NCT02453334 1VIT14039

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

Protocol No. 1VIT14037

PROTOCOL DATE: 02 April 2014

AMENDMENT I DATE: 05 August 2014

AMENDMENT II DATE: 05 January 2015

AMENDMENT III DATE: 13 July 2015

CZECH REPUBLIC AMENDMENT IV DATE: 02 June 2016

# 16. APPENDICES

## 16.1 Study Information

### 16.1.1 Protocol and Protocol Amendments

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**LUITPOLD PHARMACEUTICALS, INC.**

**PROTOCOL**

**No. 1VIT14037**

**IND #: 73,076**

# A Double-Blind, Multi-Center, Randomized, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) in the Treatment of Restless Legs Syndrome (RLS)

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**PROTOCOL DATE: 02 April 2014**
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**AMENDMENT II DATE: 05 January 2015**
**AMENDMENT III DATE: 13 July 2015**
**CZECH REPUBLIC AMENDMENT IV DATE: 02 June 2016**

**SIGNATURES OF AGREEMENT FOR PROTOCOL**

30 NOV 2016

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**STUDY SYNOPSIS**
Protocol 1VIT14037

**Title:** A Double-Blind, Multi-Center, Randomized, Placebo-Controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) in the Treatment of Restless Legs Syndrome (RLS).

**Investigational Drug:** Injectafer® (Ferric Carboxymaltose)

**Objectives:** The primary objective of this study is to evaluate the efficacy and safety of intravenous Injectafer® in subjects with Restless Leg Syndrome (RLS).

**Study Design:** This will be a Phase III, double blind, multi-center, randomized, placebo-controlled study. All subjects who meet the inclusion requirements and no exclusion criteria will qualify to enter up to a 7 day Screening Phase to enroll 200 eligible subjects for study drug treatment. All eligible subjects will be stratified at baseline by RLS medication-related augmentation (no augmentation, uncertain augmentation, definitive augmentation). Randomization will occur in a 1:1 ratio within each stratum to receive Injectafer® or Placebo on Days 0 and 5. All treated subjects will be followed for efficacy and safety for 12 months. Subjects will **visit the clinic** on Days 0 and 5 for treatment, and then on Days 14, 42, 168, and 365. In between the clinic visits subjects will be contacted remotely (phone) on Days 28, 84,126, 210, 252, 294, and 336. The subject's participation in the study will be for 1 year from Day 0.

**Study Drug Treatment:** The duration of treatment will be 5 days. On Day 0 (start of Treatment Phase) subjects will be randomized to receive either a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded Placebo (15 ml of Normal Sterile Saline [NSS]) IV push at 2 ml/minute. On Day 5 subjects will receive the same blinded treatment as given on Day 0.

**Tapering Algorithms of RLS Treatment Regimens:** Each subject will be tapered from the prescribed RLS medication post treatment beginning on the evening of Day 5 or starting on Day 6. The tapering regimen will depend on the subject's current medication and dosing (see Appendix III). It is expected that all subject's will be tapered off their current treatment for RLS, but in the rarity a subject, at the end of the allotted tapering period, is unable to achieve a dose of zero (0) the subject should maintain on the lowest dose level attained at the end of the tapering period and that dose should remain stable for the duration of the subjects participation in the study. During the tapering period and through Day 42 subjects will continue to keep an RLS diary to record their symptoms related to their RLS.

**Additional Treatment Post Day 42:** Subjects who have not had an intervention may receive additional blinded study drug treatment at the discretion of the Investigator after Day 42. An intervention is defined as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, or 3) resumption of the previous medication prescribed for RLS, or 4) increase in dosage from the RLS medication achieved at the end of the tapering period. The subject will receive the same blinded study medication that was previously assigned. Subjects will receive either a **single blinded** dose of Injectafer® at 750 mg undiluted at 100mg/minute or a Placebo (15 ml of Normal Sterile Saline [NSS]) IV push at 2 ml/minute on two independent days separated by 5 days. Dosing should mirror the original treatment / follow-up period (dosing 5 days apart with safety follow-up visits, to include laboratory assessments only, on 14 and 42 Days post the first dose). No subject assessments are completed unless the dosing or follow-up days fall on an assessment day in the follow-up period. Eligible subject will have met the following requirements prior to receiving additional treatment:

- IRLS score ≥15
- TSAT <45% (confirmation can be through a local laboratory)
- Ferritin <300 ng/mL (confirmation can be through a local laboratory)

No additional iron may be administered between Day 320 and the Day 365 visit.

**Efficacy and Safety Follow-up:** The duration of the study will be 12 months. After treatment on Days 0 and 5 subjects will visit the clinic on Days 14, 42, 168, and 365. In between the clinic visits subjects will be contacted remotely (phone) on Days 28, 84, 126, 210, 252, 294, and 336. Subjects will be considered to have reached the end of the study for efficacy when intervention is required for RLS symptoms and the subjects will continue the follow-up phase for safety.

**Efficacy and Safety Evaluations (see Table 1, Schedule of Events, for details)**

Efficacy evaluations will include:

1. Clinical Global Impression (CGI) performed by Investigator (CGI-I)
2. International Restless Legs Syndrome (IRLS) Score
3. Clinical Global Impression (CGI) performed by Subject (CGI-S)
4. Restless Legs Syndrome Quality of Life (RLS-QLI)
5. Medical Outcome Study (MOS) Sleep Scale
6. Fatigue Linear Analog Scale

Safety Evaluations will include:

1. Adverse events
2. Laboratory assessments, including hematology (Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count ), iron indices (serum iron, serum ferritin, and total iron binding capacity (TIBC), percentage serum transferrin saturation (TSAT)), clinical chemistry (sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, gamma-GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate) and other (transferrin receptor and Lymphocyte samples)
3. Vital signs
4. Physical examinations

**Intervention:**

**Intervention is defined** as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, 3) resumption of the previous medication prescribed for RLS or, 4) increase in dosage from the RLS medication achieved at the end of the tapering period. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and be evaluated for safety.

**Inclusion Criteria:**

1. Male or female subject's ≥18 years of age, willing and able to give informed consent to the study.
2. RLS symptoms affirming diagnosis. The IRLS Diagnostic Criteria must be met:
    a. An urge (distressing need) to move the legs usually associated with painful or uncomfortable sensations in the legs. The urge to move may be present without the uncomfortable sensations. The arms or other body parts may be involved in addition to the legs.
    b. The urge to move or unpleasant sensations are worse or exclusively present at rest or inactivity, such as lying down or sitting.

   c. The urge to move or unpleasant sensations are partially/temporarily relieved with walking or moving the legs.
   d. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. When symptoms are severe, the worsening at night may not be noticeable but must have been previously present.
3. Subjects should be on monotherapy for RLS. Treatment should be stable for at least 8 weeks prior to screening (See approved RLS Therapies/Regimen in Appendix III).
4. A score ≥15 on the IRLS Rating Scale at screening and on Day 0 prior to dosing.
5. Subjects on anti-depressants and sleep medications must be on a stable dose for at least 6 months.
6. Subject has regular sleep hours between 9 pm and 9 am.
7. All patients must use one highly reliable contraception with reliability index < 1 for example IUD, sterilization of one of the partners, assuming one sexual partner relationship during the clinical trial will occur, hormonal implants, injections, patches, pills, accompanied with one barrier form of contraception with spermicide. Men should always use condom. Use of two barrier methods simultaneously with spermicide is considered a reliable contraceptive method. A sexual abstinence throughout the clinical trial is allowed only if this is a lifestyle choice of the patient

**Exclusion Criteria:**

1. RLS 2° to other disease or injury.
2. Disorders that require treatment with the same medications used for RLS include: peripheral neuropathy and neurodegenerative disorders (i.e. Parkinson's Disease or Dementia).
3. Stage 4 – 5 CKD, subjects on dialysis or anticipated to start dialysis while participating in this study.
4. Any pain related (e.g., frequent muscle cramps, myalgia, fibromyalgia) or sleep related disorders (e.g. sleep apnea, unless on stable Continuous Positive Airway Pressure [CPAP]) which may confound the outcome measures.
5. Subjects with multiple sclerosis.
6. History of neuroleptic akathisia.
7. Parenteral iron use within 6 weeks prior to screening.
8. History of >10 blood transfusions in the past 2 years.
9. Anticipated need for blood transfusion during the study.
10. Known hypersensitivity reaction to any component of Injectafer® (Ferric Carboxymaltose).
11. Previously randomized to Injectafer® (FCM or VIT-45) in a clinical trial.
12. Current, active or acute or chronic infection other than viral upper respiratory tract infection
13. Malignancy (other than basal or squamous cell skin cancer or the subject has been cancer free for ≥ 5 years).
14. Pregnant or lactating women.
15. Seizure disorder currently being treated with medication.
16. Baseline ferritin ≥300 ng/mL.
17. Baseline TSAT ≥45%.
18. History of hemochromatosis, hemosiderosis, or other iron storage disorders.
19. AST or ALT greater than 2 times the upper limit of normal (ULN).
20. Hemoglobin greater than the ULN.
21. Known positive hepatitis B antigen (HBsAg), unless positive test can be attributed to receipt of hepatitis B vaccination in childhood or hepatitis C viral antibody (HCV) with evidence of active hepatitis (i.e., AST/ALT greater than the upper limit of normal).
22. Known positive HIV-1/HIV-2 antibodies (anti-HIV).
23. Received an investigational drug within 30 days before randomization.
24. Chronic alcohol or drug abuse within the past 6 months.

25. Any other pre-existing laboratory abnormality, medical condition or disease, which per the investigator may put the subject at risk if they participate in the study.
26. Subject unable or unwilling to comply with the study requirements.

**RLS**
**Therapy:**

All subjects should be on a stable RLS monotherapy regimen (see Appendix III) for at least 8 weeks prior to screening. These therapies should remain unchanged until the tapering process begins post Day 5 treatment with study drug. An algorithm of RLS medication taper regimens is provided (Appendix III). If and when the subject is tapered off the RLS medication, the goal will be for the subject to remain off their medication or remain on the lowest dose level achieved for the duration of the study. If during the course of the study it becomes necessary to restart therapy via subject and physician decision, these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis.

**Study Endpoints:**

The co-primary efficacy variables will be IRLS total score change from baseline to Day 42 and the proportion of patients rated as "much" or "very much" improved with the Clinical Global Impression (CGI) performed by Investigator (CGI-I) on Day 42.

The major secondary endpoints will be tested in a hierarchical order, that is, statistical significance for major secondary efficacy endpoint will be declared only if the primary efficacy test (IRLS and CGI-I on Day 42) is statistically significant. Because a hierarchical testing scheme is used, no adjustments of the alpha level will be needed at each stage of testing. All tests will be done at an alpha $\leq 0.05$.

The major secondary efficacy endpoints in ranked order of testing include:

1. Clinical Global Impression (CGI) performed by Subject (CGI-S) on Day 42.
2. Restless Legs Syndrome Quality of Life (RLS-QLI) change from baseline to Day 42.
3. Medical Outcome Study (MOS) Sleep Scale change from baseline to Day 42.
4. Fatigue Linear Analog Scale change from baseline to Day 42.

Other efficacy endpoints:

1. Proportion of responders (any improvement) based on CGI-I at each time point.
2. IRLS total score change from baseline at each time point.
3. Proportion of responders based on CGI-S at each time point.
4. RLS-QLI scores change from baseline at each time point.
5. MOS Sleep scale total score change from baseline at each time point.
6. Fatigue Linear Analog Scale total score change from baseline at each time point.
7. Augmentation Scale change between baseline, Day 42, Day 168 and end of study (Day 365).
8. Proportion of subjects require intervention for RLS.
9. Number of days from Day 5 to next dose of study drug.

The safety endpoints include:

1. Incidence of treatment emergent adverse events (TEAE) and incidence of serious adverse events (SAE)

2. Change in clinical laboratory tests
3. Change in vital signs
4. Change in Columbia-Suicide Severity Rating Scale (C-SSRS)

**Blinding:**

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

- Randomizing the subject on Day 0 through IRT system.
- Preparing, concealing and administering the study drug on Day 0 and 5 (as Injectafer® is reddish-brown and slightly viscous).[1]
- Completing the Study Drug Accountability Form, study drug dosing record and applicable electronic case report form pages.
- Assessment of blinded laboratory parameters (iron indices and phosphorus).
- Retention of any source documents to which the investigator and the site study team is blinded (i.e. post-randomization IRLS questionnaires/scores, subjects' CGI scores, dosing information).

**Study Duration:**

- Screening Phase: up to 7 days
- Treatment Phase: 5 days
- Follow-up Phase: 12 months

**Number of Subjects:**

Enrollment is planned for 200 subjects (100 per group) at study sites in the United States (US), Poland, Hungary, Czech Republic, Ukraine and Spain.

**Sample Size:**

Sample size estimates were based on the modified intent to treat (MITT) population for Study 1VIT05009. The last observation carried forward (LOCF) and observed cases (OC) results on Day 28 were used for the co-primary efficacy endpoint (CGI) and first-ranked secondary endpoint (IRLS). It is unclear how treatment differences on Day 42 results might differ from Day 28, apart from a higher dropout rate, but it is reasonable to assume that treatment differences will decrease. Therefore, power calculations were based on smaller treatment differences and larger standard deviations.

Co-primary efficacy endpoint (IRLS): The smallest treatment difference for change from baseline to Day 28 was 4.4 with a standard deviation of 8.5. A sample size of per 100/group provides 95% power under this scenario.

Co-primary efficacy endpoint (CGI-I): The smallest treatment difference on Day 28 was 45% versus 15% of patients in the FCM and placebo groups, respectively, who reported much or very much improvement on the patient CGI. A sample size of 100/group provides >99% power. A sample size of per 100/group has at least 90% power when the treatment difference is as small as 45% versus 22%.

**Statistical Methods:**

Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using region (US, Europe) as the stratification factor. Treatment group differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for region (US, Europe) and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test.

The primary imputation method for the CGI and change in total/domain scores will be LOCF. Sensitivity analyses will assess the impact of missing values on inferences.

Time from Day 5 to the next dose of study drug will be analyzed with the log-rank test. Subjects who discontinue or complete the study before an intervention will be censored at last study visit.

Analyses of safety data will be descriptive and no formal statistical comparisons will be made.

