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# PROTOCOL

**Protocol No.: 1VIT15042**

**andomized, placebo-controlled trial of ferric carboxymaltose in Restless Legs Syndrome patients with iron-deficiency anemia**

**NCT Number: 02826681**

**Date: 25APR2016**

**LUITPOLD PHARMACEUTICALS, INC.**

# PROTOCOL

**No. 1VIT15042**

**IND #: 73,076**

# Randomized, placebo-controlled trial of ferric carboxymaltose in Restless Legs Syndrome patients with iron-deficiency anemia

**SPONSOR**

**Luitpold Pharmaceuticals, Inc.**
**Clinical Research and Development**
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**PROTOCOL DATE: 25 April 2016**

## SIGNATURES OF AGREEMENT FOR PROTOCOL

26 APR 2016

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Sr. Medical Director, Clinical Development
Luitpold Pharmaceuticals, Inc.

Date

26 APR 2016

Syed Quadri, MD
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26 APR 2016

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27 Apr 2016

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28 April 2016

Christopher J. Earley MB, BCh, PhD, FRCPI
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Date

# STUDY SYNOPSIS
Protocol 1VIT15042

**Title:** Randomized, placebo-controlled trial of ferric carboxymaltose in Restless Legs Syndrome patients with iron-deficiency anemia

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

**Treatment Phase I and II Primary Objective:** To evaluate the efficacy and safety of FCM (750 mg dose x 2) for treatment of Restless Legs Syndrome (RLS) in patients with iron-deficiency anemia (IDA).

**Long-Term Extension Phase III Primary Objective:** To evaluate the duration of effect of prior FCM treatment and to determine the effectiveness of further iron repletion with FCM when RLS symptoms worsen or reoccur.

**Study Design:** This will be a Phase II, randomized, placebo-controlled study. All subjects who meet the inclusion criteria, with no exclusion criteria, will qualify to enter the Screening Phase. The study will enroll 70 eligible subjects to receive **blinded** study drug in Treatment Phase I. All eligible subjects will be randomized in a 1:1 ratio to receive a **blinded** dose of either FCM 750 mg undiluted slow intravenous (IV) push at 100 mg/minute or a Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute on Day 0 and 7.

> A subject will be defined at Day 42 as a **Responder** if the International Restless Legs Syndrome Severity Scale (IRLSS) score is ≤10 or if the IRLSS score is >10 with a Clinical Global Impression-Improvement (CGI-I) score of much or very much improvement and the subject does not request further treatment for RLS. A subject will be defined as a treatment **Non-Responder** if neither of these criteria are met.

**Non-Responders** who do not meet the laboratory criteria for additional dosing will be discontinued from the study and treated for RLS as deemed appropriate by the referring physician. Subjects who are **Non-Responders** at the end of Treatment Phase I and met the necessary laboratory criteria (ferritin <300 ng/mL and a TSAT <45%) will consented for enrollment in Treatment Phase II of the study. These subjects will receive the first of two **unblinded** doses of FCM (undiluted slow IV push 750 mg 100 mg/minute) on Day 0 of Phase II, which will occur within 7 days of the completing Treatment Phase I visit. The subjects will then receive the second dose of FCM (undiluted slow IV push 750 mg 100 mg/minute) on Day 7. All treated subjects will have blood samples taken for hematology, chemistries and iron indices on Day 14. Treatment efficacy (IRLSS score), medication review and adverse events assessment by phone will be done on Day 28. All subjects will return to the clinic on Day 42 for end of study assessments. Subjects completing Treatment Phase II will be re-evaluated on Day 42 and defined as either a **Responder** or **Non-Responder**, using the same criteria described above. Subjects deemed as treatment **Non-Responders** will be discontinued from the study after final assessments are complete.

Subjects who are evaluated on Day 42 (Week 6) as **Responders** from either Treatment Phase I or Treatment Phase II will continue through into the 46-Week, Long-Term Extension Phase III of the study, and be monitored and assessed by phone for RLS symptoms (IRLSS and Hopkins RLS-Sleep Quality Questionnaire [HRSQ]) and adverse events on (approximately every 9 weeks) Weeks 15, 25, 34, 43 and 52 (final follow-up visit). During Phase III subjects may receive additional unblinded treatments with FCM if at any time the subject reports worsening of RLS symptoms (an increase >4 points on the IRLSS compared to the last evaluation captured for that subject) and laboratory criteria are met (ferritin <300 ng/mL and a TSAT <45%). Subjects will receive a single FCM 750 mg undiluted slow IV push at 100 mg/minute. See section 6.6 for dosing and assessment outline. No additional treatment will be allowed after the Week 46. A final face-to-face study visit will occur on Week 52 (approximately 365 days since initial Day 0 Treatment). If a clinic visit is not possible, final evaluation will be completed by phone.

All subject assessments (screening through end of study) are in the schedule of events (section 3.2.1).

**Study Drug Dosing Regimen:**

**Treatment Phase I**: Subjects will be randomized to receive either a 750 mg undiluted slow IV push (100 mg/minute) of FCM or Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute on Day 0 and 7.

**Treatment Phase II:** Non-Responders from Phase I who qualify will receive an unblinded 750 mg undiluted slow IV push (100 mg/minute) of FCM on Day 0 and 7 of Phase II.

**Long-Term Extension Phase III**: Qualified subjects can potentially receive an unblinded single 750 mg undiluted slow IV push (100 mg/minute) of FCM when RLS symptoms worsen or reoccur.

**Efficacy and Safety Follow-up:**

Primary efficacy endpoint in **Treatment Phase I** is to determine the effectiveness of FCM in improving RLS severity associated with IDA. Effectiveness will be evaluated by:

- IRLSS score change from baseline to Day 42 with comparison between FCM vs. Placebo.
- CGI-I at Day 42.

Primary efficacy endpoint in **Treatment Phase II** is to determine the effectiveness of an additional unblinded single FCM treatment in improving RLS severity in non-responders from Treatment Phase I. Effectiveness will be evaluated by:

- IRLSS score change from baseline (For Phase II the "baseline" is established on Day 42 of Phase I) compared to Day 42 of Treatment Phase II
- 
- CGI-I at Day 42 in Treatment Phase II.

Secondary efficacy endpoints evaluated in both Treatment Phase's I and II are:

- Number of treatment responders at Day 42 (Treatment Phase I).
- Number of treatment responders at Day 42 (Treatment Phase II).
- IRLSS score change from Baseline (For Phase II the "Baseline" is established on Day 42 of Phase I) compared to Day 42 of Treatment Phase II.

- Number of Responders at Day 42 who receive FCM vs. Placebo in Treatment Phase I.
- Number of Responders at Day 42 in Treatment Phase II who receive FCM vs. Placebo in Treatment Phase I.
- CGI-I and PGI-I at each visit and percentage of subjects who are much or very much improved at Day 42. (Treatment Phase I and II).
- Change in IRLSS score from Day 42 (Treatment Phase I and II).
- Change from baseline brain MRI-determined iron concentration in the substantia nigra at or within 4 days after Day 42 (Treatment Phase I and II).
- Change in sleep quality, Medical Outcome Survey for Sleep (MOS), from Day 42 for Treatment Phase I and II subjects.

Primary efficacy endpoint in **Long-Term Extension Phase III** is to evaluate the duration of effect of FCM as defined as the number of weeks from the initial treatment without need for further treatment. Initial treatment is defined as Day 0 of Phase I for Responders in Phase I and Day 0 of Phase II for Responders in Phase II.

Secondary object is to determine the effectiveness (number of subjects who remain in the study) of additional FCM treatment, in the Long-Term Extension, in those who have worsening of RLS symptoms after the initial response.

