IV Iron Precautions

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

- The subject 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 heart rate and blood pressure will be assessed pre-, immediately post, and 30 minutes post administration. If the subject 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 patients receiving IV iron therapies. Subjects 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 subjects 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 intravenous 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 Injectafer®. They will not allow Injectafer® 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 registered in the study, or to investigators not listed on the FDA 1572. When the study is completed, or if it is prematurely terminated, a final inventory of all clinical supplies must be compiled and the remainder of used and unused Injectafer® will be returned to Luitpold Pharmaceuticals, Inc. (or their designee). All data regarding Injectafer® must be recorded on the Drug Accountability Forms provided by the sponsor.

Investigators will keep adequate records of the administration and disposition of IV Injectafer® used for patients selected for the trial.

## 5.5 Concomitant Medication

Concomitant medications along with their route of administration and duration must be recorded in the electronic case report form (eCRF) from 30 days prior to consent. **No additional iron preparations (IV iron from 4 weeks prior to consent or oral iron including multivitamins with iron, from time of consent), will be allowed. No prophylactic medications may be administered prior to Injectafer® administration without prior approval from Luitpold Pharmaceuticals, Inc.**

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

# 6.0 STUDY PROCEDURES

## 6.1 Informed Consent

Prior to any study specific procedures, the investigator must explain to each subject 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 subject (who for this trial is 1 -17 years old) must assent, if appropriate and his/her legal guardian (who is above age of legal consent) voluntarily sign an informed consent statement (Required Elements of Informed Consent, 21 CFR 50.25). The Code of Federal Regulations (CFR) is a codification of

rules and regulations of the United States government. The subject's legal guardian will be given a copy of the signed consent form.

## 6.2 Screening (up to 14 days)

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

- Obtain screening number from EDC
- Medical history, including prior iron therapy use
- Vitals signs (including sitting heart rate and blood pressure)
- Hematology, Chemistries and iron indices
- Serum pregnancy test for female subjects of child bearing potential (negative results must be obtained prior to registering the subject for study drug dosing).
- Concomitant medications assessment
- ESA therapy stability ( if applicable)

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

## 6.3 Study Visits

### 6.3.1. Day (-1)

Once it's confirmed during the screening period that the subject continues meet the entry criteria all eligible subjects will return to the clinic on Day – 1, blood samples will be drawn at 8am, 12pm and 8pm to characterize the subject iron profile.

### 6.3.2 Day 0

On Day 0, prior Injectafer® dosing the following will occur:

- Re-verify the inclusion and exclusion criteria
- Update any relevant history
- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Height
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Log on to the EDC system and register subject for study drug dosing. The EDC system will assign the subject into Cohort 1 or 2 treatment group.

After assignment of the treatment group (Cohort 1 and 2) the following will occur:

- Blood samples for PK/PD before start of dose.
- Weight in kg without shoes

- Verify amount of single Injectafer® dose (7.5 or 15 mg/kg up to a maximum dose of 750 mg whichever is smaller).
- Document start and stop time of Injectafer® administration, the total dose administered and if diluted.
- Obtain sitting heart rate and blood pressure immediately pre-dose, immediately post-dose, and 30 minutes post Injectafer® administration. Body temperature taken pre-dose
- Adverse event assessment (starting at beginning of Injectafer® injection).

Blood samples for PK/PD will be drawn at 1, 2, 6 and 12 hours post the Day 0 Injectafer® dose.

### 6.3.2. Days 1 and 2 (24 and 48 hour)

- Blood samples for PK/PD
- Adverse events assessment

### 6.3.3. 72 hour, and Days 14 and 28 (weeks 2 and 4)

- Blood samples for PK/PD (72 hour visit only)
- Vital signs
- Hematology, chemistries and iron indices
- Adverse events assessment
- Concomitant medications assessment
- ESA stability/use ( if applicable)

### 6.3.4. Day 35 (week 5) End of Study

- Basic physical exam including clinical assessment of skin, cardiovascular, pulmonary, abdominal and central nervous system.
- Vitals signs
- hematology, chemistries and iron indices
- Concomitant medications assessment
- ESA stability/use ( if applicable)
- Adverse events assessment
- Log onto EDC and enter subject as complete

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

### 6.3.5. Pharmacokinetics and Pharmacodynamics (PK/PD)

Blood samples will be collected for PK/PD assessment pre-dose and at 1, 2, 6, 12, 24, 48 and 72 hours post dose. Blood samples should be taken at approximately the same time of day as the initial pre-dose sample on Day 0.

Prior to Day 0, subjects will return to the clinic on Day -1 at which time blood samples will be drawn at 8am, 12pm and 8pm to characterize the subjects specific iron profile.