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## LIST OF ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| 2º | Secondary |
| bpm | Beats per minute |
| °C | Degree celsius |
| CFR | Code of Federal Regulations |
| CGI-I | Clinical Global Impression-Global Improvement |
| CGI-S | Clinical Global Impression- Subject |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CKD | Chronic Kidney Disease |
| CNS | Central Nervous System |
| CRF | Case Report Form |
| CSF | Cerebral Spinal Fluid |
| CPAP | Continuous Positive Airway Pressure |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DAWS | Dopamine agonist withdraw syndrome |
| eCRF | Electronic Case Report Form |
| °F | Degree Fahrenheit |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| g/dL | Grams per deciliter |
| Hgb | Hemoglobin |
| IBD | Inflammatory Bowel Disease |
| ICH | International Clinical Harmonization Guideline |
| IRB | Investigational Review Board |
| IRLS | International Restless Legs Syndrome |
| IRLSSG | International Restless Legs Syndrome Study Group |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LASA | Linear Analog Scale Assessment |
| LLN | Lower Limit of Normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| mL | Milliliter |
| mITT | Modified Intent-to-treat |
| MOS | Medical Outcomes Study |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| Ng | Nanogram |
| NSS | Normal Sterile Saline |
| PD | Peritoneal Dialysis |
| PET | Positron Emission Tomography |
| PLMS | Periodic Limb Movements of Sleep |
| PLMA | Periodic Limb Movements while awake |
| PSG | Polysomnogram measurement of sleep |
| Qod | every other day |
| Q3d | every 3 days |
| Q5d | every 5 days |

| | |
|---|---|
| QOL | Quality of Life |
| RLS | Restless Legs Syndrome |
| RLS-QLI | Restless Legs Syndrome – Quality of Life |
| SAE | Serious adverse event |
| SOC | System Organ Class |
| TEAE | Treament Emergent Adverse Event |
| TFR | Transferrin Receptor |
| TSAT | % Transferrin Saturation |
| ULN | Upper Limit of Normal |
| US | United States |
| WNL | Within Normal Limit |

# 1.0 INTRODUCTION

## 1.1 The Natural History, Disease Understanding, and Treatment Guidance for Restless Legs Syndrome (RLS)

Restless legs syndrome (RLS), is a circadian disorder of sensory-motor integration that may be related to dysregulation of iron transport across the blood-brain barrier.[1] Epidemiologic data suggest geographic variation in the prevalence of RLS, with estimates ranging from 2-10% in general populations, and as high as 20 % in certain target populations with secondary RLS/.[2-5] Pharmacologic therapy for primary RLS are broadly based on short-term randomized, controlled trials that enrolled highly-selected patient populations with long-term, high-moderate to very severe symptoms.[6-8] Current treatment regimens for RLS include dopamine agonists, calcium channel alpha-2-delta (α2δ) ligands, opioids, and benzodiazepines.[9-11] While these medications reduce RLS symptoms and improve outcomes related to sleep-specific quality of life, adverse effects and treatment withdrawal due to adverse effects have been common.[6] Medication tolerance, augmentation, and symptom, if not worsening of symptoms, are concerns with sustained RLS treatment effect.[9,11-13] Evidence-based guidelines and practice support investigations that target trials of intravenous (IV) iron in RLS.[9]

## 1.2 Role of Iron in the Pathogenesis and Pathophysiology of RLS

As early as the 1950s, the role of iron was hypothesized to have a role in the onset and treatment of RLS.[14] Nordlander first associated anemia from various causes (gastric ulcer, leukemia, and chronic nephritis) with the development of restless legs and as well as symptom resolution following blood transfusions.[15] Subsequent associations of RLS have been reported with conditions such as in pregnancy, hemodialysis, and frequent blood donations.[2,3,16] Several findings have contributed to the disease understanding of low central nervous system iron stores in RLS as follows:

- In 2000, C. J. Earley *et al.* reported a comparison of 16 patients with idiopathic RLS compared to 8 age-matched healthy control subjects.[17] Cerebrospinal fluid (CSF) ferritin levels were lower (1.11$\pm$ 0.25 mg/L versus 3.50 $\pm$ 0.55 mg/L; p =0.0002) and CSF transferrin levels were higher (26.4 $\pm$ 5.1 mg/L versus 6.71 $\pm$ 1.6 mg/L; p = 0.018) in idiopathic RLS subjects compared with control subjects.[17] There were no differences in serum ferritin and serum transferrin levels between the 2 groups.
- In 2001, R.P. Allen *et al.* reported a study of 5 RLS patients and 5 control subjects that assessed brain iron concentrations.[18] A magnetic resonance imaging (MRI) measurement utilizing relaxation rates of both hemispheres ($R_2^1$ and $R_2$) identified that $R_2^1$ was significantly decreased in the substantia nigra, and somewhat less significantly in the putamen, of subjects with RLS, both in proportion to the RLS severity.[18]
- In 2003, J.R. Connor *et al.* demonstrated reduced iron concentrations in the substantia nigra using MRI techniques and concluded that RLS may be a functional disorder resulting from impaired iron acquisition in the central nervous system (CNS).[19]
- Subsequent studies over the past decade support that reduction in CNS iron among patients with RLS may be a functional consequence to impaired iron acquisition by the neuromelanin cells, with a putative defect in regulation of the transferrin receptors.[20-24]

In 2013, the report from the International Restless Legs Syndrome Study Group included evidence-based guidelines and clinical consensus on best practice guidance for RLS. The report summarized that "Long-term clinical experience with the treatment of patients with RLS has revealed both the significance of problems that arise during the short term (e.g., weight gain, impulse control disorders [ICDs], mood disturbances) and the emergence of new problems during long-term treatment (e.g., augmentation, loss of efficacy)."[9] Overall, extensive RLS research has led to the conclusion that the pathophysiology of idiopathic RLS involves iron homeostatic dysregulation and that there is a role for iron treatment in RLS.

## 1.3 The Role of Iron Treatment in RLS

In studied populations, iron therapy appears to treat the specific mechanism of RLS pathology in some patients with low iron levels in the brain.[25] Very early after the identification of the condition, IV treatment with saccharated oxide of iron was shown to be quite successful.[26] Nordlander reported that IV iron therapy (generally given as 100 – 200 mg every 1 to 4 days) was completely effective at eliminating symptoms in 21 of 22 patients (95.5%) for periods of up to 3-9 months, as well as effective in eliminating symptoms even in patients without anemia and with normal serum iron.[26] Earley *et al.* reported similar efficacy in an open label study of 10 RLS patients, of whom 60% reported complete remission of RLS symptoms for 3 to 36 months after intravenous iron dextran.[27]

In 2005, Earley *et al.*evaluated the efficacy and safety of repeated infusions of IV iron to maintain symptomatic RLS improvements achieved with a prior single 1,000 mg infusion of iron dextran.[28] If symptoms returned at any time in the 2-year period after initial iron treatment, supplemental infusions of 450 mg of iron gluconate infusions could be given, provided the ferritin was <300 mcg/l. Five out of 10 subjects received supplemental iron, three of whom received between 2-4 courses of supplemental iron over the 2 year study period.[28] The authors concluded that achieving high ferritin levels was not a guarantee of sustained improvements.[28] In a randomized, placebo controlled study of IV iron in RLS in 25 subjects with end stage renal disease (ERSD), 1,000 mg (given at <6 mg/min) of IV iron dextran produced a significant reduction in the symptoms of RLS as measured by the RLS severity score.[29] In a multicentered, placebo-controlled clinical trial of IV ferric carboxymaltose (FCM) treatment for RLS, FCM significantly improved primary and secondary outcomes compared to placebo.[30] In the comparison of FCM to placebo treatment, the IRLS severity scale mean (SD) decrease was 8.9 (8.52) versus 4.0 (6.11), p=0.040, and the Clinical Global Inventory of Change (CGI-1) score of very much or much improved was 48.3% versus 14.3%, p=0.004; there were no significant adverse events.[30] The conclusions from this study were that IV FCM provided a safe and effective treatment for RLS that lasted for at least 24 weeks for patients.[30]

Oral iron has been demonstrated to be effective in RLS patients with iron deficiency but not in patients without iron deficiency.[31-33] The explanation in part may be due to the poor absorption of oral iron in non iron deficient patients and that large iron doses are required to cross the blood brain barrier. Silber and Richardson described a RLS patient population who were identified as having iron deficiency and a history of frequent blood donations.[16] The hemoglobin range was 10.6 to 15.5 gm/dl in this cohort and all 8 patients were iron deficient (defined as low serum ferritins ranges 3 to 15 μg/l). After correction of iron stores with oral iron, symptoms of RLS resolved in 2 patients and 2 others were able to discontinue other RLS medications.[16]

The 2012 Cochrane Database Systematic Review of iron for RLS provided a summary of 192 subjects from six studies.[29,33-38] In the four trials that used the IRLS severity scale, there were trials of IV iron sucrose (N=2), oral iron (N=1), and IV FCM (N=1).[33,35,36,38] The combined IRLS data from these RLS trials was not associated with clear benefit (mean difference in scores of -3.79, 95% CI: -7.68 to 0.10, p = 0.06), yet the placebo-controlled trial of FCM and of oral iron (in low-normal ferritin subjects) reported significant treatment benefit compared to placebo.[33,35] The subsequent data in the publication of the FCM trial was aligned with the preliminary findings reported in the Cochrane Database Systematic Review.[30,34,35]

## 1.4 Injectafer® (Ferric Carboxymaltose)

### 1.4.1 Key features of Injectafer®

Injectafer® (Ferric Carboxymaltose Injection) is a stable Type I polynuclear iron (III)-hydroxide carbohydrate complex developed as an IV iron replacement therapy for the treatment of IDA. After IV administration, Injectafer® is mainly found in the reticaloendothelial system (RLS) which includes the liver, spleen, and bone marrow. The iron slowly dissociates from the complex and can be efficiently used in the bone marrow for hemoglobin synthesis. The carbohydrate moiety of Injectafer® is metabolized by the glycolytic pathway. Injectafer® is approved for the treatment of IDA and an investigational product on the study of RLS.

### 1.4.2 Injectafer® versus Other Parenteral Iron Agents

There is considerable efficacy and safety experience with the various available parenteral iron preparations. 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 IV iron preparations.

Iron dextran, the first parenteral iron product available in the US, has been associated with an incidence of anaphylaxis/anaphylactoid reactions (i.e., dyspnea, wheezing, hypotension, urticaria, angioedema) as high as 1.7%. Over the last 20 years, 30 deaths have been attributed to the use of IV iron dextran. The anaphylaxis/anaphylactoid reactions are believed to be caused by the formation of antibodies to the dextran moiety. Iron dextran is limited to second-line therapy for treatment of iron deficiency. High molecular weight (HMW) iron dextran is reportedly 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.

Non-dextran IV irons like iron sucrose and iron gluconate do not contain the dextran moiety, but they have significant dosage and administration rate limitations. If the body's ability to handle (i.e., sequester, store, and transport) iron is overwhelmed, a reaction to excess free iron referred to as a bioactive iron reaction may occur. These 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. Injectafer® a slow delivery of the complexed iron to endogenous iron binding sites and has an acute toxicity in animals approximately 1/5 that of iron sucrose. These characteristics of Injectafer® make it possible to administer much higher single doses over shorter periods of time iron gluconate or iron sucrose, resulting in fewer administrations to replenish iron stores, and convenient outpatient use **(Table 1.3.2.1).** Ferumoxytol is a modified-dextran derivative currently indicated for IDA associated with chronic kidney disease (CKD). It was recently withdrawn from use in the EU and given a black box warning in the US.

### 1.4.3 Injectafer® Human Experience: Marketed Use and the RLS indicator

The Injectafer® clinical development program demonstrated the safety and effectiveness of IV Injectafer® in the treatment of IDA. The drug is indicated for the treatment of IDA in adult populations who have intolerance to oral iron or have had unsatisfactory responses to oral iron or non-dialysis dependent CKD (see Appendix I). 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.

Important details of pre-clinical and clinical safety and efficacy can be found in the Investigator's Brochure. Ferric carboxymaltose received approval from the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency (MHRA) approval on June 15, 2007 for the use of Injectafer® (EU Trade name: Ferinject) in 18 European Union (EU) 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 approval for the treatment of IDA from the Food and Drug Administration (FDA) on July 25, 2013.

## 2.0 TRIAL OBJECTIVE

### 2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy and safety of an IV Injectafer® in subjects with Restless Leg Syndrome (RLS).

## 3.0 RATIONALE AND OVERALL STUDY DESIGN

### 3.1 Rationale

Injectafer® is a non-dextran IV iron approved by the US Food and Drug Administration (FDA). In an earlier phase II study (1VIT05009) Injectafer® was found to be safe and well tolerated for the treatment of RLS.[30] Based on these findings a larger phase III trial will be conducted to further investigate and confirm the use of Injectafer® in the treatment of RLS.

Further justification is also based on the pathophysiology of iron in RLS as summarized in the Introduction (Section 1.0)

### 3.2 Trial Design

This is a Phase III, double blinded, multi-center, randomized, placebo-controlled study. All subjects who meet the inclusion requirements and no exclusion criteria will qualify to enter up to a 7 day Screening Phase to enroll 200 eligible subjects for study drug treatment. All eligible subjects will be stratified at baseline by RLS medication-related augmentation (no augmentation, uncertain augmentation, definitive augmentation) on standard of care RLS therapy. Subjects will be randomized in a 1:1 ratio within each stratum to receive either Injectafer® or IV Placebo on Days 0 and 5. All treated subjects will be followed for efficacy and safety for 12 months. Subjects will **visit the clinic** on Days 0 and 5 for treatment, and then on Days 14, 42, 168, and 365. In between the clinic visits subjects will be contacted remotely (phone) on Days 28, 84, 126, 210, 252, 294, and 336. The subject's participation in the study will be for 1 year from Day 0.

- Subjects will receive either a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded IV Placebo (15 ml of Normal Sterile Saline [NSS]) IV push at 2ml/minute on Days 0 and 5.

After treatment on Days 0 and 5 subjects will visit the clinic on Days 14, 42, 168, and 365. In between the clinic visits subjects will be contacted remotely (phone) on Days 28, 84, 126, 210, 252, 294, and 336. Subjects will be considered to have reached the end of the study for efficacy when intervention is required for their RLS symptoms; those subjects will continue the follow-up phase for safety. Table 3.2.1 below summarizes the Schedule of Events.

Table 3.2.1 Schedule of Events

| | **Scr.** | **Treatment** | | | | | **Efficacy and Safety Follow-up** *** Contact completed remotely via phone* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-7 (+ 2 days)** | **0** | **5** | **14** | *28*** | **42** | *84*** | *126*** | **168** | *210*** | *252*** | *294*** | *336*** | **365** |
| Informed Consent | x | | | | | | | | | | | | | |
| Eligibility | x | x | | | | | | | | | | | | |
| Medical History[8] | x | | | | | | | | | | | | | |
| D/C oral iron products | x | | | | | | | | | | | | | |
| Site contact IRT | x[1] | x[2] | | | | | | | | | | | | x |
| Physical exam | x | | | | | x | | | x | | | | | x |
| Vital Signs | x[3] | x[4] | x[4] | | | x[3] | | | x[3] | | | | | x[3] |
| Height and Weight without shoes | x | | | | | | | | | | | | | |
| Augmentation Subject Questionnaire | x[12] | | | | | | | | | | | | | |
| Augmentation Investigator Assessment | x[13] | | | | | x | | | x | | | | | x |
| RLS Diary[15] | x | x | x | x | x | x | | | | | | | | |
| Phone contact treatment phase | | | | | x | | | | | | | | | |
| IRLS Scale | x | x | x | | x | x | *x* | *x* | x | *x* | *x* | *x* | *x* | x |
| CGI-I and CGI-S | | | x[I,S] | | *x*[s] | x[I,S] | *x*[s] | *x*[s] | x[I,S] | *x*[s] | *x*[s] | *x*[s] | *x*[s] | x[I,S] |
| RLS QLI | x[5] | x[5] | | | | x | | | x | | | | | x |
| MOS Sleep Scale | x[5] | x[5] | x | | | x | | | x | | | | | x |
| Fatigue Linear Analog Scale | x[5] | x[5] | x | | | x | | | x | | | | | x |
| C-SSRS[14] | x | | | | | x | | | x | | | | | x |
| Hematology | x | | x | x | | x | | | x | | | | | x |
| Iron Indices | x | | x | x | | x | | | x | | | | | x |
| Chemistry | x | | x | x | | x | | | x | | | | | x[7] |
| Pregnancy test[9] | x | | | | | | | | | | | | | |
| Transferrin receptor | x | | | | | x | | | x | | | | | |
| Study Drug Dosing | | x | x | | | | **See section 6.3.5 for additional study drug dosing requirements** | | | | | | | |
| RLS Treatment Stability[11] / Tapering review / assessment | x | x | x[10] | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant Meds | x | x | x | | x | x | *x* | *x* | x | *x* | *x* | *x* | *x* | x |
| Adverse Events[6] | | x | x | x | x | x | *x* | *x* | x | *x* | *x* | *x* | *x* | x |

[1] Contact IRT for screening number assignment during screening, and on Day 365 to complete subject from the study.
[2] Contact IRT for randomization assignment, unblinded site personnel
[3] Vital Signs includes sitting BP and heart rate.
[4] On study drug dosing days 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 dosing on Days 0 and 5.
[5] RLS QLI, MOS Sleep Scale, and Fatigue Linear Analog Scale may be completed at screening or prior to dosing on Day 0.
[6] Adverse event assessments will start at the time of the first dose of study drug. All events noted prior to the 1st dose of study drug should be considered history and captured on the medical history page of the eCRF.
[7] If the phosphorous is below the LLN at the time of early termination or end of the study (Day 365) the subject should return (as directed by the Investigator) for repeat phosphorous until the value is back WNL's or the subject's baseline.
[8] To include past and present treatment for RLS.
[9] Female subjects only.