Primary safety endpoint is to determine the safety of FCM in RLS patients with IDA

- Safety Evaluations will include:
  - Adverse events
  - 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)
  - Vital signs
  - Physical examinations.

**Exploratory Aims**:

1. Evaluate potential predictors of Day 42 (Treatment Phases I and II) treatment response using clinical, hematologic, and brain MRI data.
2. The change from baseline in MRI-determined iron concentration for other brain regions.
3. Correlation between changes in brain iron distribution and measures of peripheral iron status, RLS severity, and sleep quality.

4. Correlation between CBC, iron indices, and change from Baseline to Day 42 (Treatment Phases I and II) RLS severity, sleep, and PGI-I.
5. Correlation of baseline Vitamin D and post dose change in phosphate.
6. Vitamin D at each visit.

**Inclusion Criteria:**

1. Male or female subject ≥18 years of age who is able to give informed consent.
2. Confirmed diagnosis of RLS based on the Cambridge-Hopkins Diagnostic Questionnaire (CHDQ) and the Hopkins-Hening Telephone Diagnostic Interview (HDTI).
3. IRLSS score ≥15 plus RLS symptoms for at least 3 months and currently occurring ≥2 nights per week.
4. Iron-deficiency anemia defined as an Hgb <12 g/dl with a ferritin <20 ng/mL, or ferritin <100 when TSAT is <18%.
5. Subjects on sleep medication must be on a stable dose for at least 6 months prior screening.
6. Subjects at risk for pregnancy must have a negative pregnancy test at screening and be practicing an acceptable form of birth control, have had a hysterectomy or tubal ligation, or otherwise be incapable of pregnancy, or have practiced any of the following methods of contraception for at least one month prior to study entry: hormonal contraceptives, spermicide with barrier, intrauterine device, or partner sterility.

**Exclusion Criteria**

1. Disorders that require treatment with the same medications used for RLS include: peripheral neuropathy and neurodegenerative disorders (i.e. Parkinson's disease or dementia).
2. Current (past 4 weeks) use of drugs that may cause or treat RLS, e.g. opioids, calcium channel alpha-2-delta ligands, anti-depressants, dopaminergic agonist or antagonists, or centrally-acting antihistamines.
3. Any medical conditions contraindicated to MRI.
4. Abnormal MRI at baseline that would confound the outcome measures.
5. Secondary RLS due to neurological conditions or head trauma.
6. History of hemochromatosis, hemosiderosis, other iron storage disorders or iron metabolism disorders.
7. Women with clinically significant uterine bleeding (>200 cc blood loss) during the six months prior to screening.
8. Liver transaminases (AST or ALT) greater than two times the upper limit of normal (ULN).
9. Known positive Hepatitis B antigen (HBs Ag), 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 two times the ULN).
10. Known positive HIV-1 or HIV-2 antibodies (anti-HIV).
11. Active acute or known chronic infections.
12. Rheumatoid arthritis with symptoms or signs of active inflammation.

13. Pregnant and lactating women.
14. Known hypersensitivity reaction to any component of Injectafer® (ferric carboxymaltose).
15. Previously randomized to Injectafer® (FCM or VIT-45) in a clinical trial.
16. Previous IV iron treatment for RLS.
17. Parenteral iron, erythropoiesis stimulating agent use or blood transfusion within six weeks prior to the screening visit.
18. Planned elective surgery during the study year.
19. Chronic alcohol or drug abuse within the past six months.
20. Any other pre-existing laboratory abnormality, medical condition, or disease that, in the opinion of Investigator, may cause the subject to be unsuitable for the study or place the subject at potential risk from being in the study, e.g. a malignancy, uncontrolled hypertension, unstable ischemic heart disease, or uncontrolled diabetes mellitus.
21. Subject is unwilling or has conditions that would prohibit them from complying with the study requirements.

**RLS Therapy:**

Subject should not be receiving treatment for RLS. All treatment for RLS should be discontinued at least 4 weeks prior to screening.

**Study Duration – One year:**

- Screening Phase: up to 14 days
- Treatment Phase I: 42 days
- Treatment Phase II: 42 days
- Long-term Extension Phase III: up to 46 weeks

**Number of Subjects / Sample Size:**

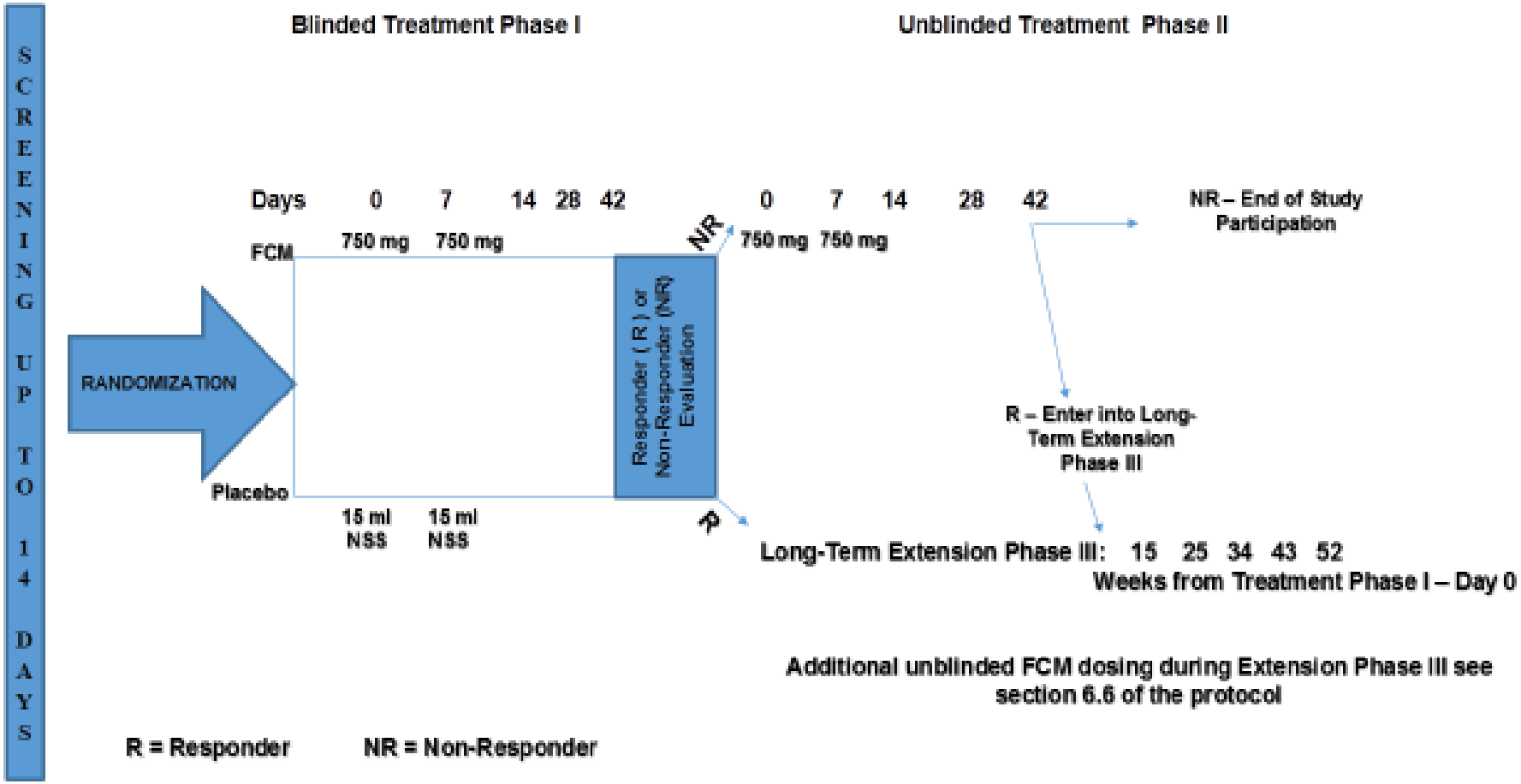
Enrollment is planned for completion (reaching Day 42 final assessment) of 70 randomized subjects (35 per treatment group). Based on Study 1VIT05009 in RLS subjects without IDA, approximately 50% of subjects in the FCM group and 15% of subjects in the placebo group are anticipated to have much or very much improvement on the CGI-I.[35] The proposed sample size provides >85% power to detect this difference with the chi-square test. The mean treatment difference and standard deviation of 5.0 (7.3) is estimated for change from Baseline to Day 42 for IRLSS score. The proposed sample size provides >80% power to detect this difference with the unpaired t-test.