Total blood volume (regular hematology, chemistry, iron indices and PK/PD) collected per day and during the 35 Day study is provided below:

| | Screening | Day (-1) | Day 0 | 24hr | 48hr | 72hr | Day14 | Day 28 | Day 35 | **Total Blood Volume** |
|---|---|---|---|---|---|---|---|---|---|---|
| Hem/Chem/II (10ml) | 10ml | | | | | 10ml | 10ml | 10ml | 10ml | |
| PK/PD (2ml) | | 6ml | 10ml | 2ml | 2ml | 2ml | | | | |
| **TOTAL** | **10ml** | **6ml** | **10ml** | **2ml** | **2ml** | **12ml** | **10ml** | **10ml** | **10ml** | **72ml / approx. 14.6 tsps.*** |

***4.93 mL = 1 tsp.**

## 6.4 Central Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. All serum laboratory testing will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 35 laboratory, this laboratory may be obtained after notification of the Sponsor. The laboratory assessments will be determined as listed in Section 3.2.3.

| | |
|---|---|
| Hematology: | Hb, 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, bicarbonate and magnesium |
| Iron indices: | serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT) |
| Other: | Serum pregnancy test |

# 7.0 ASSESSMENT OF SAFETY

## 7.1 Adverse Events

Any untoward medical event experienced by a subject 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 investigator will make a judgment as to its clinical significance. If the laboratory value is outside the normal limits and is felt to represent a clinically significant worsening from the baseline value, it should be considered an adverse event and should be recorded on the Adverse Events page of the eCRF. If the laboratory value is outside the normal range, but not an adverse event, the investigator should comment on the findings (i.e. “not clinically significant” or “unchanged from baseline”) in the source documentation [laboratory report].
For the purposes of this study, non-serious anemia (Hb or Hct below the normal range or worsened from baseline) or iron deficiency (iron indices below the normal range or worsened from baseline) will not be considered adverse events. Anemia or iron deficiency will be considered end points if an intervention is required.

To quantify the severity of adverse events, the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), Version 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 Injectafer® through the completion of the study Day 35. AE's will be captured 28 days post the last dose of Injectafer® for subjects who early terminate from the trial. This can be completed via a phone call. All ongoing adverse events related to Injectafer® 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 Injectafer® 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*.

* For the purposes of this trial, "study drug" is defined as: **Injectafer®** (known in the EU as **Ferinject®**)

## 7.2 Reporting of Adverse Events

Adverse experiences will be elicited by nonspecific questions such as “Have you noticed any problems?” Subjects will be encouraged to report adverse events at their onset.
Any adverse experience spontaneously reported by, elicited from the subject 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 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:** All SAEs will be reported from the initial treatment with Injectafer® through the completion of the study Day 35. SAEs will be captured 28 days post the last dose of Injectafer® for subjects who early terminate from the trial. This can be completed via a phone call. 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 lead to prolongation of hospital stay should not be considered SAE’s. 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 (within 24 hours of learning of the event) 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 IRB / Ethics Committee per their reporting guidelines.

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

## 8.0 STATISTICS

No hypothesis testing will be performed for this study.

### 8.1 Sample Size Rationale

Sixteen subjects per cohort will provide adequate data to estimate the primary PK parameters.

### 8.2 Analysis Populations

There will be 2 analysis populations:

- Safety population: Includes all subjects who receive Injectafer®.
- PK/PD population: Includes all subjects in the safety population who have evaluable iron profiles and no protocol violation that could affect the PK/PD of Injectafer®.

### 8.3 Demographic Characteristics

Demographic characteristics will be summarized for the Safety and PK/PD populations. The number and percentage of subject's who are registered, treated, prematurely discontinue, and complete the study will be summarized after the study's conclusion.

Subjects with clinically important protocol deviations will be identified for each analysis population, treatment group, and type of deviation. The clinical team will identify deviations and the deviations will be identified in the database.

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

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class (SOC) and preferred term for all subjects.

## 8.4 Endpoints and Definitions

### 8.4.1 Clinical Endpoints

Clinical endpoints include:

- Efficacy: change from baseline to each scheduled visit for hemoglobin, ferritin, and TSAT.
- Safety:

    - ✓ Proportion of subjects reporting treatment-emergent adverse events, overall and related, by SOC and preferred term
    - ✓ Subjects reporting treatment-emergent serious adverse events, overall and related, will be identified
    - ✓ Mean change from baseline to each scheduled visit for clinical laboratory values
    - ✓ Incidence of treatment-emergent potentially clinically significant (PCS) clinical laboratory values
    - ✓ Incidence of treatment-emergent PCS vital sign values.

## 8.5 Pharmacokinetics and Pharmacodynamics (PK/PD) Endpoints

The primary and secondary pharmacokinetic parameters will be determined for each subject as appropriate, based on serum concentration. The baseline parameters will be subtracted from all measured samples.

The primary parameters are the maximum serum concentration ($C_{max}$), the area under the serum concentration-time curve from time zero to the last sampling time (t) with a quantifiable concentration ($AUC_{0\text{-time last measured concentration}}$), the extrapolated area under the serum concentration- time curve from time zero to infinity ($AUC_{0\text{-infinity}}$), and the half-life ($T_{1/2}$). $C_{max}$ is calculated as a non-compartmental variable, which is a more conservative method than if it were calculated using a compartmental paradigm. $T_{1/2}$ incorporates the calculation of the rate elimination constant ($K_{el}$).

The secondary parameters are the mean residence time (MRT), the apparent serum clearance (Cl), and the apparent volume of distribution ($V_d$), which includes the initial volume of distribution following the injection ($Vd_c$), the volume of distribution at the steady state ($Vd_{ss}$), and the volume of distribution at the final elimination ($Vd_{area}$).

Pharmacodynamic parameter will include serum ferritin, transferrin, transferrin saturation (TfS) UIBC, HGB, reticulocyte count and transferrin receptors.

The Pharmacokinetic and Pharmacodynamic parameters performed in this study for analysis will be outlined in a Statistical and Analytical Plan.