[10] After dosing on Day 5 the site will review the tapering requires with the subject.
[11] Assess compliance of tapering. Once the taper period is complete assess stability (off meds, decrease dose, baseline dose).
[12] Augmentation questionnaire should be completed at screening prior to the Investigator's Augmentation Assessment.
[13] Augmentation assessment can be done either at screening or prior to dosing on Day 0 but after the subject has completed the augmentation questionnaire.
[14] The Columbia-Suicide Severity Rating Scale will be used throughout the study to assess the subjects suicide ideation or behavior. This scale is an assessment tool, it is ultimately the Investigators responsibility to evaluate each subject's risk and treat as appropriate.
[15] Subject Diary reviewed for compliance at Day 0,5,14 and 28. The completed diary will be returned by the subject to the site on Day 42.
[I,S] Investigator and Subject Assessment.
[S] Subject only Assessment.

## 4.0 SUBJECT SELECTION

### 4.1 Number and Type of Subjects

Two hundred (200) subjects (100 per group) who have given written informed consent with a diagnosis of RLS who fulfill the inclusion criteria and, do not meet any of the exclusion criteria, will be randomized to receive Injectafer® or IV Placebo.

### 4.2 Screening Phase

Once a subject enters the screening phase, they will be assigned a unique screening number, via the Interactive Response Technologies (IRT) system.

#### 4.2.1 Inclusion Criteria

1. Male or female subject's ≥18 years of age or older, able and willing to give informed consent to the study.
2. RLS symptoms affirming diagnosis. The IRLS Diagnostic Criteria for RLS must be met:
    a. An urge (distressing need) to move the legs usually associated with painful or uncomfortable sensations in the legs. The urge to move may be present without the uncomfortable sensations. The arms or other body parts may be involved in addition to the legs.
    b. The urge to move or unpleasant sensations are worse or exclusively present at rest or inactivity, such as lying down or sitting.
    c. The urge to move or unpleasant sensations are partially/temporarily relieved with walking or moving the legs.
    d. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. When symptoms are severe, the worsening at night may not be noticeable but must have been previously present.
3. Subjects should be on monotherapy for RLS. Treatment should be stable for at least 8 weeks prior to screening. (See approved RLS Therapies/Regimen in Appendix III).
4. A score ≥15 on the IRLS Rating Scale at screening and on Day 0 prior to dosing.
5. Subjects on anti-depressants and sleep medications must be on a stable dose for at least 6 months.
6. Subject has regular sleep hours between 9 pm and 9 am.
7. All patients must use one highly reliable contraception with reliability index < 1 for example IUD, sterilization of one of the partners, assuming one sexual partner relationship during the clinical trial will occur, hormonal implants, injections, patches, pills, accompanied with one barrier form of contraception with spermicide. Men should always use condom. Use of two barrier methods simultaneously with spermicide is considered a reliable contraceptive method. A sexual abstinence throughout the clinical trial is allowed only if this is a lifestyle choice of the patient.

### 4.2.2 Exclusion Criteria

1. RLS 2° to other disease or injury.
2. Disorders that require treatment with the same medications used for RLS include: peripheral neuropathy and neurodegenerative disorders (i.e. Parkinson's Disease or Dementia).
3. Stage 4 – 5 CKD, subjects on dialysis or anticipated to start dialysis while participating in this study.
4. Any pain related (e.g., frequent muscle cramps, myalgia, fibromyalgia) or sleep related disorders (e.g. sleep apnea, unless on stable Continuous Positive Airway Pressure [CPAP]) which may confound the outcome measures.
5. Subjects with Multiple Sclerosis.
6. History of neuroleptic akathisia.
7. Parenteral iron use within 6 weeks prior to screening.
8. History of >10 blood transfusions in the past 2 years.
9. Anticipated need for blood transfusion during the study.
10. Known hypersensitivity reaction to any component of Injectafer® (Ferric Carboxymaltose).
11. Previously randomized to Injectafer® (FCM or VIT-45) in a clinical trial.
12. Current, active, or acute or chronic infection other than viral upper respiratory tract infection.
13. Malignancy (other than basal or squamous cell skin cancer or the subject has been cancer free for ≥ 5 years).
14. Pregnant or lactating women.
15. Seizure disorder currently being treated with medication.
16. Baseline ferritin ≥300 ng/mL.
17. Baseline TSAT ≥45%.
18. History of hemochromatosis or hemosiderosis or other iron storage disorders.
19. AST or ALT greater than 2 times the upper limit of normal.
20. Hemoglobin greater than the upper limit of normal.
21. Known positive hepatitis B antigen (HBsAg) unless positive test can be attributed to receipt of hepatitis B vaccination in childhood or hepatitis C viral antibody (HCV) with evidence of active hepatitis (i.e., AST/ALT greater than the upper limit of normal).
22. Known positive HIV-1/HIV-2 antibodies (anti-HIV)
23. Received an investigational drug within 30 days before randomization.
24. Chronic alcohol or drug abuse within the past 6 months.
25. Any other pre-existing laboratory abnormality, medical condition or disease which per the investigator may put the subject at risk if they participate in the study.
26. Subject unable or unwilling to comply with the study requirements.

## 4.3 Subject Assignment and Randomization Process

Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this 12 month study. Subjects will be stratified by augmentation (no augmentation, uncertain augmentation, definitive augmentation) and randomized in a 1:1 ratio via an IRT system to receive either a blinded dose of IV Injectafer® or a blinded dose of Placebo.

- Each subjects will receive either a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded IV Placebo (15ml of Normal Sterile Saline [NSS]) IV push at 2ml/minute on Days 0 and 5.

### 4.4 RLS Standard of Care Therapy: Tapering Procedures

Each subject will be tapered from the current RLS medication, post treatment on Day 5. The tapering regimen will depend on the subject's current medication and dosing (see tapering schedule in Appendix III). Starting at screening, during the tapering period and through Day 42 subjects will be asked to keep an RLS diary to record their progress.

### 4.5 Duration of Study / Withdrawal from Study

All subjects will be followed for efficacy. The subset of subjects requiring intervention for treatment of RLS will continue to be followed for safety of efficacy or until Day 365.

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.

If withdrawal is prior to Day 42, the Day 42 procedures should be performed at the time of withdrawal. If the withdrawal occurs after Day 42, then the procedures for the Day 365 visit must be performed.

In the event the subject has received any study drug and discontinues early at a minimum the subject should be contacted 28 days following the last dose of study drug to assess adverse events, if possible.

### 4.6 Intervention

**Intervention is defined** as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, 3) resumption of the previous medication prescribed for RLS, or, 4) increase in dosage from the RLS medication achieved at the end of the tapering period. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety.

## 5.0 STUDY DRUG

### 5.1 Formulation Packaging and Storage

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

Injectafer® (Ferric carboxymaltose injection) will be supplied as 15 mL vials, containing 750 mg of iron 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.

Injectafer® supplied by Luitpold Pharmaceuticals, Inc. 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 vials (used and unused) should be kept and returned to Luitpold Pharmaceuticals, Inc., after drug accountability has been completed by the monitor.**

## 5.2 Study Drug Blinding/Administration

### 5.2.1 Study Drug Blinding

All subjects, investigators, and study personnel will be blinded to the content of study drug with the exception of the unblinded study personnel. All study personnel will be blinded to the iron indices (after randomization) throughout the study.

#### 5.2.1.1 Unblinded Personnel

The **unblinded study personnel** will be responsible for the following:

- Randomizing the subject on Day 0 through IRT system
- Preparing, concealing and administering the study drug on Day 0 and 5 (as Injectafer® is reddish-brown and slightly viscous).[1]
- Completing the Study Drug Accountability Form, study drug dosing record and applicable electronic case report form pages.
- Assessment of blinded laboratory parameters (iron indices and phosphorus).
- Retention of any source documents to which the investigator and the site study team is blinded (ie. post-randomization IRLS questionnaires/scores, subjects' CGI scores, dosing information).

#### 5.2.1.2 Blinded Personnel

The **blinded study personnel** will be responsible for all other study related activities. During the period of study drug administration the blinded personnel will not be present. However, the Principal Investigator or designee will be available in the event of an emergency and/or the need for adverse event assessment. All study personnel will be blinded to the post-treatment iron indices as the values may reveal the blind.

The blinding will be maintained until the study is complete and the database has been locked. In the event of an emergency that would require the investigator to be aware of the treatment allocation prior to database lock; the investigator can obtain this information, on a per subject basis, from the Sponsor's electronic database at the Investigative site. **It is recommended to contact the sponsor's Medical Monitor or designee prior to unblinding.** If a subject's treatment assignment is unblinded, the sponsor must be contacted immediately via telephone.

#### 5.2.1.3 Investigator Blinding

In addition to the above, the blinded investigator will be blinded to the IRLS score and subject CGI score for each subject after randomization.

## 5.3 Study Drug Administration

On Days 0 and 5, subjects will either receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded Placebo (15 ml of Normal Sterile Saline [NSS]) IV push at 2ml/minute.

## 5.4 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-dosing, 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.
    - In the event a serious acute reaction is seen, the site must have the capability to provide appropriate resuscitation measures. These may include IV NSS, IV epinephrine, steroids, and/or antihistamines.

### 5.5 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 randomized 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. All data regarding Injectafer® must be recorded on the Drug Accountability Forms provided by the sponsor.

### 5.6 Concomitant Medication

Concomitant medications along with their route of administration and duration must be recorded in the electronic case report form (eCRF). **No additional iron preparations, IV iron from 6 weeks prior to screening or oral iron including multivitamins with iron from time of consent will be allowed. No blood transfusions or erythropoiesis stimulating agents will be allowed. Once a subject is randomized, additional anti-depressants, anti-seizure, sleep medications, dopamine agonists, benzodiazepines, narcotics, or other RLS treatments are not permitted for the duration of the study**. Non-narcotic analgesics are permitted.

All subjects should be on a stable RLS monotherapy regimen (see Appendix III) for at least 8 weeks prior to screening. These therapies should remain unchanged until the tapering process begins post Day 5 treatment with study drug. Once the subject is tapered off RLS medication (Appendix III) the subject should stay removed from medication for the duration of the study, but if a subject, at the end of the allotted tapering period, is unable to achieve a dose of zero (0) the subject should be maintained on the lowest dose level attained at the end of the tapering period and that dose should remain stable for the duration of the study. If during the course of the study it becomes necessary to restart or increase therapy via physician decision, these data points will be

collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis.

**No pre-treatment prophylactic medications may be administered prior to Injectafer® administration without prior approval from Luitpold Pharmaceuticals, Inc.**

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

### 6.2 Screening

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

- Obtain screening number from IRT system
- Medical history, including prior iron therapy use
- All prior medications, to include current treatments for RLS and side effects associated with those medications
- IRLS scale will be completed
- Medical Outcome Study (MOS) Sleep Scale (range 0-100)
- Restless Legs Syndrome Quality of Life (RLS-QLI)
- Fatigue Linear Analog Scale
- Columbia Suicide Severity Rating Scale (C-SSRS): The Columbia-Suicide Severity Rating Scale will be used throughout the study to assess the subject's suicide ideation or behavior. This scale is an assessment tool, it is ultimately the Investigators responsibility to evaluate each subject's risk and treat as appropriate.
- Physical exam
- Vital signs (sitting heart rate and blood pressure)
- Height and Weight without shoes
- Blood samples for hematology, chemistries, iron indices and transferrin receptor, fasting if indicated. A serum pregnancy test will be performed on female subjects.
- All oral iron products will be discontinued on the day of the first screening visit
- RLS Diary:
  - Three-item RLS diary. Subjects will complete the RLS diary daily, screening through Day 42. The diary should be completed around the same time each day. The following 3 questions will be assessed:

    1. How many hours did you nap/sleep in the prior 24 hours? _____
    2. For the nap/sleep hours, how many times were you interrupted by your symptoms of restless legs syndrome? _____

3. For the awake time, how many times were you interrupted by your symptoms of restless legs syndrome? _____

- Augmentation subject questionnaire to be completed
- Augmentation Investigator assessment (can be completed in screening, once the subject questionnaire is complete or on Day 0 prior to randomization). The physician will assess the subject and provide the following:
    - Step 1. Please provide a percent (%) score using the scale outline below for the following question:
        - How likely is it that the subject has developed augmentation to the RLS medication? _____%
    - Step 2. Convert this percentage estimate to the strata category for randomization

| Step 1 percentage (%) | Randomization Strata |
|---|---|
| 0% to < 25% | No Augmentation |
| 25% to ≤ 75% | Uncertain Augmentation |
| >75% | Definitive Augmentation |

    - Step 3. Randomize the subject via the augmentation strata

Subjects who do not meet the entry criteria should be entered into the IRT 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 above will need to be repeated.

## 6.3 Study Days 0 - 365

### 6.3.1 Day 0

The following must be obtained **PRIOR** to dosing the subject:

- Confirm the subject continues to meet the Inclusion/Exclusion criteria
- IRLS scale will be completed
- Vital signs to include temperature
- Concomitant medications, to include RLS treatment stability
- The investigator will assess the subject's augmentation status (if not completed during screening): no augmentation, uncertain augmentation, definitive augmentation. See section 6.2
- Review RLS Diary for compliance
- Subject will complete the following, ***if not already completed during screening***:
    - ✓ Medical Outcome Study (MOS) Sleep Scale (range 0-100)
    - ✓ Restless Legs Syndrome Quality of Life (RLS-QLI)
    - ✓ Fatigue Linear Analog Scale
- Unblinded personnel will perform dosing assignment through the IRT.

A separate Dosing Record will be maintained by the **unblinded study personnel** responsible for preparation and administration of the study drug. See Section 5.0 for details of study drug administration, blinding and precautions.

The Dosing Record will include:

- ✓ Starting and stopping time of study drug administration
- ✓ Total dose in mg and ml of Injectafer® administered (i.e. 750 mg / 15 ml)
- ✓ Total volume of Normal Sterile Saline administered (15 ml)

The following will be obtained/conducted by **blinded study personnel** following administration of the study drug (review Sections 5.0):

- ✓ blood pressure and heart rate, immediately post and 30 minutes post-study drug administration
- ✓ Adverse events, starting with the first dose of study drug
- ✓ If there are no significant signs or symptoms at the 30 minute post-study drug vital sign assessments, the subject will be released.

### 6.3.2. Day 5

Prior to administering study drug, the following must be confirmed or obtained in the following order:

- Adverse events
- Concomitant medications, to include RLS treatment stability
- IRLS scale will be completed
- Physician will complete the Investigator CGI-I Score. The physician is to remain blinded to the IRLS Scale and the subject CGI-S Score after randomization.
- Subject will independently complete the following:
  - ✓ Subject CGI-S Score
  - ✓ MOS Sleep Scale
  - ✓ Fatigue Linear Analog Scale
- Review RLS Diary for compliance
- Blood sample for hematology, chemistries and iron indices
- Vital signs to include temperature
- Study drug dosing

A separate Dosing Record will be maintained by the **unblinded study personnel** responsible for preparation and administration of the study drug. See Section 5.0 for details of study drug administration, blinding and precautions.

The Dosing Record will include:

- ✓ Start and stop time of study drug administration
- ✓ Total dose in mg and ml of Injectafer® administered (i.e. 750 mg / 15 ml)
- ✓ Total volume of Normal Sterile Saline administered (15 ml)

The following will be obtained / conducted by **blinded study personnel** following administration of the study drug (review Sections 5.0):

- ✓ blood pressure and heart rate, immediately post and 30 minutes post-study drug administration
- ✓ Adverse events, starting with the first dose of study drug
- ✓ If there are no significant signs or symptoms at the 30 minute post-study drug vital sign assessments, the subject will be released.

Once dosing is complete, an overview of the tapering algorithm (see Appendix III) will be discussed with the subject. The subject will be instructed on the appropriate tapering regimen depending on the RLS medication and dose of that medication that the subject is currently taking. At the end of the tapering period those subjects off medication, decreased the dose, or remained on baseline dose should remain stable throughout the trial Day 365. Any new, resumption, or increase in medication will be considered an intervention (See Section 4.6).

### 6.3.3. Days 14, 42, and 168 (in-clinic visits)

#### 6.3.3.1 Day 14

The subject will return to the clinic on Day 14 for blood samples (hematology, chemistries and iron indices), subject RLS diary review, RLS treatment tapering progress, and assessment of concomitant medications and adverse events only.