**Statistical Analyses:**

The percentage responding to treatment will be evaluated for each drug condition in Treatment Phase I to determine the treatment difference at Day 42. This will be calculated from the IRLSS as change from Baseline and for the CGI-I with response determined as much or very much improved (scores of 1 or 2). All scores greater than 2 on the CGI-I are considered to indicate no significant response. For Phase II, the proportion of treatment non-responders in Phase I who

respond to FCM in Phase II will be estimated and the IRLSS score, CGI-I, and PGI-I will be summarized at Day 42. The duration of treatment over the follow-up to end of study will be described as the percentage of responders and the IRLSS score change from Baseline at each time point. Time to first FCM dose after start of Phase III will be estimated with Kaplan-Meier methodology.

Study Design



## CONTACT PERSON FOR THE STUDY

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**Tables**

## LIST OF ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| bpm | Beats per minute |
| °C | Degree Celsius |
| CFR | Code of Federal Regulations |
| CGI-I | Clinical Global Impression- Improvement |
| CHDQ | Cambridge-Hopkins Dianostic Questionnaire |
| 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 |
| °F | Degree Fahrenheit |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| g/dL | Grams per deciliter |
| Hgb | Hemoglobin |
| HDTI | Hopkins-Hening Telephone Diagnostic Interview |
| HRSQ | Hopkins RLS-Sleep Quality Questionnaire |
| ICH | International Clinical Harmonization Guideline |
| IRB | Investigational Review Board |
| IRLSS | International Restless Legs Syndrome Severity Scale |
| IRLSSG | International Restless Legs Syndrome Study Group |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LAM | Leg Activity Meters |
| 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 Survey for Sleep |
| MRI | Magnetic Resonance Imaging |
| NCI | National Cancer Institute |
| ng | Nanogram |
| NSS | Normal Sterile Saline |
| PGI-I | Patient Global Impression-Improvement |
| PD | Peritoneal Dialysis |
| PET | Positron Emission Tomography |
| PSG | Polysomnogram Measurement of Sleep |
| QOL | Quality of Life |
| RLS | Restless Legs Syndrome |

| | |
|---|---|
| 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

Restless Legs Syndrome (RLS) is a chronic, disabling, sensory (akathisia) disorder that significantly disrupts sleep and markedly affects an individual's health and quality of life. Altered iron homeostatic mechanism appears to be a primary component underlying RLS pathology and is seen most prominently as decreased brain iron in the substantia nigra demonstrated in brain magnetic resonance imaging (MRI), brain ultrasonography, and post-mortem brain tissue.[3] These changes in brain iron are present despite normal blood levels of iron. Peripheral iron status does, however, relates to RLS severity [2] and both oral and IV iron treatments significantly reduce RLS symptoms compared to placebo even in persons who are not anemic.[3, 38] Thus, there appears to be a relation between peripheral and brain iron homeostasis. In keeping with the concept of peripheral-brain relation to iron homeostasis, conditions associated with severe iron deficiency (e.g., pregnancy and IDA) show a five to six-fold increase in the prevalence of RLS.[3]

The National Heart Lung and Blood Institute estimates that "about 1 in 5 women of childbearing age has iron-deficiency anemia".[5] Based on a 2010 United States (US) Bureau of Statistics survey, there are 62 million women of childbearing age (14-44 years) in the US, of whom at least 12.4 million have IDA. These estimates suggest roughly 25% of women aged 14-44 years of age may have moderate to severe RLS. In a hematology practice for the management of IDA, 32% of patients self-reported RLS, relatively higher than the estimated 5% RLS prevalence in the general population.[3] The majority (75%) of this sample also reported moderate to severe RLS, which was substantially higher than the 30% estimate for the general population. Additionally, patients with moderate to severe RLS have been reported to have greater disabilities and diminished quality of life.[4]

Findings from a pilot study of treatment for RLS with IDA reported 65% of subjects had rapid improvements in RLS symptoms after receipt of 1000 mg of low molecular weight iron dextran.[6] This sentinel study in RLS with IDA also reported that a single iron dextran 1000 mg dose resulted in a mean hemoglobin response of 11.6 g/dL, suggesting that this dose was inadequate iron repletion for the majority of the subjects. Additionally, one-third of treatment responders did not have sustained improvement beyond six months. Finally, it would have been expected that after the IDA was corrected the RLS symptoms would have returned to the prevalence seen in the general population (5%) and this did not occur in this study. The findings from this exploratory study suggest that a single iron infusion of 1000 mg was inadequate to achieve and maintain iron levels sufficient enough to resolve or prevent brain iron insufficiency.

### 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.[19] Nordlander first associated anemia from gastric ulcer, leukemia, and chronic nephritis with the development of restless legs.[20] Subsequent associations of RLS have been reported with conditions such as pregnancy, hemodialysis, and frequent blood donations.[7,8,21] Several findings have contributed to the disease understanding of low central nervous system iron stores in RLS.[22-29]

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, mood disturbances) and the emergence of new problems during long-term treatment (e.g., augmentation, loss of efficacy)."[14] Overall, extensive RLS research has led to the hypothesis that the pathophysiology of idiopathic RLS involves iron homeostatic dysregulation and that there is a role for iron treatment in RLS.

## 1.3 Injectafer® (Ferric Carboxymaltose)

### 1.3.1 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 reticuloendothelial system 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 as an investigational product on the study of RLS.

### 1.3.2 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.

Due to its structure, Injectafer® is more stable than iron gluconate and iron sucrose. Injectafer® is a slow delivery of the complexed iron to endogenous iron binding sites, and has an acute toxicity in animals approximately $1/5^{th}$ that of iron sucrose. These characteristics of Injectafer® make it possible to administer much higher single doses over shorter periods of time than iron gluconate or iron sucrose, resulting in 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.

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

The Injectafer® clinical development program demonstrated the effectiveness and safety of Injectafer® in the treatment of IDA. The drug is approved for the treatment of IDA in adult populations who have intolerance to oral iron or have had unsatisfactory responses to oral iron or who have 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 demonstrated a fast initial elimination of radioactively labeled iron (Fe) $^{52}Fe/^{59}Fe$ Injectafer (ferric carboxymaltose injection) 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 of radioactively-labeled Fe was still detected 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) on June 15, 2007 (EU Trade name: Ferinject). Injectafer® now has marketing authorization in 63 countries and is currently marketed in 55 of these countries. 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

To evaluate the efficacy and safety of FCM (750 mg dose x 2) for treatment of RLS with IDA.

## 3.0 RATIONALE AND OVERALL STUDY DESIGN

### 3.1 Rationale

Since Norlander [31] proposed the relationship between the administration of iron and the resolution of symptoms associated with RLS in 1953, many studies have been conducted to identify the mechanism for this relationship and the ideal treatment regimen. To date, studies suggest that the specific iron preparation, the amount of iron administered, and the timing of the administered iron may contribute to the magnitude and duration of the treatment effect. Nonetheless, few human clinical studies have investigated these treatment factors or the plausible mechanisms of action for RLS.