## 8.6 Statistical Analyses of Safety

The Medical Dictionary for Regulatory Activities (MedDRA) Terminology will be used to classify all adverse events with respect to system organ class and preferred term.
The number and proportion of subjects who report treatment-emergent adverse events will be summarized for each treatment group. A similar summary will be provided for all treatment emergent serious adverse events.

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 to study drug. Relationship to study drug will be categorized as related (possibly or probably related) and unrelated. Events with unknown severity or relationship will be counted as unknown.

Subjects 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 subject reports multiple preferred terms for a system organ class (SOC), the subject will be counted only once for that SOC.

Change in vital signs from baseline to each scheduled study visit will be summarized descriptively with the mean, median, standard deviation, minimum value, and maximum value. The number and percent of patients with potentially clinically significant vital signs will be summarized for each treatment group.

### 8.7 DSMB Analyses

A DSMB will review safety information for subjects in Cohort 1 before dosing begins for Cohort 2. A Charter will be developed outlining the DSMB processes.

## 9.0 ADMINISTRATIVE CONSIDERATIONS

### 9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including electronic copies of 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 Pharmaceutical 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 subject must be maintained, that includes the signed Informed Consent form and copies of all study documentation related to that subject. 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 subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the Investigator Brochure, including potential risks and side effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

8. Maintain adequate and accurate records, in accordance with 21 CFR 312.62 and to make those records available for inspection with the Sponsor, their designated representative, the FDA or any agency authorized by law.
9. Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for initial and continuing review and approval of the clinical study.
10. Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (including amendments and IND safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subjects.
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 subjects into the study.

### 9.4 Advertisement for Subject Recruitment

All advertisements for subject recruitment must be reviewed and approved by the Sponsor and the site's IRB prior to implementation. Advertisements may include but is not limited to newspaper, fliers, radio, television, etc. Any compensation to the subject 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 subject 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 subjects 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 (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 principal 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. 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 United States (US) Code of Federal Regulations on Protection of Human Subjects (21 CFR 50), IRB regulations (21 CFR 56), the 2000 Edinburgh, Scotland Revision of the Declaration of Helsinki, all applicable local and state regulations, 21 CFR Part 312 and applicable ICH guidelines.

### 9.7.2 Institutional Review Board

The protocol and the Informed Consent / Assent 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 US Regulations (21 CFR 56). Investigators are responsible for the following:

- Obtain IRB approval of the protocol, Informed Consent / Assent and any advertisements to recruit subjects; 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 serious adverse events that occur or are reported to you by the Sponsor.

### 9.7.3 Informed Consent

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

The Informed Consent / Assent documents the information the Investigator provides to the subject and the subject'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 / Assent must be signed and dated by each subject and/or legal representative before entering the study and prior to the performance of any study specific procedures.

### 9.7.4 Good Clinical Practice

The conduct of the study will conform to the recommendations for clinical studies in human subjects as set out in the current version of the Edinburgh, Scotland Revision of the “Declaration of Helsinki”, the local legal requirements and the guidelines on “Good Clinical Practice”, [21 CFR Part 312 and ICH guidelines].

## 9.8 Data Handling and Record Keeping

### 9.8.1 Electronic Case Report Form (eCRF)

- eCRFs will be provided for each subject on this study. The participants in this study will be identified only by initials and subject 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 eCRFs are to be reviewed by the Clinical Monitor at Luitpold Pharmaceuticals, Inc. (or designee). Source data will be reviewed by the Clinical Monitor 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 subjects 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, DSMB, investigator, or study 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 subjects, failure of the investigator to enroll subjects 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 subject 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, which 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.

## 10.0 GOVERNANCE COMMITTEE

### 10.1 Data and Safety Monitoring Board

The DSMB will be composed of approximately 3-5 senior academic individuals, including the DSMB Chair. They will have high-level expertise in pediatric iron deficiency anemia and/or statistics. A senior statistician assigned to the trial from the group performing data management services for this trial will oversee the provision of interim data reports for use by the DSMB. The data management group for this trial will transfer pre-agreed datasets to the DSMB. During the Open Session of the DSMB meetings, the Study Chair or Luitpold representatives may present updates on the trial status or the safety profile of Injectafer®, but will not be privy to discussions of the data conducted during the Closed Sessions and will not vote. Proceedings and minutes of the Closed Session will be held in strict confidence and will not be shared outside the DSMB while the trial is ongoing.

The DSMB will be responsible for the interests of the patients and, to this end, will undertake reviews of the safety data. The DSMB will have access to an agreed subset of the study data as listed in the DSMB charter (updated as necessary during the trial) throughout the study duration. In addition, the DSMB will evaluate the data approximately (as outlined in the Charter) either by face to face meeting or teleconference. The DSMB will evaluate the safety from both cohorts 1 and 2 (7.5 or 15 mg/kg of Injectafer®). Only after all subjects in

cohort 1 have completed through week 4 and the DSMB has evaluated the safety data as acceptable will registration into cohort 2 be granted. The DSMB will determine if it believes the trial should be terminated early because clear evidence of a significant safety concern exists.