#### 6.3.3.2 Day 42 and 168

The following should be assessed or obtained:

- Adverse events
- Concomitant medications
- Subjects' tapering period is complete and compliance should be assessed.
- Physical exam
- IRLS scale will be completed
- Physician will complete the Investigator CGI-I Score. The physician is to remain blinded to the IRLS Scale and the subject CGI-S Score after randomization.
- Augmentation Assessment by Investigator
- C-SSRS: The Columbia-Suicide Severity Rating Scale will be used throughout the study to assess the subject's suicide ideation or behavior. This scale is an assessment tool, it is ultimately the Investigators responsibility to evaluate each subject's risk and treat as appropriate.
- Subject will independently complete the following:
  - ✓ Subject CGI-S Score
  - ✓ Restless Legs Syndrome Quality of Life (RLS-QLI)
  - ✓ MOS Sleep Scale
  - ✓ Fatigue Linear Analog Scale
- Subject completed diary should be returned to the site (Day 42 only)
- Blood sample for hematology, chemistries, iron indices and transferrin receptor, fasting if indicated
- Vital signs (sitting heart rate and blood pressure)

### 6.3.4. Days 28, 84, 126, 210, 252, 294, and 336 (remote contact by phone)

The following should be assessed or obtained via a phone contact:

- ✓ IRLS scale (principle investigator completing the CGI-I is to remain blinded to score)
- ✓ Subject CGI-S Score (principle investigator completing the CGI-I is to remain blinded to score)
- ✓ Concomitant medication
- ✓ Adverse events
- ✓ Subjects' tapering period is complete and compliance should be assessed.
- ✓ Compliance with Subject diary (Day 28 only)

### 6.3.5 Additional Treatment Post Day 42

Subjects who have not had an intervention may receive additional blinded study drug treatment after Day 42 at the discretion of the Investigator. An intervention is defined as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, or 3) resumption of the previous medication prescribed for RLS, or 4) increase in dosage from the RLS medication achieved at the end of the tapering period. The subject will receive the same blinded study medication as previously randomized to receive during the treatment phase. Subjects will receive either a **single blinded** dose of either Injectafer® at 750 mg undiluted at 100mg/minute or a Placebo (15 ml of Normal Sterile Saline [NSS]) IV push at 2 ml/minute on two independent days separated by 5 days. Dosing should mirror the original treatment / follow-up period (dosing 5 days apart with follow-up visits, to include laboratory assessments only, on 14 and 42 Days post the first dose). No subject assessments are completed unless the dosing or follow-up days fall on an assessment day in the follow-up period.

Eligible subject will have met the following requirements prior to receiving additional treatment:

- IRLS score ≥15
- *TSAT <45% (confirmation can be through a local laboratory)
- *Ferritin <300 ng/mL (confirmation can be through a local laboratory)

*Central laboratory results obtained during the Day 42 or Day 168 visit can be used to qualify a subject for additional dosing if those labs have occurred with 14 days of the first dose of study medication.

No additional iron may be administered between Day 320 and the Day 365 visit.

If the subject qualifies to receive additional dosing the following will be required /collected:

- Unblinded personnel will perform dosing assignment

A separate Dosing Record will be maintained by the **unblinded study personnel** responsible for preparation and administration of the study drug. See Section 5.0 for details of study drug administration, blinding and precautions.

The Dosing Record will include:

- ✓ Start and stop time of study drug administration
- ✓ Total dose in mg and ml of Injectafer® administered (i.e. 750 mg / 15 ml)
- ✓ Total volume of Normal Saline administered (15 ml)

The following will be obtained /conducted by **blinded study personnel** following administration of the study drug (review Sections 5.0):

- ✓ Blood pressure and heart rate, immediately post and 30 minutes post-study drug administration
- ✓ Adverse events, starting with the first dose of study drug

If there are no significant signs or symptoms at the 30 minute post-study drug vital sign assessments, the subject will be released.

### 6.3.6. Day 365 (End of Study)

The following should be assessed or obtained:

- Adverse events
- Concomitant medications
- Subjects' tapering compliance
- Physical exam
- IRLS scale will be completed
- Physician will complete the Investigator CGI-I Score. The physician is to remain blinded to the IRLS Scale and the subject CGI-S Score after randomization.
- Augmentation assessment by Investigator
- C-SSRS: The Columbia-Suicide Severity Rating Scale will be used throughout the study to assess the subjects suicide ideation or behavior. This scale is just an assessment tool, it is ultimately the Investigators responsibility to evaluate each subject's risk and treat as appropriate.
- Subject will independently complete the following:
  - ✓ Subject CGI-S Score
  - ✓ Restless Legs Syndrome Quality of Life (RLS-QLI)
  - ✓ MOS Sleep Scale
  - ✓ Fatigue Linear Analog Scale
- Vital signs (sitting heart rate and blood pressure)
- Blood sample for hematology, chemistries and iron indices
- Contact IRT to complete the subject from the study

****NOTE: If the subject early terminates or the Day 365 phosphorus value is below the LLN the subject should return (as directed by the Investigator) for a repeat blood sample until the value is back Within Normal Limit's (WNL).****

## 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 results will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 42 laboratory test, this test may be obtained after notification to the Sponsor. If a subject's phosphorous is below the LLN at Day 365 the subject should return (as directed by the Investigator) for repeat phosphorous until the value is back WNL's. The following laboratory assessments will be determined as listed in Section 3.2.1

Hematology: Hgb, Hct, RBC, WBC, MCV, MCH, MCHC, RDW, platelets, differential count, and reticulocyte count

Iron indices: serum iron, serum ferritin, and total iron binding capacity (TIBC), and percentage serum transferrin saturation (TSAT)

Chemistry: sodium, potassium, chloride, BUN, creatinine, albumin, alkaline phosphatase, total bilirubin, gamma-GGT, AST, ALT, LDH, calcium, phosphorus, glucose, bicarbonate, and magnesium

Other: transferrin receptor and serum pregnancy

## 7.0 ASSESSMENT OF SAFETY

### 7.1 Adverse Events

Any untoward medical event (clinical), at any dose, experienced by a subject during the course of this clinical trial, whether or not it is related to the investigational product, must be recorded on the Adverse Event page of the case report form.

A distinction of symptomology, when feasible, should be made for study drug versus RLS medication taper.

For any laboratory abnormality, the physician will make a judgment as to its clinical significance. If the laboratory value is outside the safety 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 case report form. 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, worsening of RLS symptoms, low or high iron indices will not be considered adverse events. These values are reported in efficacy summaries.

To quantify the severity of adverse events the National Cancer Institute, NCI-Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0 should be used to grade all events. These criteria are provided in the trials study guide.

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 4.0**

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

| | | |
|---|---|---|
| 4 | Life-threatening | Life-threatening consequences; urgent intervention indicated. |
| 5 | Death | Results in Death due to the AE |

**Timing:** Non-serious adverse events will be reported from the initial treatment with study drug through the completion of the study Day 365. AE's will be captured during a follow-up phone call 28 days following their last dose of study drug for subjects who are randomized and early terminate from the trial. All ongoing adverse events related to study drug (i.e., Injectafer® or Normal Sterile Saline) should be followed until they are no longer related, have taken a confounding medication or return to baseline grade.

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

- NONEThere *no*is 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® or Normal Sterile Saline.**

### 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 the 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 (SAE)

**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. In contrast, a stroke, which results in only a limited degree of disability may be considered a mild stroke, but would be a SAE.

**Timing:** All SAEs will be reported from the day of initial treatment with study drug through the completion of the study Day 365. The SAEs will be captured during a follow-up phone call 28 days following the last dose of study drug for subjects who are randomized and early terminate from the trial. **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 the Investigator becoming aware 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.

### 7.4 Other Reportable Information

As part of the continuous assessment of the risk-benefit profile for the life cycle of pharmaceutical products, regulatory agencies require monitoring of occurrences that while not considered adverse events, are considered "other reportable information". For this protocol, other reportable information refers to: tapering of RLS medications (Section 7.5) as well as drug exposure during pregnancy and / or lactation exposure (irrespective of any reported fetal abnormalities or any adverse effect in mother and/or child). Pregnancy exposure and lactation exposure should be reported to the Luitpold's Pharmacovigilance Department by email and/or fax using the pregnancy tracking form to the contact listed below:

Safety Monitor

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

### 7.5 Events associated with tapering of RLS medications

The dose-specific, time-varying taper of the subject's study entry RLS medications will begin on day 6 after receipt of the second dose of study medication (day 5). The withdrawal from the standard of care RLS medications must not be abrupt. The discontinuation of the standard of care RLS medications must be tapered (see Appendix III). Abrupt discontinuations of the standard of care RLS medications have been reportedly associated with severe and life-threatening events inclusive dopamine agonist withdrawal syndrome (DAWS) and the neuroleptic malignant syndrome (dopamine agonists), seizures (calcium channel α2δ ligands), and the acute abstinence syndrome (opioids).[8,39] The response to the recommended tapering regimen of the dopamine agonists, calcium channel α2δ ligands, and opioids will be variable yet there are expectant class-specific signs and symptoms of withdrawal (Table 7.5.1) along with potential for mild, moderate, or severe worsening of RLS symptoms during the taper regimen and especially for the initial 10-day interval after the taper regimen is complete. The first 96 hours (4 days) of the RLS standard of care drug-free interval from the entry RLS monotherapy regimen may be associated with severe insomnia and ongoing withdrawal (Table 7.5.1).

**Table 7.5.1 Class-specific adverse events and withdrawal signs and symptoms during taper of RLS medications**

| **Class (medications)** | **Adverse events**** | **Withdrawal signs and symptoms** |
|---|---|---|
| **Dopamine agonist** (pramipexole, ropinirole, rotigotine patch, levodopa) | Nausea, vomiting, somnolence, asthenia, constipation, dyspepsia, dizziness, orthostatic hypotension, hallucinations, impulse control disorders | Dopamine agonist withdrawal syndrome (DAWS) inclusive of anxiety, panic attacks, dysphoria, depression, agitation, irritability, suicidal ideation, fatigue, orthostatic hypotension, nausea, vomiting, diaphoresis, generalized pain, and drug cravings.[8,39] Neuroleptic malignant syndrome (hyperpyrexia, confusion). |
| **Calcium channel α2δ ligand** (gabapentin enacarbil, gabapentin, pregabalin) | Angioedema, suicidal behavior and ideation, CNS effects (emotional lability, hostility, thought disorder, hyperkinesia), peripheral edema, weight gain, ophthalmological effects (eg, blurred vision, decreased visual acuity, visual field changes), creatinine kinase elevations, decreased platelet count, PR interval prolongation, hypersensitivity reactions, DRESS/ multi-organ hypersensitivity, dizziness, unsteadiness, somnolence, sedation | Insomnia, nausea, headache, anxiety, hyperhidrosis, diarrhea |

| | | |
|---|---|---|
| **Opioid** (methadone, oxycodone, hydrocodone, tramadol) | Respiratory depression, miosis, QT prolongation, seizures, myoclonus, hypotension, apnea, circulatory collapse, cardiac arrest, anaphylactoid reactions, biliary colic, urinary retention, renal toxicity, decreased gastrointestinal motility, ileus, bradycardia, serotonin syndrome, skeletal muscle rigidity, spasm of the sphincter of Oddi, increased serum amylase, hypersensitivity reactions, drowsiness, dizziness, constipation | Restlessness, lacrimination, rhinorrhea, yawning, perspiration, gooseflesh, mydriasis, anxiety, weakness, muscle twitching, kicking movements, severe backache, severe abdominal and leg pains, abdominal and muscle cramps, hot and cold flashes, insomnia, nausea, vomiting, anorexia, coryza, repetitive sneezing, and increase in body temperature, blood pressure, heart rate, and respiratory rate. |

CNS = central nervous system
DRESS = drug-reaction with eosinophilia and systemic symptoms
**Additional resources can be found within the FDA approved package insert for each medication.
[8]Nirenberg MJ. Drugs & Aging 2013.
[39]Pondal M. J Neurol Neurosurg Psychiatry 2015.

In addition to the reporting of adverse events (Section 7.2) and serious adverse events (Section 7.3), the potential risks associated with the taper and withdrawal from RLS medication will be elicited and determined by the study investigator to be related or not related to the taper and the withdrawal of the RLS medication and captured in the eCRF. The signs and symptoms associated with taper and withdrawal from RLS medications may include worsening of RLS symptoms, inclusive of an increase in limb movements, periodic leg movement symptoms defined as Periodic Limb Movement of Sleep (PLMS) or Periodic Limb Movement while Awake (PLMA), insomnia, decreased daytime alertness, low mood, depression, anxiousness, and hallucinations. Reported class-specific events associated with the tapering and withdrawal of RLS medications, as potentially distinct from adverse events (Section 7.2) and serious adverse events (Section 7.3) are listed in Table 7.5.1. The dopamine agonist withdrawal syndrome (DAWS) has been defined as a severe, stereotyped cluster of physical and psychological symptoms that correlate with dopamine agonist withdrawal in a dose-dependent manner.[8,39] The severity and prognosis of DAWS (Table 7.5.1) is variable in duration. While there are several potential adverse events associated with the calcium channel α2δ ligands, the withdrawal symptoms likely include insomnia, nausea, headache, anxiety, hyperhidrosis, diarrhea (Table 7.5.1). The high-potency opioids and opioid agonist have several known adverse events and withdrawal symptoms (Table 7.5.1). It is anticipated that in the monitoring for adverse events and severe adverse events, as distinct from mediation withdrawal events, some subjects may experience benefits associated with withdrawal of the RLS medications such as decrease, if not resolution, of the symptoms of augmentation (symptoms earlier in the day after an evening dose of medication, including earlier onset of symptoms, increased intensity of symptoms, or spread of symptoms to the arms).[6]

## 8.0 STATISTICS

### 8.1 Sample Size Rationale

Sample size estimates were based on the mITT population for Study 1VIT05009. The last observation carried forward (LOCF) and observed cases (OC) results on Day 28 were used for the co-primary efficacy endpoints (CGI) and first ranked secondary endpoint (IRLS). It is unclear how treatment differences on Day 42 results might differ from Day 28, apart from a higher dropout rate, but it is reasonable to assume that treatment

differences will decrease. Therefore, power calculations were based on smaller treatment differences and larger standard deviations.

Co-primary endpoint (IRLS): The smallest treatment difference for change from baseline to Day 28 was 4.4 with a standard deviation of 8.5. A sample size of 100/group provides 95% power under this scenario.

Co-primary efficacy endpoint (CGI-I): The smallest treatment difference on Day 28 was 45% versus 15% of patients in the FCM and placebo groups, respectively, who reported much or very much improvement on the patient CGI (Tables 3.7.1.1 and 3.7.2.1). A sample size of 100/group provides >99% power. A sample size of 100/group has at least 90% power when the treatment difference is as small as 45% versus 22%.

## 8.2 Analysis Populations

There will be 2 analysis populations:

- Safety population: All subjects who receive at least one dose of randomized treatment.
- Full analysis set (FAS) population: All subjects who received at least one dose of randomized treatment and had at least one post-randomization measurement of the IRLS and Clinical Global Impression performed by Investigator (CGI-I).

## 8.3 Disposition and Baseline Characteristics

Disposition and baseline characteristics will be summarized by treatment group for the Safety and FAS populations. The number and percentage of subjects, who are randomized, treated, prematurely discontinued, and completed 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.
Baseline characteristics (e.g., sex and race) will be summarized with the number and categorical 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 Primary Endpoints

The co-primary efficacy variables will be IRLS total score change from baseline to Day 42 and the proportion of patients rated as much or very much improved per the CGI-I performed by Investigator (CGI-I) on Day 42. Baseline values used for evaluation will be defined as the latest value obtained prior to the first dose of study drug. For those subjects with only one value prior to dosing, the single value will be used as baseline.

### 8.4.2 Secondary Endpoints

The major secondary endpoints will be tested in a hierarchical order, that is, statistical significance for major secondary efficacy endpoint will be declared only if the primary efficacy test (IRLS and CGI-I on Day 42) is statistically significant. Because a hierarchical testing scheme is used, no adjustments of the alpha level will be needed at each stage of testing. All tests will be done at an alpha $\leq 0.05$.