Studies of IV iron dextran suggest robust results in the control of RLS symptoms lasting two to 48 months.[31,32] Given that iron dextran preparations are associated with significant risk of anaphylaxis, severe hypersensitivity reactions, and death, other IV iron formulations are now being investigated. Allen et al. [35] reported the results of a 46-subject trial that compared FCM 500mg X 2, FCM 1000 mg, and placebo.[35] Subjects treated with either dose of FCM demonstrated a reduction of RLS symptoms lasting for up to 24 weeks without additional need for alternative RLS medications. Currently, a 200-subject multicenter trial of FCM versus placebo is underway to expand upon these results in subjects with iron deficiency with or without IDA (NCT02397057). These studies utilize the FDA approved dose of 750mg X 2 that has been shown to be safe and effective in the treatment of IDA. This proposed trial will investigate the approved FCM 750mg X 2 dose in RLS-associated IDA patients and provide data on the long-term need for subsequent IV iron dosing in RLS subjects who respond to FCM therapy.

An altered iron homeostatic mechanism appears to be a primary component underlying RLS pathology and is reported to date as most prominently noted decreased brain iron in the substantia nigra.[30] This decreased brain iron is present in RLS patients even with normal peripheral iron stores. Systemic iron deficiency as seen with IDA appears to further accentuate this iron homeostatic imbalance, leading to a six-fold increase in RLS expression.[30] In this study, RLS subjects with IDA will undergo pre- and post-treatment brain MRI scans for comparative characterization of brain iron concentrations.

### 3.2 Trial Design

This will be a Phase II, randomized, placebo-controlled study. All subjects who meet the inclusion requirements and no exclusion criteria will qualify to enter the Screening Phase. Seventy enrolled subjects will receive **blinded** study drug in Treatment Phase I after 1:1 randomization as either FCM 750 mg undiluted slow IV push at 100 mg/minute or Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute) on Day 0 and 7 for a total dose 1500 mg. All treated subjects will have blood samples taken for hematology, chemistries and iron indices on Day 14. Treatment efficacy (IRLSS), medication review and adverse events assessment by phone will be done on Day 28. The primary endpoint for efficacy will be a face-to-face visit at the end of Treatment Phase I (Day 42) during which all subjects will be interviewed by the PI, complete questionnaires, have adverse events assessment, medication review, physical exam and complete set of blood studies will be done. At Day 42 visit, subjects will also be categorized as either treatment responders or treatment non-responders defined as:

> **Responder:** IRLSS score ≤10 or >10 with a CGI-I score of much or very much improvement and the patient does not request further treatment for RLS.
> **Non-Responder** if these criteria are not met.

**Non-Responders** who do not meet the laboratory criteria for additional dosing will be discontinued from the study and treated for RLS as deemed appropriate by the referring physician. Subjects who are **Non-Responders** at the end of Treatment Phase I and who have met the necessary laboratory criteria (ferritin <300 ng/mL and a TSAT <45%) will consent for enrollment in Treatment Phase II study. These subjects will receive the first of two **unblinded** doses of FCM (undiluted slow IV push 750 mg 100 mg /minute) on Day 0 of Phase II, which will occur within 7 days of completing the Treatment Phase I visit. The subjects will then receive the second dose of FCM (undiluted slow IV push 750 mg 100 mg / minute) on Day 7. All treated subjects will have blood samples taken for hematology, chemistries and iron indices on Day 14. Treatment efficacy (IRLSS), medication review and adverse events assessment by phone will be done on Day 28. All subjects will return to the clinic on Day 42 for end of study assessments. Subjects completing Treatment Phase II will be re-evaluated on Day 42 and defined as either a **Responder** or **Non-Responder**, using the same criteria described above. Those subjects deemed as treatment **Non-Responders** will be discontinued from the study after final assessments are complete.

Subjects who are evaluated on Day 42 (Week 6) as **Responders** from either Treatment Phase I or Treatment Phase II will continue through into the 46-Week, Long-Term Extension Phase III of

the study, and be monitored and assessed by phone for RLS symptoms (IRLSS and HRSQ) and adverse events on Weeks 15, 25, 34, 43 and 52 (final follow-up visit). During Phase III, subjects may receive additional unblinded treatments with FCM if at any time the subject reports worsening of RLS symptoms (an increase >4 points on the IRLSS compared to the last evaluation captured for that subject) and laboratory criteria are met (ferritin <300 ng/mL and a TSAT <45%). Subjects will receive a single FCM 750 mg undiluted slow IV push at 100 mg/minute. See section 6.6 for dosing and assessment outline. No additional treatment will be allowed after the Week 46. A final face-to-face study visit will occur on Week 52. If a clinic visit is not possible, final evaluation will be completed by phone.

## Table 3.2.1 Schedule of Events Treatment Phase I and Treatment Phase II

| | SCREENING | Treatment Phase I and Treatment Phase II | | | | |
|---|---|---|---|---|---|---|
| **STUDY VISIT PROCEDURES** | **-14** | **DAY 0** | **DAY 7** | **DAY 14** | **DAY 28 (PHONE CONTACT)** | **DAY 42** |
| Informed Consent | X | | | | | X** |
| Eligibility | X | X | | | | X |
| Medical History, including prior iron therapy | X | X | | | | |
| RLS History | X | X | | | | |
| D/C oral iron products | X | | | | | |
| Site contact IRT | X | | | | | |
| Physical exam | X | | | | | X |
| Vital Signs | X | X | X | | | X |
| Height and Weight without shoes | X | | | | | |
| CHDQ | X | | | | | |
| HTDI | X | | | | | |
| IRLSS | X | X | | | X | X |
| HRSQ | | X | | | | X |
| CGI-I | | | | | | X |
| PGI-I | | | | | | X |
| MOS Sleep Scale | | X | | | | X |
| Hematology | X | X | X | X | | X |
| Iron Indices | X | X | X | X | | X |
| Chemistry | X | X | X | X | | X |
| Vitamin D | | X | X | X | | X |
| Erythropoietin | | X | | | | X |
| Trace Element | | X | | | | |
| Urine Pregnancy test | X | | | | | |
| Study Drug | | X | X | | | |
| Brain MRI | X | | | | | X |
| Concomitant Meds | X | X | X | | X | X |
| Adverse Events | | X | X | | X | X |

**** All Subject will be consented to participate in Treatment Phase II prior to any study procedures being completed**

## Table 3.2.2 Schedule of Events Long-Term Extension Phase III

| **STUDY VISIT PROCEDURES** | **Week 15 Phone Contact** | **Week 25 Phone Contact** | **Week 34 Phone Contact** | **Week 43 Phone Contact** | **Week 52 EOS** |
|---|---|---|---|---|---|
| IRLSS | X | X | X | X | X |
| HRSQ | X | X | X | X | X |
| MOS / PGI-I | | | | | X |
| Concomitant Meds | X | X | X | X | X |
| Adverse Events | X | X | X | X | X |
| Physical Exam / VS | **See Section 6.6 for procedures for additional FCM dosing** | | | | |
| Iron Indices / Chemistries / Hematology | | | | | X |
| FCM Dosing | | | | | |

# 4.0 SUBJECT SELECTION

## 4.1 Number and Type of Subjects

Seventy (70) subjects (35 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 into Treatment Phase I to receive a blinded dose of Injectafer® or IV Placebo. Subjects will be consented prior to entering Treatment Phase II.