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

## INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol and agree to conduct the study as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR part 50, 54, 56 and 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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# APPENDIX 1: INJECTAFER® PACKAGE INSERT

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Injectafer safely and effectively. See full prescribing information for Injectafer.**

**INJECTAFER® (ferric carboxymaltose injection)**
**For intravenous use**
**Initial U.S. Approval: 20XX**

**----------INDICATIONS AND USAGE----------**

Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients:

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

**----------DOSAGE AND ADMINISTRATION----------**

For patients weighing 50kg (110lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750mg for a total cumulative dose of 1500mg of iron per course.

For patients weighing less than 50kg (110lb): Give Injectafer in two doses separated by at least 7 days and give each dose as 15 mg/kg body weight.

Injectafer treatment may be repeated if iron deficiency anemia reoccurs. (2)

**----------DOSAGE FORMS AND STRENGTHS----------**

750 mg iron / 15 mL single-use vial(3)

**----------CONTRAINDICATIONS----------**

Hypersensitivity to Injectafer or any of its inactive components. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- **Hypersensitivity reactions:** Observe for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of each administration. (5.1)
- **Hypertension:** Monitor patients closely for signs and symptoms of hypertension following each Injectafer administration. (5.2)

**----------ADVERSE REACTIONS----------**

The most common adverse reactions (≥2%) are nausea, hypertension, flushing, hypophosphatemia, and dizziness (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact American Regent at 1-800-734-9236 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**----------USE IN SPECIFIC POPULATIONS----------**

- Nursing Mothers: Exercise caution when administered to a nursing woman. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: July 2013**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Injectafer is indicated for the treatment of iron deficiency anemia in adult patients;

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

## 2 DOSAGE AND ADMINISTRATION

For patients weighing 50 kg (110 lb) or more: Give Injectafer in two doses separated by at least 7 days. Give each dose as 750 mg for a total cumulative dose not to exceed1500 mg of iron per course.

For patients weighing less than 50 kg (110 lb): Give Injectafer in two doses separated by at least 7 days. Give each dose as 15 mg/kg body weight for a total cumulative dose not to exceed 1500 mg of iron per course.

The dosage of Injectafer is expressed in mg of elemental iron. Each mL of Injectafer contains 50 mg of elemental iron. Injectafer treatment may be repeated if iron deficiency anemia reoccurs.

Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, USP, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes.

When added to an infusion bag containing 0.9% Sodium Chloride Injection, USP, at concentrations ranging from 2 mg to 4 mg of iron per mL, Injectafer solution is physically and chemically stable for 72 hours when stored at room temperature. To maintain stability, do not dilute to concentrations less than 2 mg iron/mL.

Inspect parenteral drug products visually for the absence of particulate matter and discoloration prior to administration. The product contains no preservatives. Each vial of Injectafer is intended for single use only. Any unused drug remaining after injection must be discarded.

Avoid extravasation of Injectafer since brown discoloration of the extravasation site may be long lasting. Monitor for extravasation. If extravasation occurs, discontinue the Injectafer administration at that site.

## 3 DOSAGE FORMS AND STRENGTHS

750 mg iron / 15 mL single-use vial

## 4 CONTRAINDICATIONS

Hypersensitivity to Injectafer or any of its components [see *Warnings and Precautions (5.1)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

**Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions.** [see *Adverse Reactions (6.1 and 6.2)*]. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

### 5.2 Hypertension

In clinical studies, hypertension was reported in 3.8% (67/1,775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1,775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration [*see Dosage and Administration (2)*].

### 5.3 Laboratory Test Alterations

In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

. Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
. Hypertension *[see Warnings and Precautions (5.2)]*
. Lab test alterations *[see Warnings and Precautions (5.3)]*

### 6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.
In two randomized clinical studies [Studies 1 and 2, *See Clinical Studies (14)*], a total of 1,775 patients were exposed to Injectafer 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

Adverse reactions reported by ≥ 1% of treated patients are shown in the following table.

**Table 1. Adverse reactions reported in ≥ 1% of Study Patients in Clinical Trials 1 and 2**

| Term | Injectafer (N=1775) % | Pooled Comparators[a] (N=1783) % | Oral iron (N=253) % |
|---|---|---|---|
| Nausea | 7.2 | 1.8 | 1.2 |
| Hypertension | 3.8 | 1.9 | 0.4 |
| Flushing/Hot Flush | 3.6 | 0.2 | 0.0 |
| Blood Phosphorus Decrease | 2.1 | 0.1 | 0.0 |
| Dizziness | 2.0 | 1.2 | 0.0 |
| Vomiting | 1.7 | 0.5 | 0.4 |
| Injection Site Discoloration | 1.4 | 0.3 | 0.0 |
| Headache | 1.2 | 0.9 | 0.0 |
| Alanine Aminotransferase Increase | 1.1 | 0.2 | 0.0 |
| Dysgeusia | 1.1 | 2.1 | 0.0 |
| Hypotension | 1.0 | 1.9 | 0.0 |
| Constipation | 0.5 | 0.9 | 3.2 |

[a] Includes oral iron and all formulations of IV iron other than Injectafer

Other adverse reactions reported by ≥ 0.5% of treated patients include abdominal pain, diarrhea, gamma glutamyl transferase increased, injection site pain/irritation, rash, paraesthesia, sneezing. Transient decreases in laboratory blood phosphorus levels (< 2 mg/dL) have been observed in 27% (440/1638) patients in clinical trials.