The major secondary efficacy endpoints in ranked order of testing include:

1. Clinical Global Impression (CGI) performed by Subject (CGI-S) on Day 42
2. Restless Legs Syndrome Quality of Life (RLS-QLI) change from baseline to Day 42
3. Medical Outcome Study (MOS) Sleep Scale change from baseline to Day 42
4. Fatigue Linear Analog Scale change from baseline to Day 42
5. Time off pre-enrollment prescribed RLS medications

Other efficacy endpoints:

1. Proportion of responders (any improvement) based on CGI-I at each time point
2. IRLS total score change from baseline at each time point.
3. Proportion of responders based on CGI-S at each time point
4. CGI-I and CGI-S scores at each time point and by baseline RLS treatment group.
5. RLS-QLI scores change from baseline at each time point
6. MOS Sleep scale total score change from baseline at each time point
7. Fatigue Linear Analog Scale total score change from baseline at each time point
8. Augmentation assessment by Investigator change between baseline, Day 42, Day 168 and end of study (Day 365)
9. Proportion of subjects required intervention for RLS
10. Time from Day 5 to the next dose of study drug.

### 8.4.3 Safety Evaluations

The safety endpoints include:

1. Incidence of treatment emergent adverse events and incidence of serious adverse events
2. Change in clinical laboratory tests
3. Change in vital signs
4. Change in C-SSRS

## 8.5 Statistical Analyses of Efficacy

Categorical variables will be summarized with the number and percent of subjects in each treatment group with the characteristic. Quantitative variables will be summarized with the mean, median, standard deviation, minimum value, and maximum value. Baseline will be defined as the last value obtained before randomization.

Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using region (US, Europe) as the stratification factor. Treatment group differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for region (US, Europe) and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test.

The primary imputation method for the CGI and change in total/domain scores will be LOCF. Sensitivity analyses will assess the impact of missing values on inferences.

Time from Day 5 to the next dose of study drug will be analyzed with the log-rank test. Subjects who discontinue or complete the study before an intervention will be censored at their last study visit.

### 8.6 Statistical Analyses of Safety

Analyses of safety data will be descriptive and no formal statistical comparisons will be made.

The 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 SOC, the subject will be counted only once for that SOC.

Change in clinical laboratory and 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 clinical laboratory and vital signs will be summarized for each treatment group.

### 8.7 Interim Analyses

An interim analysis of efficacy will be conducted after 100 subjects have completed Day 42. The blinded code of the treatment groups will be broken by a third party statistician chosen by the sponsor. The un-blinded data will only be available to the sponsors experts or consultants to assist in the planning of future studies. The sponsor, blinded PI, study staff and study participant will remained blinded to the data. Therefore, no adjustment to Type I error will be made.

## 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 Injectafer® 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 Institutional Review Board (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 and may also include review of facilities, equipment, pertinent site documentation, and personnel qualifications. Notification of these audits will be sent to all investigators in advance.

## 9.7 Ethics

### 9.7.1 Ethical and Legal Issues

This study will be performed in accordance with the 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 Fortaleza, Brazil 2013 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 (IRB)

The protocol and the Informed Consent must be approved by an appropriate IRB before the study is initiated. Documentation of this approval on institutional letterhead must be provided to the Sponsor or designee. The IRB must comply with current US Regulations (21 CFR 56). Investigators are responsible for the following:

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

The Informed Consent documents the information the Investigator provides to the 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 must be signed and dated by each subject 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 most 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. 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, 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 (DSMB)

The DSMB will be composed of approximately 3-5 senior academic individuals, including the DSMB Chair. They will have high-level expertise in neurology, hematology, cardiology 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 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)

## APPENDIX I: Injectafer® Package Insert

**APPENDIX II: RLS Assessment Tools:**

1. Clinical Global Impression-performed by Investigator (CGI-I)
2. IRLS Rating Scale for RLS severity
3. Clinical Global Impression-performed by Subject (CGI-S)
4. RLS Quality of Life – RLS-QLI
5. MOS Sleep Scale
6. Fatigue Linear Analog Scale
7. Augmentation Questionnaire (modified)
8. Columbia-Suicide Severity Rating Scale (C-SSRS)
9. Subject Diary

**APPENDIX III: RLS Medications at study entry and Taper Regimen**

| Entry medication (after 4P)[1] | Maximum entry dose/day | Taper | |
|---|---|---|---|
| | | Regimen[2] | Maximum days |
| **Dopamine agonist** | | | |
| Pramipexole (not ER)[3] | 0.75 mg | 0.25 q3d | 6 |
| Ropinirole (not ER)[3] | 4 mg | 0.5 mg q3d | 21 |
| Rotigotine (patch)[3] | 3 mg | 1 mg q3d | 6 |
| Levodopa | 200 mg | 50 mg q3d | 9 |
| **Calcium channel α2δ ligand** | | | |
| Gabapentin enacarbil | 1200 mg | 600 q5d | 5 |
| Gabapentin | 2400 mg | 300 qod | 14 |
| Pregabalin | 300 mg | 75 mg q3d | 9 |
| **Opioid** | | | |
| Methadone | 15 mg | 5 mg q5d | 10 |
| Oxycodone IR/ER | 30 mg | 5 mg q3d | 15 |
| Hydrocodone IR/ER | 20 mg | 5 mg q3d | 9 |
| Tramadol | 200 mg | 50 mg q3d | 9 |

ER = extended release
IR = immediate release
[1]Standard of care yet no combination regimen permitted
[2]Dose-specific, time-varying taper after 2 doses Injectafer® (Ferric Carboxymaltose) vs. placebo to be initiated after the second dose of study drug
[3]US Food and Drug Administration approval for RLS treatment

## APPENDIX IV: Amendment I Changes

### Amendment I Changes

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| **Title Page** | |
| **Original Wording** | Protocol Date 02 April 2014 |
| **New Wording** | Protocol Date 02 April 2014<br>Amendment |
| **SIGNATURES OF AGREEMENT FOR PROTOCOL** | Remove: Ariel Abreu, MD Medical Director, Pharmacovigilance<br>Add: Syed Quadri, MD Medical Director, Pharmacovigilance |
| **Synopsis Study Design Original Wording** | This will be a double blinded, multi-center, randomized, placebo-controlled study. All subjects who meet the inclusion requirements and no exclusion criteria will qualify to enter up to a 14 day Screening Phase to get 600 eligible subjects for study drug treatment. Eligible subjects will be randomized in a 1:1 ratio to receive Injectafer® or Placebo on Days 0 and 5. All treated subjects will be followed for efficacy and safety for 12 months. Subjects will **visit the clinic** on Days 0 and 5 for treatment, and then on Days 14, 42 and 365. In between the clinic visits subjects will be contacted remotely (phone or email) on Days 28, 84, 126,168, 210, 252, 294 and 336. The subject's participation in the study will be for approximately 1 year from Day 0. |
| **Synopsis Study Design New Wording** | This will be a Phase III, double blinded, multi-center, randomized, placebo-controlled study. All subjects who meet the inclusion requirements and no exclusion criteria will qualify to enter up to a 7 day Screening Phase to get 200 eligible subjects for study drug treatment. Eligible subjects will be randomized in a 1:1 ratio to receive Injectafer® or Placebo on Days 0 and 5. All treated subjects will be followed for efficacy and safety for 12 months. Subjects will **visit the clinic** on Days 0 and 5 for treatment, and then on Days 14, 42, 168 and 365. In between the clinic visits subjects will be contacted remotely (phone or email) on Days 84,126, 210, 252, 294 and 336. The subject's participation in the study will be for approximately 1 year from Day 0. |
| **Synopsis Study Drug Treatment Original Wording** | The duration of treatment phase will be 5 days. On Day 0 (start of Treatment Phase) Group A will receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute. Group B will receive a blinded placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute. On Day 5 Group A will receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute. Group B will receive a blinded placebo (15ml of Normal Saline [NS]) IV push at 2 ml/minute. |
| **Synopsis Study Drug Treatment New Wording** | The duration of treatment phase will be 5 days. On Day 0 (start of Treatment Phase) subjects will be randomized to receive either a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute. On Day 5 subjects will receive the same blinded treatment as given on Day 0. |
| **Synopsis New Wording** | **Additional Treatment**<br>**Post Day 42:** Subjects may receive additional blinded study drug treatment after Day 42 at the discretion of the Investigator. The subject will receive the same blinded study medication that they were previously randomized to receive. Subjects will receive either a **single blinded** dose of either Injectafer® at 750 mg undiluted at 100mg/minute or a Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute on two independent days separated by 5 days. Dosing days should mirror the original |

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| | treatment / follow-up period (dosing 5 days apart with follow-up visits 14 and 42 Days post the first dose). Eligible subject will have met the following requirements prior to receiving additional treatment:<br>• IRLS score ≥ 15<br>• TSAT < 45% (confirmation can be through a local laboratory)<br>• Ferritin < 300 ng/mL (confirmation can be through a local laboratory)<br>No additional iron may be administered between Day 320 and the Day 365 visit. |
| **Rescue Medication** | **Removed** |
| **Intervention Original Wording** | **Intervention and Relapse:**<br>Intervention is defined as the initiation or resumption of equivalent or increased treatment previously prescribed by a physician used to specifically relieve the symptoms of RLS following the subject's assessment that the RLS symptoms are intolerable. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety.<br>Relapse is defined as the prescribed treatment for the subject's RLS symptom is at a lower dose than previously taken. Efficacy and safety evaluation will continue to be performed on all subjects who have relapsed. |
| **Intervention New Wording** | **Intervention is defined** as an increase or change in the treatment currently prescribed by a physician used to specifically relieve the symptoms of RLS following the subject's assessment that the RLS symptoms are intolerable or the subject meets the criteria and qualifies for additional treatment with study drug. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety. |
| **Inclusion Criteria Original Wording** | 3. Subjects not currently receiving treatment, have RLS symptoms ≥ 5 nights per week for at least the past 3 months.<br>4. A baseline score ≥ 15 on the IRLS Rating Scale. |
| **Inclusion Criteria New Wording** | 3. Subjects should be on a stable (FDA approved) RLS treatment for at least 8 weeks prior to screening.<br>4. A score ≥ 15 on the IRLS Rating Scale at screening and on Day 0 prior to dosing. |
| **New Wording** | **RLS**<br>**Therapy:**<br>All subjects should be on a FDA approved RLS therapy. The subject's therapy should be stable for at least 8 weeks prior to screening. These therapies should remain unchanged throughout the duration of the study. If during the course of the study it becomes necessary to change or start new or additional therapy via physician decision these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| **Study Endpoints in Synopsis and Section 8.4.2 Original Wording** | The primary efficacy variable will be the proportion of patients rated as much or very much improved with the Clinical Global Impression (CGI) performed by Investigator (CGI-I) on Day 42. The major secondary endpoints will be tested in a hierarchical order, that is, statistical significance for major secondary efficacy endpoint will be declared only if the primary efficacy test (CGI-I on Day 42) is statistically significant. Because a hierarchical testing scheme is used, no adjustments of the alpha level will be needed at each stage of testing. All tests will be done at an alpha ≤ 0.05. |

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| | The major secondary efficacy endpoints in ranked order of testing include:<br>1. International Restless Legs Syndrome (IRLS) Score change from baseline to Day 42<br>2. Clinical Global Impression (CGI) performed by Subject (CGI-S) on Day 42<br>3. RLS QOL measured by Restless Legs Syndrome – Quality of Life Instrument (RLS-QLI) change from baseline to Day 42<br>4. Medical Outcome Study (MOS) Sleep Scale change from baseline to Day 42<br>5. Fatigue Linear Analog Scale change from baseline to Day 42<br>6. HADS change from baseline to Day 42<br>Other efficacy endpoints:<br>1. Proportion of responders (any improvement) based on CGI-I at each time point<br>2. IRLS total score change from baseline at each time point.<br>3. Proportion of responders based on CGI-S at each time point<br>4. RLS QOL scores change from baseline at each time point<br>5. MOS Sleep scale total score change from baseline at each time point<br>6. Fatigue Linear Analog Scale total score change from baseline at each time point<br>7. HADS total score change from baseline at each time point<br>8. Proportion of subjects required intervention for RLS and time to RLS intervention<br>9. Proportion of subjects with relapse.<br>The safety endpoints include:<br>1. Incidence of treatment emergent adverse events, incidence of serious adverse events, and incidence of severe adverse events<br>2. Change in clinical laboratory tests<br>3. Change in vital signs |
| **Study Endpoints in Synopsis and Section 8.4.2 New Wording** | The co-primary efficacy variables will be IRLS total score change from baseline to Day 42 and the proportion of patients rated as much or very much improved with the Clinical Global Impression (CGI) performed by Investigator (CGI-I) on Day 42.<br>The major secondary endpoints will be tested in a hierarchical order, that is, statistical significance for major secondary efficacy endpoint will be declared only if the primary efficacy test (IRLS and CGI-I on Day 42) is statistically significant. Because a hierarchical testing scheme is used, no adjustments of the alpha level will be needed at each stage of testing. All tests will be done at an alpha $\leq 0.05$.<br>The major secondary efficacy endpoints in ranked order of testing include:<br>1. Clinical Global Impression (CGI) performed by Subject (CGI-S) on Day 42<br>2. Restless Legs Syndrome Quality of Life (RLS-QoL) change from baseline to Day 42<br>3. Medical Outcome Study (MOS) Sleep Scale change from baseline to Day 42<br>4. Fatigue Linear Analog Scale change from baseline to Day 42<br>5. HADS change from baseline to Day 42<br>Other efficacy endpoints:<br>1. Proportion of responders (any improvement) based on CGI-I at each time point<br>2. IRLS total score change from baseline at each time point.<br>3. Proportion of responders based on CGI-S at each time point<br>4. RLS QOL scores change from baseline at each time point<br>5. MOS Sleep scale total score change from baseline at each time point |

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| | 6. Fatigue Linear Analog Scale total score change from baseline at each time point<br>7. HADS total score change from baseline at each time point<br>8. Augmentation Scale change between baseline and end of study (Day 365)<br>9. Proportion of subjects require intervention for RLS<br>10. Number of days from Day 5 to next dose of study drug.<br>The safety endpoints include:<br>1. Incidence of treatment emergent adverse events, incidence of serious adverse events, and incidence of severe adverse events<br>2. Change in clinical laboratory tests<br>3. Change in vital signs |
| **Screening Period and Sample Size Original Wording** | Screening Phase: up to 14 days<br>It is planned to enroll 600 subjects (300 per group) study sites in the US and other countries. |
| **Screening Period and Sample Size New Wording** | Screening Phase: up to 7 days<br>It is planned to enroll 200 subjects (100 per group) study sites in the US and other countries. |
| **Sample Size Estimates Original Wording** | Sample size estimates were based on the MITT population for Study VIT 5009. The last observation carried forward (LOCF) and observed cases (OC) results on Day 28 were used for the primary efficacy endpoint (CGI) and first ranked secondary endpoint (IRLS). It is unclear how treatment differences on Day 42 results might differ from Day 28, apart from a higher dropout rate, but it is reasonable to assume that treatment differences will decrease. Therefore, power calculations were based on smaller treatment differences and larger standard deviations.<br>Primary efficacy endpoint (CGI): The smallest treatment difference on Day 28 was 45% versus 15% of patients in the FCM and placebo groups, respectively, who reported much or very much improvement on the patient CGI (Tables 3.7.1.1 and 3.7.2.1). A sample size of 300/group provides >99% power. A sample size of 300/group has at least 95% power when the treatment difference is as small as 28% versus 15%.<br>First ranked secondary endpoint (IRLS): The smallest treatment difference for change from baseline to Day 28 was 4.4 with a standard deviation of 8.5. Given concerns that the treatment difference could decrease and variability increase at Day 42, one standard error was subtracted from the treatment difference (4.4 – 1.8 = 2.6) and the standard deviation was rounded up to 9. A sample size of 300/group provides 95% power under this scenario. |
| **Sample Size Estimates New Wording** | Sample size estimates were based on the MITT population for Study VIT 5009. The last observation carried forward (LOCF) and observed cases (OC) results on Day 28 were used for the primary efficacy endpoint (CGI) and first ranked secondary endpoint (IRLS). It is unclear how treatment differences on Day 42 results might differ from Day 28, apart from a higher dropout rate, but it is reasonable to assume that treatment differences will decrease. Therefore, power calculations were based on smaller treatment differences and larger standard deviations.<br>Co-primary endpoint (IRLS): The smallest treatment difference for change from baseline to Day 28 was 4.4 with a standard deviation of 8.5. A sample size of 100/group provides 95% power under this scenario.<br>Co-primary efficacy endpoint (CGI-I): The smallest treatment difference on Day 28 was 45% versus 15% of patients in the FCM and placebo groups, respectively, who reported much or very much improvement on the patient CGI (Tables 3.7.1.1 and |