## 4.2 Screening Phase

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

### 4.2.1 Inclusion Criteria

1. Male or female subject ≥18 years of age, willing and able to give informed consent.
2. Confirmed diagnosis of RLS based on the Cambridge-Hopkins Diagnostic Questionnaire (CHDQ) and the Hopkins-Hening Telephone Diagnostic Interview (HDTI).
3. IRLSS score ≥15 plus RLS symptoms for at least 3 months and currently occurring ≥2 nights per week.
4. Iron-deficiency anemia defined as an Hgb <12 g/dl with a ferritin <20 ng/mL or <100 when TSAT is <18%.
5. Subjects on sleep medication must be on a stable dose for at least 6 months prior screening.
6. Subjects at risk for pregnancy must have a negative pregnancy test at screening and be practicing an acceptable form of birth control: have had a hysterectomy or tubal ligation, or otherwise be incapable of pregnancy, or have practiced any of the following methods of contraception for at least one month prior to study entry: hormonal contraceptives, spermicide with barrier, intrauterine device, or partner sterility.

### 4.2.2 Exclusion Criteria

1. Disorders that require treatment with the same medications used for RLS include: peripheral neuropathy and neurodegenerative disorders (i.e. Parkinson's disease or dementia).
2. Current (past 4 weeks) use of drugs that may cause or treat RLS, e.g. opioids, calcium channel alpha-2-delta ligands, anti-depressants, dopaminergic agonist or antagonists, or centrally-acting antihistamines.
3. Any medical conditions contraindicated to MRI.
4. Abnormal MRI at baseline that would confound the outcome measures.
5. Secondary RLS due to neurological conditions or head trauma.
6. History of hemochromatosis, hemosiderosis, other iron storage disorders or iron metabolism disorders.

7. Women with clinically significant uterine bleeding (>200 cc blood loss) during the six months prior to screening.
8. Liver transaminases (AST or ALT) greater than 2 times the upper limit of normal (ULN).
9. 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 ULN).
10. Known positive HIV-1 or HIV-2 antibodies (anti-HIV).
11. Active acute or known chronic infections.
12. Rheumatoid arthritis with symptoms or signs of active inflammation.
13. Pregnant and lactating women.
14. Known hypersensitivity reaction to any component of Injectafer® (Ferric carboxymaltose).
15. Previously randomized to Injectafer® (FCM or VIT-45) in a clinical trial.
16. Previous IV iron treatment for RLS.
17. Parenteral iron, erythropoiesis stimulating agent use or blood transfusion within six weeks prior to the screening visit.
18. Planned elective surgery during the study year.
19. Chronic alcohol or drug abuse within the past six months.
20. Any other pre-existing laboratory abnormality, medical condition, or disease that, in the opinion of Investigator, may cause the subject to be unsuitable for the study or place the subject at potential risk from being in the study, e.g. a malignancy, uncontrolled hypertension, unstable ischemic heart disease, or uncontrolled diabetes mellitus
21. Subject is unwilling or has conditions that would prohibit them from complying with the study requirements.

### 4.3 Subject Assignment and Randomization Process

Subjects who meet all inclusion requirements and no exclusionary criteria will be offered participation in this study. Subjects will initially be randomized in a 1:1 ratio via an IRT system to receive either a blinded dose of IV FCM or a blinded dose of IV Placebo.

- Each subject will be randomized to receive either a FCM 750 mg undiluted slow IV push (100 mg/minute) or Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute on Day 0 and 7.

### 4.4 Duration of Study / Withdrawal from Study

All subjects will be followed for efficacy and safety. The subset of subjects requiring withdrawal from the study or an intervention for treatment of RLS symptoms will continue to be followed for safety for at least 28 days after the last dose of study medication (Injectafer® or Placebo).

Any subject who wishes to withdraw from the study may do so at any time without the need to justify the 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.

For subjects requiring withdrawal from the study or an intervention, final study procedures should be performed at the time of withdrawal/intervention.

## 4.5 Endpoints in participation / Early termination endpoints

**Termination in participation is defined as**:

1. The subject is considered a treatment Non-Responder (see definition of non-responder below) as assessed at Day 42 of Treatment Phase I and is not eligible for Treatment Phase II.
2. The subject is considered a treatment Non-Responder (see definition of non-responder below) as assessed at Day 42 of Treatment Phase II.
3. The subject in Long-Term Extension Phase III who has "worsening of RLS" by definition but cannot receive further iron treatment because laboratory criteria are not met and wishes to have alternative treatment for RLS.
4. The subject in Long-Term Extension Phase III who wishes to have alternative treatment for RLS other than FCM.
5. Completes Long-Term Extension Phase III.

**Endpoints for early termination is defined as**:

1. Significant adverse effect during the treatment period.
2. Significant adverse event or health issues after starting the iron treatment, and before the final evaluation that was judged to require ending the study.
3. Subject decision not to continue in the study after the treatment and before the final evaluation.
4. The Principal Investigator has determined it would be harmful to the subject to continue in the study.
5. Subject is non-compliant with study requirements.
6. Use of other medications to treat RLS, other than study medication.

## 4.6 Treatment Responder and Non-Responder:

Subject will have been determined to have met the definition of Responder when the IRLSS score is ≤10 or a >10 with a CGI-I score of much or very much improvement and the subject does not request further treatment for RLS. Subjects who do not meet the primary endpoint will be deemed treatment Non-Responders.

# 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® (FCM) 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 study monitor.**

## 5.2 Study Drug Blinding/Administration

### 6.2.1 Study Drug Blinding

The treatment personnel who are not blinded will determine, through the IRT system, the treatment assignment on the day of treatment and will administer the appropriate treatment. The research coordinator will not know the subject's treatment, will not be present when the subject is treated, and will not have access to files indicating the treatment dose given. During IV treatment, the subject will be blinded to treatment administration (i.e. wear eye masks) to ensure minimal risk for detection of color differences between FCM and placebo treatments. All study personnel will be blinded to the iron indices and phosphorous (after randomization) throughout the study.

#### 5.2.1.1 Unblinded Personnel

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

- Randomization of the subject on Day 0 through IRT system.
- Preparing, concealing, and administering the study drug on Day 0 (as Injectafer® is reddish-brown and slightly viscous).[1]
- Completing the Study Drug Accountability Form, study drug dosing record and applicable CRF 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. 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 and phosphorous as the values may unmask the study assignment.

The blinding will be maintained in Phase I. 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 IRLSS score and PGI-I score for each subject after randomization.

### 5.3 Study Drug Administration

**Treatment Phase I**: On Day 0 subjects will be randomized to receive either FCM 750 mg undiluted slow IV push (100 mg/minute) or Placebo (15 ml of Normal Saline [NS]) IV push at 2 ml/minute on Day 0 and 7.

**Treatment Phase II:** Non-Responders from Phase I who qualify will receive an unblinded 750 mg undiluted slow IV push (100 mg/minute) of FCM on Day 0 and 7 of Phase II.

**Long-Term Extension Phase III**: Qualified subjects will receive an unblinded single 750 mg undiluted slow IV push (100 mg/minute) of FCM when RLS worsen or reoccur.

### 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-treatment, and 30 minutes post-treatment administration. All subjects will be discharged from the site by the Investigator only if there are no significant changes in vital signs or symptoms 30 minutes after the administration of study drug 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 IV 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®. The study drug must not be used for any purposes other than as directed by this protocol. The Investigator agrees that study medication will not be supplied to any persons other than those screened and randomized in the study. 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 the route of administration and duration must be recorded in the case report form (CRF). **No additional IV iron, blood transfusion and erythropoiesis stimulating agents (ESA) from six weeks prior to screening or oral iron from time of consent through the end of study.** Throughout the study, the subject may take any concomitant medications or treatments deemed necessary to provide adequate supportive care. When the subject is found eligible for the study, he/she is not allowed to take the medicines listed below as prohibited medications. Any concomitant medications administered while the subject is participating in the study must be recorded on the source document and transcribed into the concomitant medication form.