### 6.2 Post-marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following serious adverse reactions have been most commonly reported from the post-marketing spontaneous reports with Injectafer: urticaria, dyspnea, pruritis, tachycardia, erythema, pyrexia, chest discomfort, chills, angioedema, back pain, arthralgia, and syncope. One case of hypophosphatemic osteomalacia was reported in a

subject who received 500 mg of Injectafer every 2 weeks for a total of 16 weeks. Partial recovery followed discontinuation of Injectafer.

## 7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Injectafer .

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C

*Risk Summary*

Adequate and well controlled studies in pregnant women have not been conducted. However, animal reproduction studies have been conducted with ferric carboxymaltose. In these studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused fetal malformations and increased implantation loss at maternally toxic doses of approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area). The incidence of major malformations in human pregnancies has not been established for Injectafer. However, all pregnancies, regardless of exposure to any drug, has a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Animal Data*

Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Spontaneous abortions occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryofetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

### 8.3 Nursing Mothers

A study to determine iron concentrations in breast milk after administration of Injectafer (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving Injectafer than in lactating women receiving oral ferrous sulfate.

### 8.4 Pediatric Use
Safety and effectiveness have not been established in pediatric patients.

### 8.5 Geriatric Use
Of the 1775 subjects in clinical studies of Injectafer, 50% were 65 years and over, while 25% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

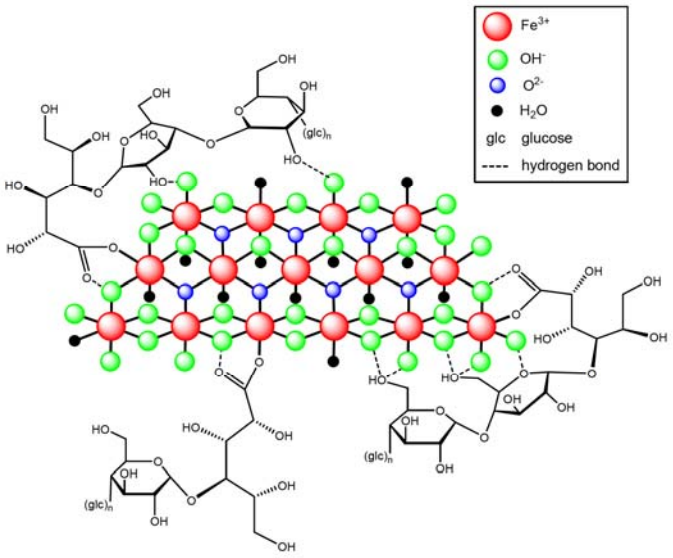
## 10 OVERDOSAGE
Excessive dosages of Injectafer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. A patient who received Injectafer 18,000 mg over 6 months developed hemosiderosis with multiple joint disorder, walking disability and asthenia . Hypophosphatemic osteomalacia was reported in a patient who received Injectafer 4000 mg over 4 months. Partial recovery followed discontinuation of Injectafer. [*see Post-marketing Experience (6.3)]*.

## 11 DESCRIPTION
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).

The chemical structure is presented below:




Injectafer (ferric carboxymaltose injection) is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Each mL contains 50 mg iron as ferric carboxymaltose in water for injection. Injectafer is available in 15 mL single-use vials. Sodium hydroxide and/or hydrochloric acid may have been added to adjust the pH to 5.0-7.0.

Vial closure is not made with natural rubber latex

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.

### 12.2 Pharmacodynamics

Using positron emission tomography (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.

### 12.3 Pharmacokinetics

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 1.21 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ferric carboxymaltose.

Ferric carboxymaltose was not genotoxic in the following genetic toxicology studies: *in vitro* microbial mutagenesis (Ames) assay, *in vitro* chromosome aberration test in human lymphocytes, *in vitro* mammalian cell mutation assay in mouse lymphoma L5178Y/TK+/- cells, *in vivo* mouse micronucleus test at single intravenous doses up to 500 mg/kg.

In a combined male and female fertility study, ferric carboxymaltose was administered intravenously over one hour to male and female rats at iron doses of up to 30 mg/kg. Animals were dosed 3 times per week (on Days 0, 3, and 7). There was no effect on mating function, fertility or early embryonic development. The dose of 30 mg/kg in animals is approximately 40% of the human dose of 750 mg based on body surface area.

## 14 CLINICAL STUDIES

The safety and efficacy of Injectafer for treatment of iron deficiency anemia were evaluated in two randomized, open-label, controlled clinical trials (Trial 1 and Trial 2). In these two trials, Injectafer was administered at a dose of 15 mg/kg body weight up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron.

### 14.1 Trial 1: Iron Deficiency Anemia in Patients Who Are Intolerant to Oral Iron or Have Had Unsatisfactory Response to Oral Iron

Trial 1 was a randomized, open-label, controlled clinical study in patients with iron deficiency anemia who had an unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2) during the 14 day oral iron run-in period. Inclusion criteria prior to randomization included hemoglobin (Hb) <12 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%. Cohort 1 subjects were randomized to Injectafer or oral iron for 14 more days. Cohort 2 subjects were randomized to Injectafer or another IV iron per standard of care [90% of subjects received iron sucrose]. The mean age of study patients was 43 years (range, 18 to 94); 94% were female; 42% were Caucasian, 32% were African American, 24% were Hispanic, and 2% were other races. The primary etiologies of iron deficiency anemia were heavy uterine bleeding (47%) and gastrointestinal disorders (17%).

Table 2 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 35 or time of intervention.