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| | 3.7.2.1). A sample size of 100/group provides >99% power. A sample size of 100/group has at least 90% power when the treatment difference is as small as 45% versus 22%. |
| **Section 3.2 Original Wording** | This will be a double blinded, multi-center, randomized, placebo-controlled study. All subjects who meet the inclusion requirements and no exclusion criteria will qualify to enter up to a 14 day Screening Phase to get 600 eligible subjects for study drug treatment. Eligible subjects will be randomized in a 1:1 ratio to receive Injectafer® (Group A) or Placebo (Group B) on Days 0 and 5. All treated subjects will be followed for efficacy and safety for 12 months. Subjects will **visit the clinic** on Days 0 and 5 for treatment, and then on Days 14, 42 and 365. In between the clinic visits subjects will be contacted remotely (phone or email) on Days 28, 84, 126,168, 210, 252, 294 and 336. The subject's participation in the study will be for approximately 1 year from Day 0.<br>• **Subjects in Group A** will receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute on Days 0 and 5.<br>• **Subjects in Group B** will receive a blinded placebo (15 ml of Normal Saline [NS]) IV push at 2ml/minute on Days 0 and 5.<br>After treatment on Days 0 and 5 subjects will visit the clinic on Days 14, 42and 365. In between the clinic visits subjects will be contacted remotely (phone or email) on Days 28, 84, 126, 168, 210, 252, 294 and 336. Subjects will be considered to have reached the end of the study for efficacy when intervention is required for their RLS symptoms; those subjects will continue the follow-up phase for safety. Subjects who relapse will continue to stay in the follow-up phase for efficacy and safety. |
| **Section 3.2 New Wording** | This will be a Phase III, double blinded, multi-center, randomized, placebo-controlled study. All subjects who meet the inclusion requirements and no exclusion criteria will qualify to enter up to a 7 day Screening Phase to get 200 eligible subjects for study drug treatment. Eligible subjects will be randomized in a 1:1 ratio to receive either Injectafer® or IV Placebo on Days 0 and 5. All treated subjects will be followed for efficacy and safety for 12 months. Subjects will **visit the clinic** on Days 0 and 5 for treatment, and then on Days 14, 42, 168 and 365. In between the clinic visits subjects will be contacted remotely (phone or email) on Days 84, 126, 210, 252, 294 and 336. The subject's participation in the study will be for approximately 1 year from Day 0.<br>• Subjects will receive either a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded IV Placebo (15 ml of Normal Saline [NS]) IV push at 2ml/minute on Days 0 and 5.<br>After treatment on Days 0 and 5 subjects will visit the clinic on Days 14, 42, 168 and 365. In between the clinic visits subjects will be contacted remotely (phone or email) on Days 84, 126, 210, 252, 294 and 336. Subjects will be considered to have reached the end of the study for efficacy when intervention is required for their RLS symptoms; those subjects will continue the follow-up phase for safety. |
| **Schedule of Event** | Updated to reflect changes noted |
| **Section 4.1 Original Wording** | Approximately six hundred (600) subjects (300 per group) who have given written informed consent with a diagnosis of Restless Leg Syndrome (RLS) who fulfill the inclusion criteria, do not meet any of the exclusion criteria will be randomized into Group A (Injectafer®) or Group B (Placebo). |
| **Section 4.1 New Wording** | Approximately two hundred (200) subjects (100 per group) who have given written informed consent with a diagnosis of Restless Leg Syndrome (RLS) who fulfill the |

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| | inclusion criteria, do not meet any of the exclusion criteria will be randomized to receive Injectafer® or IV Placebo. |
| **Section 4.3 Original Wording** | Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this approximately 12 ½ month study. Subjects will be randomized in a 1:1 ratio via an Electronic Data Capture (EDC) system to receive either a blinded dose of IV Injectafer® (Group A) or a blinded dose of Placebo (Group B).<br>• **Subjects in Group A** will receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute on Days 0 and 5.<br>• **Subjects in Group B** will receive a blinded placebo (15ml of Normal Saline [NS]) IV push at 2ml/minute on Days 0 and 5. |
| **Section 4.3 New Wording** | Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this approximately 12 ½ month study. Subjects will be randomized in a 1:1 ratio via an Interactive Web Response/Electronic Data Capture (IWR/EDC) system to receive either a blinded dose of IV Injectafer® or a blinded dose of Placebo.<br>• Subjects will receive either a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded IV Placebo (15ml of Normal Saline [NS]) IV push at 2ml/minute on Days 0 and 5. |
| **Section 4.5 Original Wording** | **Intervention and Relapse**<br>**Intervention** is defined as the initiation or resumption of equivalent or increased treatment previously prescribed by a physician used to specifically relieve the symptoms of RLS following the subject's assessment that the RLS symptoms are intolerable. Non-narcotic analgesics will not be considered an intervention. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety.<br>**Relapse** is defined as the prescribed treatment for the subject's RLS symptom is at a lower dose than previously taken. Efficacy and safety evaluation will continue to be performed on all subjects who have relapsed. |
| **Section 4.5 New Wording** | **Intervention**<br>**Intervention is defined** as an increase or change in the treatment currently prescribed by a physician used to specifically relieve the symptoms of RLS following the subject's assessment that the RLS symptoms are intolerable or the subject meets the criteria and qualifies for additional treatment with study drug . Non-narcotic analgesics will not be considered an intervention. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety. |
| **Section 5.3 Original Wording** | On Days 0 and 5:<br>o Group A will receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute.<br>o Group B will receive a blinded placebo (15 ml of Normal [NS]) IV push at 2ml/minute. |
| **Section 5.3 New Wording** | On Days 0 and 5:<br>o Subjects will either receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded Placebo (15 ml of Normal [NS]) IV push at 2ml/minute. |

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| **Section 5.6 Original Wording** | Concomitant medications along with their route of administration and duration must be recorded in the electronic case report form (eCRF). **No additional iron preparations (IV iron from 6 weeks prior to screening or oral iron including multivitamins with iron, from time of consent), will be allowed. No blood transfusions, erythropoiesis stimulating agents will be allowed. Anti-depressants, anti-seizure, sleep medications, dopamine agonists, benzodiazepines, narcotics or other RLS treatments are not permitted for the duration of the study**. Non-narcotic analgesics are permitted.<br>**No prophylactic medications may be administered prior to Injectafer® administration without prior approval from Luitpold Pharmaceuticals, Inc.** |
| **Section 5.6 New Wording** | Concomitant medications along with their route of administration and duration must be recorded in the electronic case report form (eCRF). **No additional iron preparations (IV iron from 6 weeks prior to screening or oral iron including multivitamins with iron, from time of consent), will be allowed. No blood transfusions, erythropoiesis stimulating agents will be allowed. Once a subject is randomized no additional anti-depressants, anti-seizure, sleep medications, dopamine agonists, benzodiazepines, narcotics or other RLS treatments are not permitted for the duration of the study**. Non-narcotic analgesics are permitted.<br>All subjects should be on a FDA approved RLS therapy. The subject's therapy should be stable for at least 8 weeks prior to screening. These therapies should remain unchanged throughout the duration of the study. If during the course of the study it becomes necessary to change or start new or additional therapy via physician decision these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| **Section 6.2 Additional Wording** | • All prior medications, to include current treatments for RLS<br>• RLS treatment stability<br>• Medical Outcome Study (MOS) Sleep Scale (range 0-100)<br>• Restless Legs Syndrome Quality of Life (RLS-QoL)<br>• Fatigue Linear Analog Scale<br>• HADS<br>• Augmentation Scale |
| **Section 6.3.1 Additional Wording** | • RLS treatment stability<br>• Subject will complete the following:<br>✓ Restless Legs Syndrome Quality of Life (RLS-QoL) |
| **Sections 6.3.2 and 6.3.4 Additional Wording** | • Concomitant medications, to include RLS treatment stability |
| **Sections 6.3.3, 6.3.3.1 and 6.3.3.2 Additional wording** | Add Day 168 as a face to face visit<br>Concomitant medications, to include RLS treatment stability<br>Restless Legs Syndrome Quality of Life (RLS-QoL) |
| **Section 6.3.5 New Wording** | **Additional Treatment**<br>**Post Day 42:** Subjects may receive additional blinded study drug treatment after Day 42 at the discretion of the Investigator. The subject will receive the same blinded study medication that they were previously randomized to receive. Subjects will receive either a **single blinded** dose of either Injectafer® at 750 mg undiluted at 100mg/minute or a Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute on two independent days separated by 5 days. Dosing days should mirror the original treatment / follow-up period (dosing 5 days apart with follow-up visits 14 and 42 |

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| | Days post the first dose). Eligible subject will have met the following requirements prior to receiving additional treatment:<br>• IRLS score ≥ 15<br>• TSAT < 45% (confirmation can be through a local laboratory)<br>• Ferritin < 300 ng/mL (confirmation can be through a local laboratory)<br>No additional iron may be administered between Day 320 and the Day 365 visit.<br>If the subject qualifies to receive additional dosing the following will be required /collected:<br>• Un-blinded personnel will perform dosing assignment<br>A separate Dosing Record will be maintained by the **un-blinded study personnel** responsible for preparation and administration of the study drug. See Section 5.0 for details of study drug administration, blinding and precautions.<br>The Dosing Record will include:<br>✓ Starting and stopping time of study drug administration<br>✓ Total dose in mg and ml of Injectafer® administered (i.e. 750 mg / 15 ml)<br>✓ Total volume of Normal Saline administered (15 ml)<br>The following will be obtained /conducted by **blinded study personnel** following administration of the study drug (review Sections 5.0):<br>✓ blood pressure and heart rate, immediately post and 30 minutes post-study drug administration<br>✓ Adverse events, starting with the first dose of study drug<br>If there are no significant signs or symptoms at the 30 minute post-study drug vital sign assessments, the subject will be released. |
| **Section 6.3.6 Additional Wording** | • Concomitant medications, to include RLS treatment stability<br>• Subject will independently complete the following:<br>✓ Restless Legs Syndrome Quality of Life (RLS-QoL)<br>✓ Augmentation Scale |
| **Section 8.1 Additional Wording** | Co-primary endpoint (IRLS): The smallest treatment difference for change from baseline to Day 28 was 4.4 with a standard deviation of 8.5. A sample size of 100/group provides 95% power under this scenario.<br>Co-primary efficacy endpoint (CGI-I): The smallest treatment difference on Day 28 was 45% versus 15% of patients in the FCM and placebo groups, respectively, who reported much or very much improvement on the patient CGI (Tables 3.7.1.1 and 3.7.2.1). A sample size of 100/group provides >99% power. A sample size of 100/group has at least 90% power when the treatment difference is as small as 45% versus 22%. |
| **Section 8.4.1 Original Wording** | The primary efficacy variable will be the proportion of patients rated as much or very much improved with the Clinical Global Impression (CGI) performed by Investigator (CGI-I) on Day 42. |
| **Section 8.4.1 New Wording** | The co-primary efficacy variables will be IRLS total score change from baseline to Day 42 and the proportion of patients rated as much or very much improved with the Clinical Global Impression (CGI) performed by Investigator (CGI-I) on Day 42. Baseline values used for evaluation will be defined as the latest value obtained prior to the first dose of study drug. For those subjects with only one value prior to dosing, the single value will be used as baseline. |
| **Section 8.5 Original Wording** | Categorical variables will be summarized with the number and percent of subjects in each treatment group with the characteristic. Quantitative variables will be |

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| | summarized with the mean, median, standard deviation, minimum value, and maximum value. Baseline will be defined as the last value obtained before randomization.<br>Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using study site as the stratification factor. Treatment group differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for study site and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test.<br>The primary imputation method for the CGI and change in total/domain scores will be LOCF. For the proportion of subjects with relapse, subjects who discontinue or complete the study before an intervention will be considered as not having experienced relapse. Sensitivity analyses will assess the impact of missing values on inferences.<br>Time from first dose of randomized study drug to intervention will be analyzed with the log-rank test. Subjects who discontinue or complete the study before an intervention will be censored at their last study visit. |
| **Section 8.5 New Wording** | Categorical variables will be summarized with the number and percent of subjects in each treatment group with the characteristic. Quantitative variables will be summarized with the mean, median, standard deviation, minimum value, and maximum value. Baseline will be defined as the last value obtained before randomization.<br>Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using study site as the stratification factor. Treatment group differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for study site and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test.<br>The primary imputation method for the CGI and change in total/domain scores will be LOCF. Sensitivity analyses will assess the impact of missing values on inferences.<br>Time from Day 5 to the next dose of study drug will be analyzed with the log-rank test. Subjects who discontinue or complete the study before an intervention will be censored at their last study visit. |

## APPENDIX V: Amendment II Changes

### Amendment II Changes

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| **Title Page:** | |
| **Original Wording** | Protocol Date 05 August 2014<br>Amendment I |
| **New Wording** | Protocol Date 05 January 2015<br>Amendment II |
| **Exclusion Criteria** | |
| **Original Wording** | 1 RLS 2° to other CNS disease or injury. Such disorders include: peripheral neuropathy, neurodegenerative disorders and multiple sclerosis. |
| **New Wording** | 1. RLS 2° to other CNS disease or injury. Such disorders include: peripheral neuropathy and neurodegenerative disorders. |
| **Original Wording** | 2. RLS 2 °Chronic Kidney Disease |
| **New Wording** | 2. Stage 4 – 5 CKD, subjects on dialysis or anticipated to start dialysis while participating in this study. |
| **Original Wording** | 3. Any pain related (e.g., frequent muscle cramps, myalgia, fibromyalgia) or sleep related disorders (e.g. sleep apnea, which may confound the outcome measures. |
| **New Wording** | 3. Any pain related (e.g., frequent muscle cramps, myalgia, fibromyalgia) or sleep related disorders (e.g. sleep apnea, unless on stable CPAP) which may confound the outcome measures. |
| **Exclusion Criteria** | |
| **Original Wording** | 17. AST or ALT greater than the upper limit of normal. |
| **New Wording:** | 17. AST or ALT greater than 2 times the upper limit of normal. |
| **Removed** | 11. Active inflammatory arthritis (e.g. rheumatoid arthritis, SLE). |
| **Removed** | 14. Severe peripheral vascular disease with significant skin changes |
| **Removed** | 21. Calcium or phosphorous outside the normal range. |
| **Original Wording** | All subjects should be on a FDA approved RLS therapy. The subject's therapy should be stable for at least 8 weeks prior to screening. These therapies should remain unchanged throughout the duration of the study. If during the course of the study it becomes necessary to change or start new or additional therapy via physician decision these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| **New Wording** | All subjects should be on a FDA approved RLS therapy. FDA approved therapies used outside of the United States are permitted at doses approved in the applicable country of use. The subject's therapy should be stable for at least 8 weeks prior to screening, unless the dose has been decreased. If the dose has been decreased during the 8 weeks prior to screening that reduced dose should be stable for at least 4 weeks prior to screening. These therapies should remain unchanged throughout the duration of the study. If during the course of the study it becomes necessary to change or start new or additional therapy via physician decision these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |

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| **Procedures: Screening, Day 0, 5, 42, 168, and 365** | |
| **Added:** | • C-SSRS |
| **Other Reportable Information** | As part of the continuous assessment of the risk-benefit profile for the life cycle of pharmaceutical products regulatory agencies require monitoring of occurrences that while not considered adverse events, are considered "other reportable information" For this protocol, other reportable information refers to: drug exposure during pregnancy and / or lactation exposure (irrespective of any reported fetal abnormalities or any adverse effect in mother and/or child). Pregnancy exposure and lactation exposure should be reported to the Luitpold's Pharmacovigilance Department by email and/or fax using the pregnancy tracking form to the contact listed below:<br>Safety Monitor<br>Luitpold Pharmaceuticals, Inc.<br>pv@luitpold.com<br>Tel: (610) 650-4200 Fax: (610) 650-0170 |
| **List of Abbreviations** | |
| **Added** | CPAP Continuous Positive Airway Pressure |
| **Schedule of Events** | |
| **Added** | C-SSRS: Screening, Days 5, 42, 168 and 365<br>[5] IRLS, RLS QoL, MOS Sleep Scale, Fatigue Severity Scale, HADS and C-SSRS may be completed on Day 0 prior to randomization. |
| **Other Efficacy Endpoints** | |
| **Original Wording:** | 2. IRLS total score change from baseline at each time point. |
| **New Wording** | 2. IRLS total score change from baseline at each time point and by baseline RLS treatment group. |
| **Added Wording:** | 4. CGI-I and CGI-S scores at each time point and by baseline RLS treatment group |
| **Safety Endpoints** | |
| **Added Wording** | 4. Change in C-SSRS |
| **Governance Committee: Data Safety Monitoring Board** | |
| **Added Wording** | The DSMB will be composed of approximately 3-5 senior academic individuals, including the DSMB Chair. They will have high-level expertise in neurology, hematology, cardiology 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 |

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| | 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.<br><br>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 determine if it believes the trial should be terminated early because clear evidence of a significant safety concern exists.<br><br>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. |
| **APPENDIX II: RLS Assessment Tools** | |
| **Added** | 9. Columbia-Suicide Severity Rating Scale (C-SSRS) |

**APPENDIX VI: Amendment III Changes**

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| **Title Page:** | |
| **Original Wording:** | AMENDMENT II DATE: 05 January 2015 |
| **New Wording:** | AMENDMENT III DATE: 13 JULY 2015 |
| **SIGNATURES OF AGREEMENT FOR PROTOCOL** | NEW LANGUAGE ADDED: Linda Mundy, MD, PhD<br>Sr. Medical Director, Clinical Development |
| **Updates throughout the Protocol** | Day 28 added to the remote contact by phone<br>Email deleted from remote contact visits<br>RLS-QoL changed to RLS-QLI<br>Normal Saline [NS] changed to Normal Sterile Saline [NSS]<br>Hospital Anxiety and Depression Scale (HADS) removed<br>IWR/EDC changed to IRT (Interactive Response Technologies)<br>C-SSRS: The Columbia-Suicide Severity Rating Scale will be used throughout the study to assess the subject's suicide ideation or behavior. This scale is an assessment tool, it is ultimately the Investigators responsibility to evaluate each subject's risk and treat as appropriate.<br>Minor spelling and grammatical updates were made throughout the protocol |
| **Study Synopsis Study Design:** | |
| **Original Wording** | Eligible subjects will be randomized in a 1:1 ratio to receive Injectafer® or Placebo on Days 0 and 5.<br>In between the clinic visits subjects will be contacted remotely (phone or email) on Days 84,126, 210, 252, 294 and 336. |
| **New Wording** | All eligible subjects will be stratified at baseline by RLS medication-related augmentation (no augmentation, uncertain augmentation, definitive augmentation). Randomization will occur in a 1:1 ratio within each stratum to receive Injectafer® or Placebo on Days 0 and 5.<br>In between the clinic visits subjects will be contacted remotely (phone) on Days 28, 84,126, 210, 252, 294 and 336. |
| **New Procedures Added** | **Tapering Algorithms of RLS Treatment Regimens:** Each subject will be tapered from the prescribed RLS medication post treatment beginning on Day 5. The tapering regimen will depend on the subject's current medication and dosing (see Appendix III). During the tapering period and through Day 42 subjects will continue to keep a RLS diary to record their symptoms related to their RLS. |
| **Additional Treatment New Wording throughout protocol** | Subjects who have not had an intervention may receive additional blinded study drug treatment at the discretion of the Investigator after Day 42. An intervention is defined as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, or 3) resumption of the previous medication prescribed for RLS. Dosing days should mirror the original treatment / follow-up period (dosing 5 days apart with safety follow-up visits, to include laboratory assessments only, on 14 and 42 Days post the first dose). |
| **Intervention New Wording:** | |
| **Original Wording** | **Intervention is defined** as an increase or change in the treatment currently prescribed by a physician used to specifically relieve the symptoms of RLS |

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| | following the subject's assessment that the RLS symptoms are intolerable or the subject meets the criteria and qualifies for additional treatment with study drug. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety. |
| **New Wording** | **Intervention is defined** as 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, or 3) resumption of the previous medication prescribed for RLS. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and be evaluated for safety. |
| **Inclusion Criteria Updated** | |
| **Original Wording** | 1. Male or female subjects ≥18, able to give informed consent to the study |
| **New Wording** | 1. Male or female subjects ≥18 years of age or older, able and willing to give informed consent to the study |
| **Original Wording** | 3. Subjects should be on a stable (FDA approved) RLS treatment for at least 8 weeks prior to screening. (See RLS Therapy) |
| **New Wording** | 3. Subjects should be on monotherapy for RLS. Treatment should be stable for at least 8 weeks prior to screening. (See approved RLS Therapies/Regimen in Appendix III). |
| **Exclusion Criteria Updated** | |
| **Original Wording** | 1. RLS 2° to other CNS disease or injury. Such disorders include: peripheral neuropathy and neurodegenerative disorders.<br>19. Known positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis (i.e., AST/ALT greater than the upper limit of normal). |
| **New Wording** | 1. RLS 2° to other disease or injury.<br>Added new #5<br>5. Subjects with multiple sclerosis.<br>21. Known positive hepatitis B antigen (HBsAg), unless positive test can be attributed to receipt of hepatitis B vaccination in childhood or hepatitis C viral antibody (HCV) with evidence of active hepatitis (i.e., AST/ALT greater than the upper limit of normal). |
| **Original Wording** | 12. Current or acute or chronic infection other than viral upper respiratory tract infection |
| **New Wording** | 12. Current, active, acute or chronic infection other than viral upper respiratory tract infection |
| **Original Wording** | 25. Any other pre-existing laboratory abnormality, medical condition or disease which in view of the investigator participation in this study may put the subject at risk. |

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| **New Wording** | 25. Any other pre-existing laboratory abnormality, medical condition or disease which per the investigator may put the subject at risk if they participate in the study. |
| **Original Wording** | 26. Subject unable to comply with the study requirements |
| **New Wording** | 26. Subject unable or unwilling to comply with the study requirements |
| **RLS Therapy** | |
| **Original Wording** | All subjects should be on a FDA approved RLS therapy. FDA approved therapies used outside of the United States are permitted at doses approved in the applicable country of use. The subject's therapy should be stable for at least 8 weeks prior to screening, unless the dose has been decreased. If the dose has been decreased during the 8 weeks prior to screening that reduced dose should be stable for at least 4 weeks prior to screening. These therapies should remain unchanged throughout the duration of the study. If during the course of the study it becomes necessary to change or start new or additional therapy via physician decision these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| **New Wording** | All subjects should be on a stable monotherapy regimen (see Appendix III) for at least 8 weeks prior to screening. These therapies should remain unchanged until the tapering process begins post Day 5 treatment with study drug. An algorithm of RLS medication taper regimens is provided (Appendix III). If and when the subject is tapered off the RLS medication, the goal will be for the subject to remain off medication for the duration of the study. If during the course of the study it becomes necessary to change or start new or additional therapy via subject and physician decision, these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| **Study End Points** | New language added: Change in C-SSRS |
| **Original Wording** | Restless Legs Syndrome Quality of Life (RLS-QoL) change from baseline to Day 42<br>RLS-QoL scores change from baseline at each time point<br>Augmentation Scale change between baseline, Day 42 and end of study (Day 365) |
| **New Wording** | Augmentation Scale change between baseline, Day 42, Day 168 and end of study (Day 365) |
| **Blinding** | New language added: Assessment of blinded laboratory parameters (iron indices and phosphorus). |
| **Number of Subjects** | |
| **Original Wording** | Enrollment is planned for 200 subjects (100 per group) at study sites in the Unites States (US) and in Eastern Europe |
| **New Wording** | Enrollment is planned for 200 subjects (100 per group) at study sites in the Unites States (US) and in Eastern Europe (EU) |
| **Statistical Methods** | |
| **Original Wording** | Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using study site as the stratification factor. Treatment group |

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| | differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for study site and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test. |
| **New Wording** | Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using region (US, Europe) as the stratification factor. Treatment group differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for region (US, Europe) and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test. |
| **1.3: The Role of Iron Treatment in RLS** | Updated 1.3: **The Natural History, Disease Understanding, and Treatment Guidance for Restless Legs Syndrome (RLS)** |
| **Original Wording** | Restless Legs Syndrome (RLS) is a common under-diagnosed disorder occurring in 2% to 15% of the general population depending on the source of information. It is reported principally in the elderly but may occur at any time. As early as the 1950's, iron was thought to play a role in the onset and treatment of Restless Legs Syndrome (RLS), first described by Ekbom.[1] Nordlander first associated anemia from various causes (gastric ulcer, leukemia and chronic nephritis) with the development of restless legs that disappeared following treatment with blood transfusion.[2] More recent studies have found RLS to be associated with other conditions where iron is limiting such as in pregnancy[3], hemodialysis[4], and frequent blood donations.[5] It was also noted that the incidence of the condition increased from the general population to more than 20% in these patient populations. |
| **New Wording** | Restless legs syndrome (RLS), is a circadian disorder of sensory-motor integration that may be related to dysregulation of iron transport across the blood-brain barrier.[1] Epidemiologic data suggest geographic variation in the prevalence of RLS, with estimates ranging from 2-10% in general populations, and as high as 20 % in certain target populations with secondary RLS/.[2-5] Pharmacologic therapy for primary RLS are broadly based on short-term randomized, controlled trials that enrolled highly-selected patient populations with long-term, high-moderate to very severe symptoms.[6-8] Current treatment regimens for RLS include dopamine agonists, calcium channel alpha-2-delta (α2δ) ligands, opioids, and benzodiazepines.[9-11] While these medications reduce RLS symptoms and improve outcomes related to sleep -specific quality of life, adverse effects and treatment withdrawal due to adverse effects have been common.[6] Medication tolerance, augmentation, and symptom, if not worsening of symptoms, are concerns with sustained RLS treatment effect.[9,11-13] Evidence-based guidelines and practice support investigations that target trials of intravenous (IV) iron in RLS.[9] |
| **Original Wording** | Eligible subjects will be randomized in a 1:1 ratio to receive either Injectafer® or IV Placebo on Days 0 and 5. |
| **New Wording** | All eligible subjects will be stratified at baseline by RLS medication-related augmentation (no augmentation, uncertain augmentation, definitive augmentation) |

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| | on standard of care RLS therapy. Subjects will be randomized in a 1:1 ratio within each stratum to receive either Injectafer® or IV Placebo on Days 0 and 5. |
| **Original Wording** | The combined IRLS data from these RLS trials was not associated with clear benefit (mean difference in scores of -3.79, 95% CI: -7.68 to 0.10, p = 0.06), yet the placebo-controlled trial of FCM and of oral iron (in low-normal ferritin subjects) reported significant treatment benefit compared placebo.[33,35] |
| **New Wording** | The combined IRLS data from these RLS trials was not associated with clear benefit (mean difference in scores of -3.79, 95% CI: -7.68 to 0.10, p = 0.06), yet the placebo-controlled trial of FCM and of oral iron (in low-normal ferritin subjects) reported significant treatment benefit compared to placebo.[33,35] |
| **1.4.3 Injectafer® Human Experience: Marketed Use and the RLS indicator** | |
| **Original Wording** | The drug is indicated for the treatment of IDA in adult populations who have intolerance to oral iron or have had unsatisfactory responses to oral iron or non-dialysis depended CKD (see Appendix I). 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®. |
| **New Wording** | The drug is indicated for the treatment of IDA in adult populations who have intolerance to oral iron or have had unsatisfactory responses to oral iron or non-dialysis dependent CKD (see Appendix I). 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®. |
| **Table 3.2.1: Schedule of Events** | Table and footnotes have been updated |
| **4.3: Subject Assignment and Randomization Process** | |
| **Original Wording** | Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this approximately 12 ½ month study. Subjects will be randomized in a 1:1 ratio via an Interactive Web Response/Electronic Data Capture (IWR/EDC) system to receive either a blinded dose of IV Injectafer® or a blinded dose of Placebo. |
| **New Wording** | Subjects that meet all inclusion requirements and no exclusionary criteria will be offered participation in this approximately 12 month study. Subjects will be stratified by augmentation (no augmentation, uncertain augmentation, definitive augmentation) and randomized in a 1:1 ratio via an IRT system to receive either a blinded dose of IV Injectafer® or a blinded dose of Placebo. |
| **New section added 4.4: Tapering Procedures** | Each subject will be tapered from the current RLS medication, post treatment on Day 5. The tapering regimen will depend on the subject's current medication and dosing (see tapering schedule in Appendix III). During the tapering period and through Day 42 subjects will be asked to keep an RLS diary to record their progress. |
| **4.6: Intervention** | |
| **Original Wording** | **Intervention is defined** as an increase or change in the treatment currently prescribed by a physician used to specifically relieve the symptoms of RLS |

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| | following the subject's assessment that the RLS symptoms are intolerable or the subject meets the criteria and qualifies for additional treatment with study drug. Non-narcotic analgesics will not be considered an intervention. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety. |
| **New Wording** | **Intervention is defined** as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, or 3) resumption of the previous medication prescribed for RLS. Any subject who has an intervention will no longer be evaluated for efficacy starting at the time of the intervention, however these subjects will remain in the study and will be continued to be evaluated for safety. |
| **5.2.1.1: Unblinded Personnel** | **New language added:** Assessment of blinded laboratory parameters (iron indices and phosphorus). |
| **5.2.1.2: Blinded Personnel** | |
| **Original Wording** | The blinding will be maintained until the study is complete and the database has been locked. In the event the subject's well being requires knowledge of the treatment assignment, the blind may be broken. The investigator should make every effort to contact the sponsor's Medical Director or designee prior to un-blinding. If a subject's treatment assignment is un-blinded, the sponsor must be contacted immediately via telephone. |
| **New Wording:** | The blinding will be maintained until the study is complete and the database has been locked. In the event of an emergency that would require the investigator to be aware of the treatment allocation prior to database lock; the investigator can obtain this information, on a per subject basis, from the Sponsor's electronic database at the Investigative site. **It's recommended to contact sponsor's Medical Monitor or designee prior to unblinding.** If a subject's treatment assignment is unblinded, the sponsor must be contacted immediately via telephone. |
| **5.3: Study Drug Administration** | |
| **Original Wording** | Subjects will either receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded Placebo (15 ml of Normal [NS]) IV push at 2ml/minute. |
| **New Wording** | On Days 0 and 5, subjects will either receive a 750 mg undiluted blinded dose of IV Injectafer® at 100mg/minute or a blinded Placebo (15 ml of Normal Saline [NS]) IV push at 2ml/minute. |
| **5.4 IV Iron Precautions** | |
| **Original Wording** | • 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. |

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| **New Wording** | • Sitting heart rate and blood pressure will be assessed pre-dosing, 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. |
| **Original Wording** | In the event a serious acute reaction is seen, the site must have the capability to provide appropriate resuscitation measures. These may include IV NS, IV epinephrine, steroids, and/or antihistamines |
| **New Wording** | In the event a serious acute reaction is seen, the site must have the capability to provide appropriate resuscitation measures. These may include IV NSS, IV epinephrine, steroids, and/or antihistamines |
| **5.6: Concomitant Medication** | |
| **Original Wording** | All subjects should be on a FDA approved RLS therapy. FDA approved therapies used outside of the United States are permitted at doses approved in the applicable country of use. The subject's therapy should be stable for at least 8 weeks prior to screening, unless the dose has been decreased. If the dose has been decreased during the 8 weeks prior to screening that reduced dose should be stable for at least 4 weeks prior to screening. These therapies should remain unchanged throughout the duration of the study. If during the course of the study it becomes necessary to change or start new or additional therapy via physician decision these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| **New Wording** | All subjects should be on a stable RLS monotherapy regimen (see Appendix III) for for at least 8 weeks prior to screening. These therapies should remain unchanged until the tapering process begins post Day 5 treatment with study drug. Once the subject is tapered off RLS medication (Appendix III) the subject should stay removed from medication for the duration of the study. If during the course of the study it becomes necessary to restart therapy via physician decision, these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| **6.2: Screening** | |
| **Original Wording** | Each subject who qualifies for inclusion will undergo the following clinical evaluations to confirm eligibility for the study<br>• Obtain screening number from IWR/EDC system<br>• Medical history, including prior iron therapy use<br>• All prior medications, to include current treatments for RLS<br>• RLS treatment stability<br>• Subject will complete the Subjects IRLS scale<br>• Medical Outcome Study (MOS) Sleep Scale (range 0-100)<br>• Restless Legs Syndrome Quality of Life (RLS-QoL)<br>• Fatigue Linear Analog Scale<br>• HADS<br>• Augmentation Scale<br>C-SSRS:<br>Physical exam<br>• Vital signs (sitting heart rate and blood pressure) |