The following medications **are not allowed** from baseline and until week 6 as it could potentially affect the primary endpoint:

- Any iron supplementation other than investigational drug
- Dopaminergic treatment (agonist or antagonist)
- Opioids
- Anti-depressives
- Narcotics (Pain killers)
- Cannabis
- Anti-convulsants including alpha-2-delta drugs
- Centrally-active anti-histamines.

The dose of all medications (oral contraceptives, progestins, estrogens, androgens, antifibrinolytics, NSAID, etc.) that may affect the degree of uterine bleeding must have been stable from 6 weeks prior to screening and remain stable for the entire study period. The dose and the number of days treated per month must remain stable. Hormonal agents that are not dosed in this manner (i.e. for an acute bleeding episode) are not allowed to be used in the study. NSAID may be taken on an as needed basis, but the average monthly dose should remain stable from Baseline until the end of study.

**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

During Screening and Treatment Phase II, prior to any study specific procedures, the Investigator or designee 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 (up to 14 days)

Subjects will undergo the following to confirm eligibility for the study:

- Informed Consent obtained
- Obtain screening number from IRT system
- Blood samples for hematology, iron indices, chemistries
- Physical Exam to include height and weight (without shoes)
- Vital signs (sitting heart rate and blood pressure)
- Urine pregnancy test (if indicated)
- A review of medical history, including prior iron therapy use and RLS history
- All prior medications (subjects should not be receiving treatment for RLS). All oral iron products will be discontinued on the day of the first screening visit
- If the CHDQ and IRLSS confirm the subject qualifies, the following will occur during the screening period:
    - Phone call assessment of HTDI
    - Brain MRI will be scheduled.

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 Randomization

Randomization can be completed during the screening period or on Day 0 once it is confirmed the subject qualifies for study participation. The un-blinded treatment nurse will determine the subject's treatment assignment through the IRT system.

## 6.4 Treatment Phase I / Treatment Phase II Assessments

### 6.4.1 Treatment Phase I

#### 6.4.1.1 Day 0

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

- Confirm the subject continues to meet the Inclusion/Exclusion criteria
  - Review medical / RLS history
  - Re-confirm IDA diagnosis
- Blood samples for hematology, iron indices, chemistries, Vitamin D, erythropoietin and trace elements
- IRLSS will be complete
- Subject will complete the following:
  - ✓ Medical Outcome Study (MOS) Sleep Scale (range 0-100)
  - ✓ Hopkins RLS-Sleep Quality Questionnaire (HRSQ)
- Vital signs to include temperature
- Concomitant medications.

Once the subject is determined to continue to meet entry criteria the unblinded treatment personnel will contact the IRT system for treatment assignment.

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

The Dosing Record will include:

- ✓ Starting and stopping time of study drug administration
- ✓ Total dose in mg and ml of FCM administered (i.e. 750 mg / 15 ml)
- ✓ Total volume of Normal Sterile Saline administered (250 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.

#### 6.4.1.2 Day 7

The following must be obtained in the following order:

- Adverse Events
- Vital signs to include temperature
- Concomitant medications
- Blood samples for hematology, iron indices, chemistries, and Vitamin D
- Study drug dosing.

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

The Dosing Record will include:

- ✓ Starting and stopping time of study drug administration
- ✓ Total dose in mg and ml of FCM administered (i.e. 750 mg / 15 ml)
- ✓ Total volume of Normal Sterile Saline administered (250 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.

#### 6.4.1.3 Day 14

- Blood sample for hematology, chemistries, and iron indices.

#### 6.4.1.4 Day 28 Phone contact

- Adverse events
- Concomitant medications
- IRLSS will be completed.

#### 6.4.1.5 Day 42 (End of Treatment Phase I)

The following should be assessed or obtained:

- Adverse events
- Concomitant medications
- IRLSS will be completed
- Investigator CGI-I Score

- Subject will independently complete the following:
  - ✓ Subject PGI-1 Score
  - ✓ Medical Outcome Study (MOS) Sleep Scale (range 0-100)
  - ✓ Hopkins RLS-Sleep Quality Questionnaire (HRSQ)
- Blood sample for hematology, iron indices, chemistries, and Vitamin D
- Physical exam
- Vital signs (sitting heart rate and blood pressure)
- Brain MRI will be scheduled
- Consent **Non-Responders** to participate in Treatment Phase II
- Re-educate **Responders** about the 46-week Long-term Extension (Phase III).

Subjects will be assessed by the Investigator and identified as either a treatment **Responder** or a **Non-Responder**. If the subject is a treatment **Non-Responder** in Phase I, the subject will be eligible to re-consent and enroll in Treatment Phase II (section 6.4.2). If the subject is determined to be treatment **Responder**, the subject will continue through into the Long-Term Extension Phase III (section 6.5) of the study.

For **Non-Responder** subjects that do not qualify for treatment Phase II due to laboratory parameters this will be the end of the subject's participation in the study. Subjects should be removed from the study and treated as deemed appropriate by the physician.

### 6.4.2 Treatment Phase II (Repeat Days 0 – 42)

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

- Confirm consent that the laboratory samples obtained at Day 42 in Treatment Phase I qualifies the Non-Responder for additional treatment with unblinded FCM.
  - Ferritin <300 ng/mL and a TSAT <45%

#### 6.4.2.1 Day 0 and Day 7

Prior to dosing the subject review the following:

- Adverse events
- Concomitant medications
- Vital signs to include temperature.

Once the above procedures have been completed the subject will receive unblinded single FCM at 750 mg (100 mg/minute) undiluted IV push. The following should be verified:

- ✓ Starting and stopping time of FCM administration
- ✓ Total dose in mg and ml of FCM administered (i.e. 750 mg / 15 ml)
- ✓ Blood pressure and heart rate, immediately post and 30 minutes post-study drug administration

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

#### 6.4.2.2 Day 14

- Blood sample for hematology, chemistries, iron indices, chemistries, and Vitamin D

#### 6.4.2.3 Day 28 (Phone Contact)

- Adverse events
- Concomitant medications
- IRLSS will be completed.

#### 6.4.2.4 Day 42 (End of Treatment Phase II)

The following should be assessed:

- Adverse events
- Concomitant medications
- IRLSS will be completed
- Investigator CGI-I Score.
- Subject will independently complete the following:
  - ✓ Subject PGI-1 Score
  - ✓ Medical Outcome Study (MOS) Sleep Scale (range 0-100)
  - ✓ Hopkins RLS-Sleep Quality Questionnaire (HRSQ)
- Blood sample for hematology, iron indices, chemistries, erythropoietin and Vitamin D
- MRI
- Physical exam
- Vital signs (sitting heart rate and blood pressure)
- Re- educate Responders about the 46-week Long-term Extension (Phase III).

Subjects completing Treatment Phase II will be re-evaluated on Day 42 as either a **Responder** or **Non-Responders**. Subjects evaluated as treatment **Non-Responder** will be discontinued from the study after final assessments are complete. Subjects who are evaluated as **Responder** will continue through into the Long-Term Extension Phase III.

### 6.5 Long-Term Extension Phase III (46-Week extension of Treatment Responders from Phase I or II)

**Responders** from either Treatment Phase I or Treatment Phase II will continue through into the Long-Term Extension Phase III. Subjects in this Phase will be monitored and assessed by phone for RLS symptoms (IRLSS and HRSQ) and adverse events on (approximately every 9 weeks) Weeks 15, 25, 34, 43 and 52 (final face-to-face study follow-up visit). Study evaluations during the phone contacts will include:

- IRLSS will be completed
- Concomitant medications
- Adverse event assessment.