**Table 2. Mean Change in Hemoglobin From Baseline to the Highest Value Between Day 35 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | Cohort 1 | | Cohort 2 | |
|---|---|---|---|---|
| | Injectafer (N=244) | Oral Iron (N=251) | Injectafer (N=245) | IV SC[a] (N=237) |
| Baseline | 10.6 (1.0) | 10.6 (1.0) | 9.1 (1.6) | 9.0 (1.5) |
| Highest Value | 12.2 (1.1) | 11.4 (1.2) | 12.0 (1.2) | 11.2 (1.3) |
| Change (from baseline to highest value) | 1.6 (1.2) | 0.8 (0.8) | 2.9 (1.6) | 2.2 (1.3) |
| p-value | 0.001 | | 0.001 | |

SD=standard deviation; [a]: Intravenous iron per standard of care

Increases from baseline in mean ferritin (264.2±224.2 ng/mL in Cohort 1 and 218.2 ±211.4 ng/mL in Cohort 2), and transferrin saturation (13±16% in Cohort 1 and 20±15% in Cohort) were observed at Day 35 in Injectafer-treated patients.

**14.2 Trial 2: Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease**

Trial 2 was a randomized, open-label, controlled clinical study in patients with non-dialysis dependent chronic kidney disease. Inclusion criteria included hemoglobin (Hb) ≤ 11.5 g/dL, ferritin ≤ 100 ng/mL or ferritin ≤ 300 ng/mL when transferrin saturation (TSAT) ≤ 30%.Study patients were randomized to either Injectafer or Venofer. The mean age of study patients was 67 years (range, 19 to 96); 64% were female; 54% were Caucasian, 26% were African American, 18% Hispanics, and 2% were other races.

Table 3 shows the baseline and the change in hemoglobin from baseline to highest value between baseline and Day 56 or time of intervention.

**Table 3. Mean Change in Hemoglobin From Baseline to the Highest Value Between Baseline and Day 56 or Time of Intervention (Modified Intent-to-Treat Population)**

| Hemoglobin (g/dL) Mean (SD) | **Injectafer (N=1249)** | **Venofer (N=1244)** |
|---|---|---|
| Baseline | 10.3 (0.8) | 10.3 (0.8) |
| Highest Value | 11.4 (1.2) | 11.3 (1.1) |
| Change (from baseline to highest value) | 1.1 (1.0) | 0.9 (0.92) |
| Treatment Difference (95% CI) | 0.21 (0.13, 0.28) | |
| | | |

Increases from baseline in mean ferritin (734.7±337.8 ng/mL), and transferrin saturation (30±17%) were observed at Day 56 in Injectafer-treated patients.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

| | |
|---|---|
| NDC 0517-0650-01 | 750 mg iron/15 mL Single-Use Vial Individually boxed |
| NDC 0517-0650-02 | 750 mg iron/15 mL Single-Use Vial Packages of 2 |

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See the USP controlled room temperature]. Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

- Question patients regarding any prior history of reactions to parenteral iron products.
- Advise patients of the risks associated with Injectafer.
- Advise patients to report any signs and symptoms of hypersensitivity that may develop during and following Injectafer administration, such as rash, itching, dizziness, lightheadedness, swelling and breathing problems [*see Warnings and Precautions (5)*]

Injectafer is manufactured under license from Vifor (International) Inc, Switzerland.

AMERICAN
REGENT, INC.
SHIRLEY, NY  11967

IN0602
Rev. 7/13

**Patient Information**
**INJECTAFER (ferric carboxymaltose injection)**

Please read this information carefully before taking this medication. This summary does not tell you everything about INJECTAFER. Speak with your doctor or healthcare professional if there is something you do not understand or if you would like to learn more about INJECTAFER. Your doctor or healthcare professional is your best source of information about this medicine.

## What is INJECTAFER?

Iron is a mineral that the body needs to produce red blood cells. When the body does not get enough iron, it cannot produce the number of normal red blood cells needed to keep you in good health. This condition is called iron deficiency (iron shortage) or iron deficiency anemia.

INJECTAFER is used to treat iron deficiency anemia. Iron deficiency anemia may be caused by several medical conditions including heavy menstrual bleeding, pregnancy, childbirth, inflammatory bowel disease, other malabsorption diseases, bariatric surgery, or chronic kidney disease**.**

## General information about using INJECTAFER safely and effectively

Injectable iron is administered only by or under the supervision of your health care professional.

Serious or life threatening allergic reactions have been reported with intravenous iron products. Tell your health care professional if you have ever had any unusual or allergic reaction to any IV iron.

Patients should report to their healthcare professional any signs and symptoms of an allergic reaction to INJECTAFER, in particular rashes, shortness of breath and wheezing.

Iron is not easily eliminated from the body, and its build up may be lead to a condition called iron overload which may be harmful. Certain medical conditions such as liver disease may also make you more likely to develop iron overload. Ask your doctor or healthcare professional.

## Who should not take INJECTAFER?

You should not be given INJECTAFER if you have anemia that is not caused by iron deficiency, or if you have iron overload.

If you are pregnant or plan to become pregnant please notify your doctor or healthcare professional. They will decide whether it is safe for you to receive INJECTAFER.

## How should I take INJECTAFER?

INJECTAFER is administered intravenously (into your vein) by your doctor or health care professional in two doses.