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| | • Weight without shoes<br>• Blood samples for hematology, chemistries, iron indices and transferrin receptor, fasting if indicated. A serum pregnancy test will be performed on female subjects.<br>• All oral iron products will be discontinued on the day of the first screening visit<br><br>Subjects who do not meet the entry criteria should be entered into the IWR/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 above will need to be repeated. |
| **New Wording** | Each subject who qualifies for inclusion will undergo the following clinical evaluations to confirm eligibility for the study<br>• Obtain screening number from IRT system<br>• Medical history, including prior iron therapy use<br>• All prior medications, to include current treatments for RLS and side effects associated with those medications<br>• IRLS scale will be completed<br>• Medical Outcome Study (MOS) Sleep Scale (range 0-100)<br>• Restless Legs Syndrome Quality of Life (RLS-QLI)<br>• Fatigue Linear Analog Scale<br>• Columbia Suicide Severity Rating Scale (C-SSRS): The Columbia-Suicide Severity Rating Scale will be used throughout the study to assess the subject's suicide ideation or behavior. This scale is an assessment tool, it is ultimately the Investigators responsibility to evaluate each subject's risk and treat as appropriate.<br>• Physical exam<br>• Vital signs (sitting heart rate and blood pressure)<br>• Height and Weight without shoes<br>• Blood samples for hematology, chemistries, iron indices and transferrin receptor, fasting if indicated. A serum pregnancy test will be performed on female subjects.<br>• All oral iron products will be discontinued on the day of the first screening visit<br>• RLS Diary:<br>▪ Three-item RLS diary. Subjects will complete the RLS diary daily, screening through Day 42. The diary should be completed around the same time each day. The following 3 questions will be assessed:<br><br>1. How many hours did you nap/sleep in the prior 24 hours? _____<br>2. For the nap/sleep hours, how many times were you interrupted by your symptoms of restless legs syndrome? _____ |

<table>
<tr><td></td><td>
3. For the awake time, how many times were you interrupted by your symptoms of restless legs syndrome? _____<br><br>
• Augmentation subject questionnaire to be completed<br>
• Augmentation Investigator assessment (can be completed in screening, once the subject questionnaire is complete or on Day 0 prior to randomization). The physician will assess the subject and provide the following:<br><br>
o Step 1. Please provide a percent (%) score using the scale outline below for the following question:<br><br>
• How likely is it that the subject has developed augmentation to the RLS medication? _____%<br><br>
o Step 2. Convert this percentage estimate to the strata category for randomization<br><br>
<table>
<tr><td>Step 1 percentage (%)</td><td>Randomization Strata</td></tr>
<tr><td>0% to < 25%</td><td>No Augmentation</td></tr>
<tr><td>25% to ≤ 75%</td><td>Uncertain Augmentation</td></tr>
<tr><td>>75%</td><td>Definitive Augmentation</td></tr>
</table>
o Step 3. Randomize the subject via the augmentation strata<br><br>
Subjects who do not meet the entry criteria should be entered into the IRT 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 above will need to be repeated.
</td></tr>
<tr><td>6.3.1: Day 0</td><td></td></tr>
<tr><td>Original Wording</td><td>
The following must be obtained <u>PRIOR</u> to dosing the subject:<br><br>
• Subject will complete the Subjects IRLS scale<br>
• Vital signs to include temperature<br>
• RLS treatment stability<br>
• Subject will complete the following:<br><br>
✓ Medical Outcome Study (MOS) Sleep Scale (range 0-100)<br>
✓ Restless Legs Syndrome Quality of Life (RLS-QoL)<br>
✓ Fatigue Linear Analog Scale<br>
✓ HADS<br><br>
• Un-blinded personnel will perform dosing assignment
</td></tr>
<tr><td>New Wording</td><td>The following must be obtained <u>PRIOR</u> to dosing the subject:</td></tr>
</table>

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| | • Confirm the subject continues to meet the Inclusion/Exclusion criteria<br>• IRLS scale will be completed<br>• Vital signs to include temperature<br>• Concomitant medications, to include RLS treatment stability<br>• The investigator will assess the subject's augmentation status (if not completed during screening): no augmentation, uncertain augmentation, definitive augmentation. See section 6.2<br>• Review RLS Diary for compliance<br>• Subject will complete the following:<br>✓ Medical Outcome Study (MOS) Sleep Scale (range 0-100)<br>✓ Restless Legs Syndrome Quality of Life (RLS-QLI)<br>✓ Fatigue Linear Analog Scale<br>• Unblinded personnel will perform dosing assignment through the IRT. |
| **6.3.2: Day 5** | New language added: Review RLS Diary for compliance<br>Removed: HADS<br>New language added: Once dosing is complete, an overview of the tapering algorithm (see Appendix III) will be discussed with the subject. The subject will be instructed on the appropriate tapering regimen depending on the RLS medication and dose of that medication that the subject is currently taking. At the end of the tapering period, those subjects off medication, decreased the dose, or remained on baseline dose should remain stable throughout the trial Day 365. Any new, resumption, or increase in medication will be considered an intervention (See Section 4.6) |
| **6.3.3.1: Day 14** | |
| **Original Wording** | The subject will return to the clinic on Day 14 for blood samples (hematology, chemistries and iron indices), RLS treatment stability and assessment of adverse events only. |
| **New Wording** | The subject will return to the clinic on Day 14 for blood samples (hematology, chemistries and iron indices), subject RLS diary review, RLS treatment tapering progress, and assessment of adverse events only. |
| **6.3.3.2: Day 42 and 168** | **New language** added: Subject completed diary should be returned to the site (Day 42)<br>**Removed: **NOTE: If the subjects Day 42 or Day 168 phosphorus value is below the LLN the subject should return (as directed by the Investigator) for a repeat blood sample until the value is back WNL's.**** |
| **Original Wording** | Concomitant medications, to include RLS treatment stability |
| **New Wording** | Concomitant medications<br>Subjects' tapering period is complete and compliance should be assessed. |
| **6.3.4: Days 28, 84, 126, 210, 252, and 336 (remote contact by phone)** | New language added: Compliance with subject diary (Days 28 only) |
| **Original Wording** | The following should be assessed or obtained via a phone or email contact: |

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| | ✓ Subject IRLS scale<br>✓ Subject CGI-S Score<br>✓ Concomitant medication, to include RLS treatment stability<br>✓ Adverse events |
| **New Wording** | The following should be assessed or obtained via a phone contact:<br><br>✓ IRLS scale (principle investigator completing the CGI-I is to remain blinded to score)<br>✓ Subject CGI-S Score (principle investigator completing the CGI-I is to remain blinded to score)<br>✓ Concomitant medication<br>✓ Adverse events<br>✓ Subjects' tapering period is complete and compliance should be assessed.<br>✓ Compliance with Subject diary (Day 28 only) |
| **6.3.6: Day 365 (End of Study)** | New language added: Contact IRT to complete the subject from the study<br>New language added: ****NOTE: If the subject early terminates or the Day 365 phosphorus value is below the LLN the subject should return (as directed by the Investigator) for a repeat blood sample until the value is back WNL's.****Injectafer® |
| **Original Wording** | Concomitant medications, to include RLS treatment stability<br>Physician will complete the Investigator CGI-I Score. The physician is to remain blinded to the IRLS Scale and the subject CGI-I Score after randomization.<br>Physician will complete the Investigator CGI-I Score. The physician is to remain blinded to the IRLS Scale and the subject CGI-I Score after randomization. who have not had an intervention An intervention is defined as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, or 3) resumption of the previous medication prescribed for RLS. as Injectafer® |
| **New Wording** | Concomitant medications<br>Physician will complete the Investigator CGI-I Score. The physician is to remain blinded to the IRLS Scale and the subject CGI-S Score after randomization. |
| **6.4: Central Laboratory Assessments** | |
| **Original Wording** | If a subjects phosphorous is below the LLN at Day 42 or Day 168 the subject should return (as directed by the Investigator) for repeat phosphorous until the value is back WNL's. |
| **New Wording** | If a subject's phosphorous is below the LLN at Day 365 the subject should return (as directed by the Investigator) for repeat phosphorous until the value is back WNL's. |
| **Original Wording** | Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. All serum laboratory testing will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 42 laboratory test, this test may be obtained after notification of the Sponsor. If a subject's phosphorous is below the LLN at Day 365 the subject should return (as directed by the Investigator) for |

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| | repeat phosphorous until the value is back WNL's. The following laboratory assessments will be determined as listed in Section 3.2.1 |
| **New Wording** | Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the central laboratory. All serum laboratory results will be provided to the physician for review and assessment. If the Investigator wishes to obtain a follow-up of an abnormal Day 42 laboratory test, this test may be obtained after notification to the Sponsor. If a subject's phosphorous is below the LLN at Day 365 the subject should return (as directed by the Investigator) for repeat phosphorous until the value is back WNL's. The following laboratory assessments will be determined as listed in Section 3.2.1 |
| **7.3: Serious Adverse Event** | |
| **Original Wording** | **Reporting**: **Any SAE, starting with the first dose of study drug, that is to be reported (as outlined in Timing section above) must be reported immediately (by the end of the next business day) to Luitpold Pharmaceuticals, Inc. by telephone, email and/or fax of the written SAE report form to the contacts listed below:** |
| **New Wording** | **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 the Investigator becoming aware of the event) to Luitpold Pharmaceuticals, Inc. by telephone, email and/or fax of the written SAE report form to the contacts listed below:** |
| **New section added** | **7.5: Events Associated with Tapering of RLS Medications**<br><br>**Table 7.5.1: Class-specific adverse events and withdrawal signs and symptoms during taper of RLS medications** |
| **8.4.2: Secondary Endpoints** | **New language added:** Time off RLS SoC medications |
| **Original Wording New section added** | Restless Legs Syndrome Quality of Life (RLS-QoL) change from baseline to Day 42<br>IRLS total score change from baseline at each time point and by baseline RLS treatment group.<br>RLS-QoL scores change from baseline at each time point<br>Augmentation Scale change between baseline and end of study (Day 365)<br>Time from Day 5 to the next dose of study drug will be analyzed with the log-rank test. |
| **New Wording:8.4.2 Secondary Endpoints** | Restless Legs Syndrome Quality of Life (RLS-QLI) change from baseline to Day 42<br>IRLS total score change from baseline at each time point.<br>RLS-QLI scores change from baseline at each time point<br>Augmentation Scale change between baseline, Day 42, Day 168 and end of study (Day 365)<br>Time from Day 5 to the next dose of study drug. **New language added:** Time off RLS SoC medications |
| **8.5: Statistical Analyses of Efficacy Original Wording** | Restless Legs Syndrome Quality of Life (RLS-QoL) change from baseline to Day 42<br>IRLS total score change from baseline at each time point and by baseline RLS treatment group.<br>RLS-QoL scores change from baseline at each time point |

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| | Augmentation Scale change between baseline and end of study (Day 365)<br>Time from Day 5 to the next dose of study drug will be analyzed with the log-rank test. |
| **Original Wording** | Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using study site as the stratification factor. Treatment group differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for study site and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test |
| **New Wording** | Treatment group differences for CGI scores will be assessed with the Cochran-Mantel-Haenszel test using region (US, Europe) as the stratification factor. Treatment group differences for changes in total and domain scores of rating scales (eg, IRLS) will be assessed with the analysis of covariance with fixed factors for region (US, Europe) and treatment and with baseline score as a covariate. Treatment differences for proportions will be assessed with the continuity-corrected chi-square test. |

## APPENDIX VII: Amendment IV Changes

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| **Title Page** | |
| Original Wording | Amendment III Date: 13 July 2015 |
| New Wording | Amendment IV Date: |
| | |
| **SIGNATURES OF AGREEMENT FOR PROTOCOL** | Removal: Sylvan Hurewitz, MD<br>Medical Director, Clinical Development<br>Syed Quadri, MD<br>Medical Director, Pharmacovigilance |
| | |
| **Synopsis - Tapering algorithms of RLS Treatment Regimens** | |
| Original Wording | Each subject will be tapered from the prescribed RLS medication post treatment beginning on Day 5. The tapering regimen will depend on the subject's current medication and dosing (see Appendix III). During the tapering period and through Day 42 subjects will continue to keep an RLS diary to record their symptoms related to their RLS. |
| New Wording | Each subject will be tapered from the prescribed RLS medication post treatment beginning on the *evening of Day 5 or starting on Day 6. The tapering regimen will depend on the subject's current medication and dosing (see Appendix III). It is expected that all subject will be tapered off their current treatment for RLS, but in the rarity a subject, at the end of the allotted tapering period, is unable to achieve a dose of zero (0) the subject should maintain on the lowest dose level attained at the end of the tapering period and that dose should remain stable for the duration of the subjects participation in the study.* During the tapering period and through Day 42 subjects will continue to keep an RLS diary to record their symptoms related to their RLS. |
| | |
| **Synopsis - Additional Treatment Post Day 42 and Intervention is defined and 4.6 Intervention and 6.3.5 Additional Treatment Post Day 42** | |
| Additional wording | *4) increase in dosage from the RLS medication achieved at the end of the tapering period*<br><br>*No subject assessments are completed unless the dosing or follow-up days fall on an assessment day in the follow-up period.* |
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| **Synopsis - RLS Therapy** | |
| Additional wording | If and when the subject is tapered off the RLS medication, the goal will be for the subject to remain off their medication *or remain on the lowest dose level achieved* for the duration of the study. |
| | |
| **Synopsis - Number of Subjects** | |
| Additional wording | Spain added |
| | |
| **LIST OF ABBREVIATIONS AND DEFINITIONS** | |
| Additional wording | Qod every other day<br>Q3d every 3 days<br>Q5d every 5 days |
| | |
| **3.2.1 Schedule of Events** | |
| Additional wording | Added + 2 day window to 7 day screening period, deletion of fasting and renumbering of footnotes. |
| | |
| **4.4 RLS Standard of Care therapy: Tapering Procedures** | |
| Additional wording | *Starting at screening*, during the tapering period and through Day 42 subjects will be asked to keep an RLS diary to record their progress. |
| | |
| **5.6 Concomitant Medication** | |
| Additional wording | *if a subject, at the end of the allotted tapering period, is unable to achieve a dose of zero (0) the subject should be maintained on the lowest dose level attained at the end of the tapering period and that dose should remain stable for the duration of the study*. If during the course of the study it becomes necessary to restart *or increase* therapy via physician decision, these data points will be collected and the subject will no longer be evaluated for efficacy, but the subject will continue in the study for safety analysis. |
| | |
| **6.3.1 Day 0** | |
| Additional wording | Subject will complete the following, ***if not already completed during screening***: |
| | |
| 6.3.5 Additional Treatment Post Day 42 | |

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| New wording | *Central laboratory results obtained during the Day 42 or Day 168 visit can be used to qualify a subject for additional dosing if those labs have occurred with 14 days of the first dose of study medication. |
| | |
| **8.7 Interim Analyses** | |
| New wording | An interim analysis of efficacy will be conducted after 100 subjects have completed Day 42. The blinded code of the treatment groups will be broken by a third party statistician chosen by the sponsor. The un-blinded data will only be available to the sponsors experts or consultants to assist in the planning of future studies. The sponsor, blinded PI, study staff and study participant will remained blinded to the data. Therefore, no adjustment to Type I error will be made. |
| | |
| **Appendix III** | |
| New wording | Ropinirole (not ER) maximum entry dose 4mg; maximum taper days 21 |
| | |
| Additional wording | [2]Dose-specific, time-varying taper after 2 doses Injectafer® (Ferric Carboxymaltose) vs. placebo to be initiated *after the second dose of study drug* |
| | |
| | |

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