There will be a final face-to-face study visit on Week 52 (approximately 365 days since initial Day 0 Treatment). If a clinic visit is not possible, final evaluation will be completed by phone and recommend that blood studies be completed. The subject will complete the following during the face-to-face study visit:

- IRLSS
- PGI-I
- MOS-sleep
- Hopkins RLS-Sleep Quality Questionnaire (HRSQ)
- Blood samples for hematology, iron indices, and chemistries
- Adverse event and concomitant meds assessment.

### 6.6 Long-Term Extension Phase III Treatment

During Phase III, subjects could potentially receive additional, unblinded single FCM treatment if, at any time during this Phase, subjects report worsening of RLS symptoms (an increase >4 points on the IRLSS compared to the last evaluation captured for that subject). Blood samples will be taken prior to dosing to make certain the laboratory criteria are met (ferritin <300 ng/mL and a TSAT <45%). Subjects will receive a single FCM 750 mg undiluted slow IV push at 100 mg/minute. On Day 14 and 42, subjects will have a serum phosphate assessed. The subject will have a RLS symptoms (IRLSS and HRSQ) and adverse event assessment on Day 28 and 42 Days post dose by phone. No additional treatment will be allowed after the Week 46.

### 6.7 Laboratory Assessments

Serum samples for laboratory analyses must be obtained at all appropriate visits and will be analyzed by the 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 laboratory test, this test may be obtained after notification to the Sponsor. If a subject's phosphorous is below the LLN at the end of study participation the subject should return, as directed by the Investigator, for repeat phosphorous laboratory tests until the value is back WNL.

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: urine pregnancy (if indicated), other metals (serum copper and zinc), 1,25 dihydroxy Vitamin D (1,25 $[OH]_2D$); 25 hydroxy Vitamin D (25OH-D) and erythropoietin.

## 7.0 ASSESSMENT OF SAFETY

### 7.1 Adverse Events

Any untoward medical (clinical) event 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 CRF.

For any laboratory abnormality, the physician will make a judgment as to its potential clinical significance. If the laboratory value is outside the safety limits and deemed 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 and 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 trial's 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 or a follow-up phone call 28 days following the last dose of study drug for subjects who are randomized and terminate early from the trial. All ongoing adverse events related to study drug (i.e., FCM or Placebo) should be followed until they are no longer related, have taken a confounding medication or return to baseline grade.

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

- NONE There is *no* evidence of any causal relationship.
- UNLIKELY There is *little* evidence to suggest there is a causal relationship. There is *another reasonable explanation* for the event (e.g., the 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 Placebo (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 CRF. 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 CRF. 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 or 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 CRF 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: 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

## 8.0 STATISTICS

### 8.1 Sample Size Rationale

Enrollment is planned for 70 randomized subjects (35 per treatment group). Based on Study 1VIT05009 in patients without IDA, approximately 50% of patients in the FCM group and 15% of patients in the placebo group are anticipated to have much or very much improvement on the CGI-I. The proposed sample size provides >85% power to detect this difference with the chi-square test. The mean treatment difference and standard deviation for change from baseline to Day 42 for IRLSS is anticipated to be 5.0 (7.3). The proposed sample size provides >80% power to detect this difference with the unpaired t-test.

### 8.2 Analysis Populations

The following analysis populations will be defined:

- Safety population: All subjects who receive randomized treatment.
  - Treatment Phase I Safety population: All subjects who receive randomized treatment.
  - Treatment Phase II Safety Population: All treatment non-responders in Treatment Phase I who receive FCM in Treatment Phase II.
  - Long-Term Extension Phase III Safety Population: All treatment responders in Treatment Phase I or Phase II who enter the Phase III assessment period.

- Treatment Phase I Full analysis set (FAS) population: All subjects who received randomized treatment and had a post-randomization measurement of the IRLSS and Clinical Global Impression performed by Investigator (CGI-I) in Phase I.
- Treatment Phase II FAS population: All subjects with a measurement of the IRLSS and CGI-I in Phase II.
- Long-Term Extension Phase III FAS population: All subjects in the Phase III Safety population with at least one telephone contact or treatment intervention during the Phase III assessment period.

## 8.3 Disposition and Baseline Characteristics

Disposition and baseline characteristics will be summarized by treatment group for each analysis population. For Phase I, the number and percentage of subjects, who are randomized, treated, prematurely discontinued, and completed the study phase will be summarized. For Phases II and III, the number and percentage of subjects, who are treated with FCM, prematurely discontinued, and completed the study phase will be summarized.

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 analysis population will be summarized for investigative site.

Baseline characteristics (e.g., sex, race, and ethnicity) 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

**Treatment Phase I** co-primary endpoints are:

- Change in IRLSS score from Baseline to Day 42 with comparison between FCM vs. Placebo, and
- Percentage of subjects who are much or very much improved at Day 42 as measured by the CGI-I.

**Treatment Phase II** primary efficacy endpoints are:

- IRLSS score change from Baseline (For Phase II the "baseline" is established on Day 42 of Phase I) compared to Day 42 in phase II.
- CGI-I at Day 42 in Treatment Phase II.

**Long-Term Extension Phase III** primary efficacy endpoints are:

- Estimate the time from first dose of FCM (Day 0 in either Phase I or Phase II) to time of FCM treatment intervention.

### 8.4.2 Secondary Endpoints

**Phase I and Phase II:**

- Change in IRLSS score from Baseline to Day 42. (Treatment Phase I and II)
- IRLSS score change from Baseline (For Phase II the "Baseline" is established on Day 42 of Phase I) compared to Day 42 of Treatment Phase II.
- CGI-I and PGI-I at each visit and percentage of subjects who are much or very much improved at Day 42. (Treatment Phase I and II)
- Change in sleep quality (MOS Sleep) from Baseline to Day 42. (Treatment Phase I and II)
- Estimate the proportion of treatment non-responders in Phase I who respond to FCM in Phase II for each randomized treatment group. (Phase II only)
- Change in substantia nigra iron index from Baseline to Day 42. The index will be determined using measures of MRI relaxation rate (R2*) or Quantitative Susceptibility Mapping (QSM). (Treatment Phase I and II)
- Change in iron index (R2* or QSM) for thalamus and motor cortex from Baseline to Day 42. (Treatment Phase I and II).

**Phase III:**

- Change in IRLSS from Baseline to each scheduled assessment.
- Number of subjects who remained in the study to Week 52.

### 8.4.3 Safety Evaluations

Safety Evaluations will include:

- Adverse events
- Laboratory assessments
- Vital signs
- Physical examinations.

## 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.

**Phase I**

The treatment differences for the changing IRLSS score from Baseline to Day 42 will be assessed with the analysis of covariance with treatment as a fixed effect and baseline value as a covariate.

The treatment difference for the percentage of subjects who are much or very much improved at Day 42 as measured by the CGI-I will be assessed with the chi-square test.

Change from Baseline for IRLSS at Day 28, MOS at Day 42, and brain iron distribution at Day 42 will be assessed with the same method as IRLSS at Day 42. The percentage of subjects who are much or very much improved at Day 42 as measured by the PGI-I will be assessed with the chi-square test.

**Phase II and III**

All analyses will be descriptive.

For Phase II, the proportion of treatment **Non-Responders** in Phase I who respond to FCM in Phase II will be estimated and the IRLSS, CGI-I, PGI-I and brain iron distribution will be summarized at Day 42.

The Kaplan-Meier method will be used to estimate time from first dose of FCM to treatment intervention. Subjects in Phase III who discontinue the study before requiring treatment intervention will be censored on the day of the last contact with the Investigator.