**What should I avoid while taking INJECTAFER?**

You should not take iron supplements by mouth if you are receiving iron injections. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

**What are the possible side effects of INJECTAFER?**

The side effects of INJECTAFER are infrequent, usually mild and generally do not cause patients to stop treatment. The most common side effects are nausea, injection site reactions (including pain or bruising at the injection site), asymptomatic reductions in blood phosphorus, flushing, headache, hypertension, dizziness, and increased alanine aminotransferase. Potentially long lasting brown staining of skin near injection site may occur.

These are not all the possible side effects of INJECTAFER. For more information ask your doctor or healthcare professional.

Talk to your doctor if you think you have side effects from taking INJECTAFER.

# APPENDIX 2: **WEIGHT CHARTS FOR BOYS AND GIRLS**

## **Boys (White) Weight Chart age 0-36 months** (http://www.halls.md/chart/boys-weight-w.htm)

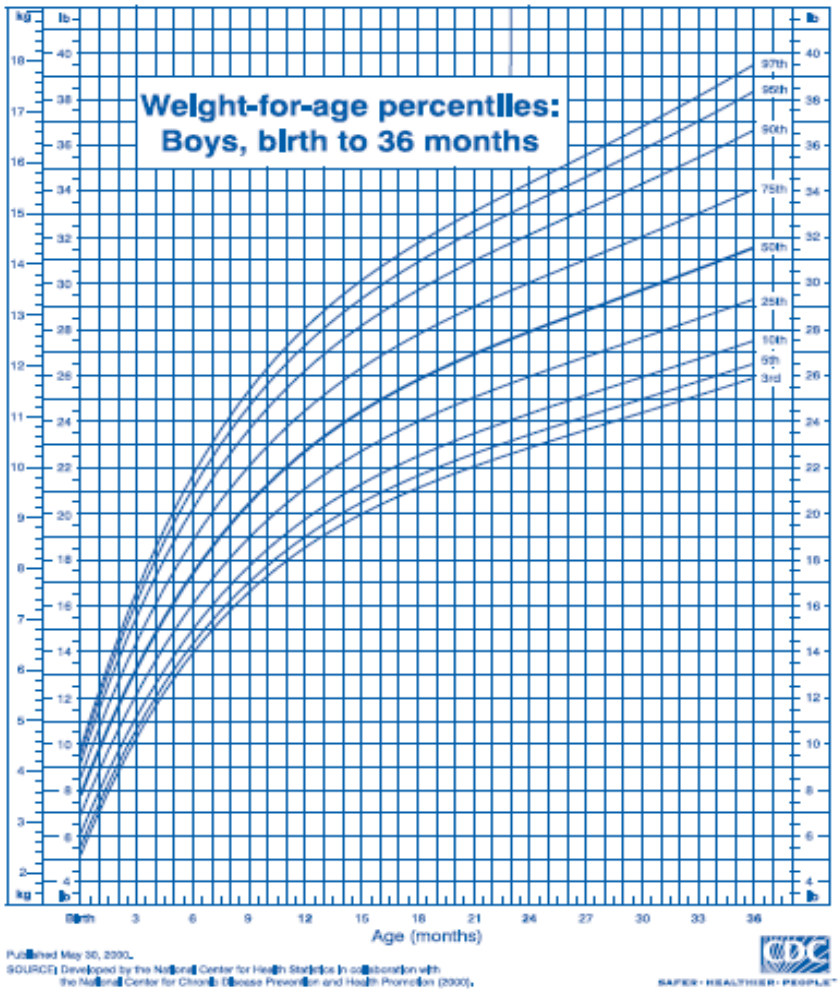
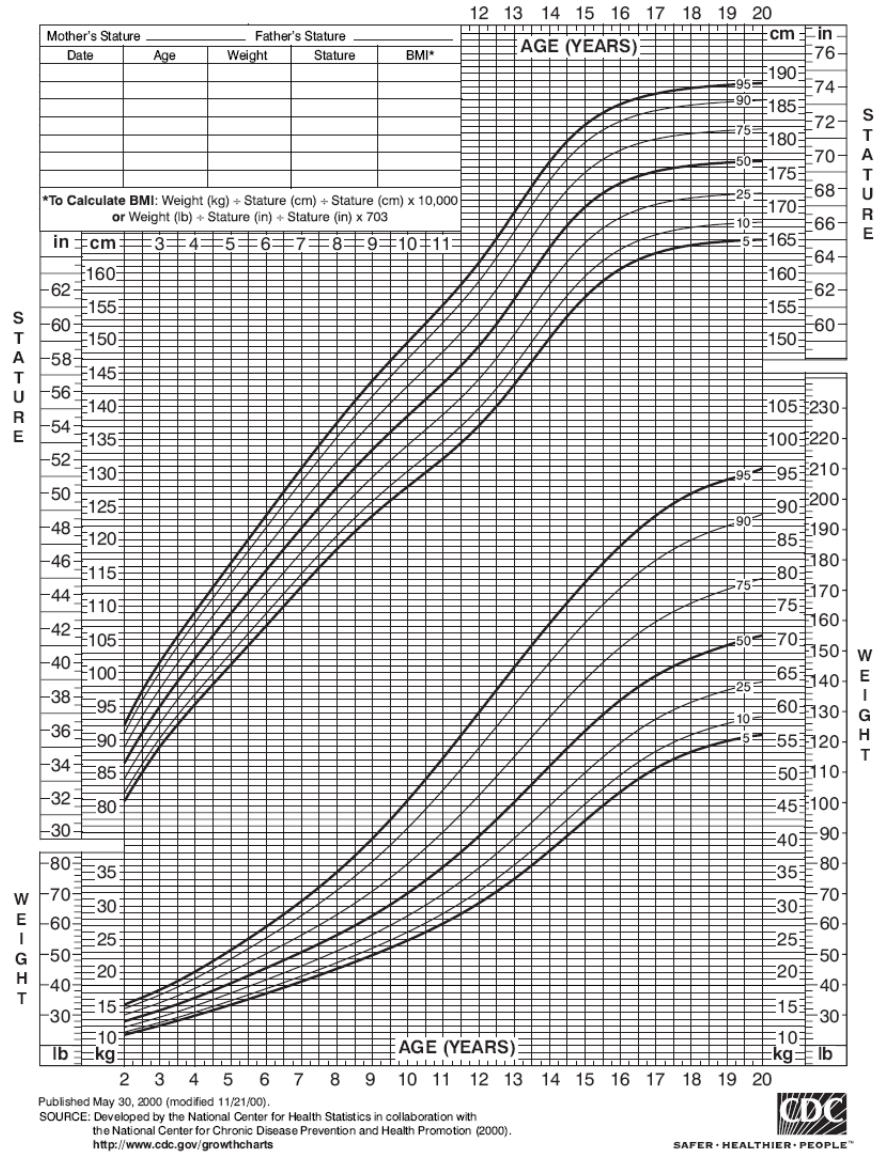



Figure 1. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Boys weight-for-age

# BOYS (WHITE) WEIGHT CHART AGE 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L021.PDF)



**Girls (White) Weight Chart age 0-36 months** (http://www.halls.md/on/girls-weight-w.htm)

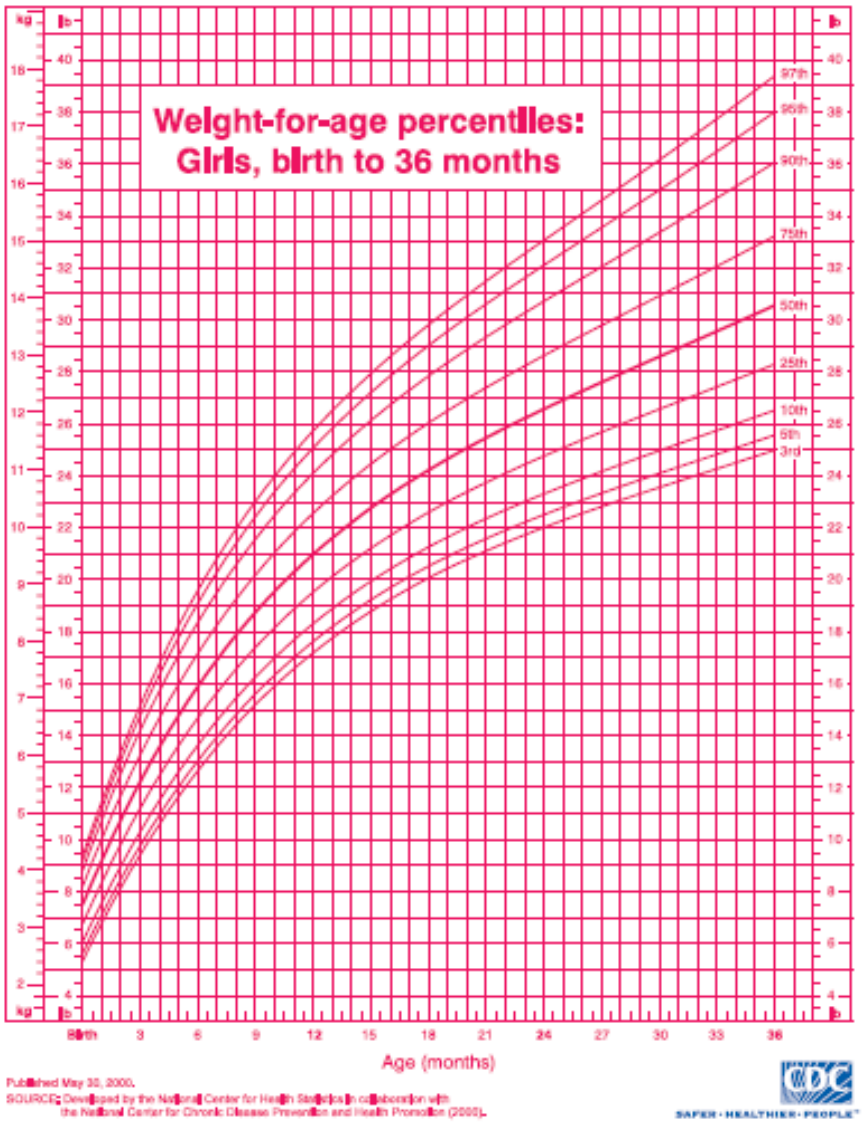



Figure 2. Individual growth chart 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97th percentiles, birth to 36 months: Girls weight-for-age

# GIRLS (WHITE) WEIGHT CHART AGES 2-20 YRS

(HTTP://WWW.CDC.GOV/GROWTHCHARTS/DATA/SET1CLINICAL/CJ41L022.PDF)