### 8.5.1 Exploratory Analyses

- Evaluate for possible predictors of Day 42 (Treatment Phases I and II) treatment response using clinical variables, hematologic, and brain MRI data.
- Evaluate for possible predictors of Day 42 treatment responders (Phase I) in correlation of baseline trace element levels (i.e. copper, zinc)
- Correlation of baseline Vitamin D and post dose change in phosphate
- Vitamin D at each visit.
- The change from baseline in brain MRI-determined iron concentration for other brain regions.
- Correlation between changes in brain iron and measures of peripheral iron status, RLS severity and MOS.
- Correlation between CBC/iron indices and changes from Baseline to Day 42 (Treatment Phases I and II) RLS severity and MOS.

## 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

No formal interim analyses are planned.

## 9.0 ADMINISTRATIVE CONSIDERATIONS

### 9.1 Retention and Availability of Records

Investigators are required to maintain all study documentation, including electronic copies of CRFs 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 a supplemental application for the drug for the indication being investigated or until two years after the drug investigational program is discontinued. Permission should be obtained from Luitpold Pharmaceuticals, Inc. prior to destroying any study records.

The Investigator must make study data accessible to the monitor, Sponsors, or other authorized representatives of the Sponsor and Regulatory Agency (i.e., FDA inspectors.) A case history for each subject must be maintained, that includes the signed Informed Consent form and copies of all study documentation related to that subject. The Investigator must ensure the availability of source documents from which the information on the eCRF was derived.

## 9.2 Investigator Responsibilities

By signing the Form FDA 1572 the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet Federal guidelines, as stated in 21 CFR, parts 50 and 56.
5. Report to the Sponsor any adverse events that occur in the course of the study, in accordance with 21 CFR 312.64.
6. Have read and understood the 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 study obligations and 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 US Food and Drug Administration (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 CRFs will be checked for completeness and accuracy. Source documents from which the data are obtained will be made available to the Clinical Monitor 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 Investigator 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 CRFs. 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 the investigator in advance.

## 9.7 Ethics

### 9.7.1 Ethical and Legal Issues

This study will be performed in accordance with the (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 by that site's IRB.

The Informed Consent documents the information the Investigator or designee 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 of the "Declaration of Helsinki", the local legal requirements and the guidelines on "Good Clinical Practice", [21 CFR Part 312 and ICH guidelines].

## 9.8 Data Handling and Record Keeping

### 9.8.1 Case Report Form (CRF)

- CRFs 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.
- CRFs must be reviewed and verified for accuracy by the Principal Investigator. A copy of the CRF will remain at the site at the completion of the study.
- All CRFs are to be reviewed by the Clinical Monitor at Luitpold Pharmaceuticals, Inc. (or designee) 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 Clinical 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 can be implemented. The protocol revision will also 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** There will be no Data Safety Monitoring Board for this study

## 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: RLS Assessment Tools:**

1. **Clinical Global Impression-Improvement (CGI-I):** This is performed by the Investigator. This was developed and validate by the National Institute of Mental Health[19] and has been used in many RLS treatment trial including prior FCM trial in RLS studies [3, 16-18]. CGP-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.
2. **International RLS Severity Scale (IRLSS):** This is a validated, 10-item severity scale with each item on the scale having five severity categories form 0 to 4[15]. The total score is used for a severity measure with values range from 0-40. The scale has been used in several RLS clinical trial including the FCM study in RLS[3, 16-18].
3. **Personal Global Impression-Improvement (PGI-I):** This is performed by the subject. Similar to the CGI-I except this is self-reported, 7-item scale for assessment of symptoms after treatment with the rating as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.
4. **Medical Outcome Survey of Sleep Scale (MOS-Sleep):** The MOS-Sleep is a 12-item standardized, validated questionnaire for sleep assessment [27-28], which has been used in prior RLS treatment trials and has been demonstrated to be sensitive to RLS treatment effects [29]. This questionnaire provides information about sleep quality. Individual questions can be used for analysis but summary or index scores of a group of questions, is more commonly used in analysis [30] .
5. **Cambridge-Hopkins Diagnostic Questionnaire (CHDQ):** Used at the screening visit, this is a validated, self-report, 13-item questionnaire, developed by the Johns Hopkins RLS group and used in prior studies [10-11]. Responses on Questions 11 and 12 are also used as part of the inclusion criteria. The sensitivity and specificity for diagnosing RLS is 87.2% and 94.4% and specificity for Not-RLS is 98%. The diagnosis based on the CHDQ is the primary outcome measure of RLS prevalence with adjustments in the estimate based on the HTDI. The diagnostic categories are: definite RLS, probable RLS, possible RLS, not RLS, and unknown[10, 12].
6. **Hopkins-Hening Telephone Diagnostic Interview (HTDI):** The HDTI is an 18-item scripted interview that was developed and validated by the Johns Hopkins RLS group [12-13] and used in several RLS epidemiology studies[9, 14]. The HTDQ is considered the "gold standard" for making the diagnosis of RLS and is used to support the accuracy of CHDQ-determined diagnosis. The five diagnostic categories defined by the HDTI are: definite RLS, probable RLS, possible RLS, not RLS, and unknown [10, 12].
7. **Hopkins RLS-Sleep Quality Questionnaire (HRSQ):** This is a 13-item questionnaire, which includes a question on "weakness" and on "energy" and a series of questions related to how RLS might affect sleep. The questions are part of a larger set of questions used in the NIH/NIA Baltimore Longitudinal Study on Ageing, and were used in our pilot study of Dr Auerbach's IDA population. The data from the questionnaire will be to validate the HRSQ against other measured of severity that will be used in this study.

## References

1. Wijemanne S. Jankovic J. Restless legs syndrome: clinical presentation, diagnosis, and treatment. Sleep Med 2015; 16(6):678-90.

2. Sun, E.R., et al., Iron and the restless legs syndrome. Sleep, 1998. 21(4): 371-7.

3. Allen, R.P., et al., The prevalence and impact of restless legs syndrome on patients with iron deficiency anemia. Am J Hematol, 2013, 88(4):261-4.

4. Earley, C.J. and M.H. Silber, Restless legs syndrome: Understanding its consequences and the need for better treatment. Sleep Medicine, 2010, 11(9): 807-815.

5. NIH/NHLBI, O.o.D.S., Exploring iron deficiency anemia. Available online: http://dietary-supplements.info.nih.gov/factsheets/iron.asp, 2011.

6. Mehmood, T., et al., Response to intravenous iron in patients with iron deficiency anemia (IDA) and restless leg syndrome (Willis–Ekbom disease). Sleep Medicine, 2014, 15(12):1473-1476.

7. Lee KA, Zaffke ME, Baratte-Beebe K. Restless Legs Syndrome and sleep disturbance during pregnancy: the role of folate and iron. J. Women's Health Gender Based Med 2001; 10: 335-45.

8. Collado-Seidel V. et al. Clinical and biochemical findings in uremic patients with and without Restless Leg Syndrome. (1998). Am J. Kidney Dis 1998; 31(2):324-328.

9. Garcia-Borreguero D, Williams A. An update on restless legs syndrome. (Willis-Ekbom disease): clinical features, pathogenesis and treatment. Current Opinion in Neurology 2014; 27(4):493-501.

10. Güler S, et al. The prevalence of restless legs syndrome in Edirne and its districts concomitant comorbid conditions and secondary complications. Neurol Sci. 2015 Oct; 36(10):1805-12, doi: 10.1007/s10072-015-2254-6. Epub 2015 May 20.

11. Wilt TJ, MacDonald R, Ouellette J, Khawaja IS, Rutks I, Butler M, Fink HA. Pharmacologic therapy for primary restless legs syndrome: A systematic review and meta-analysis. JAMA Intern Med 2013; 173(7):496-505.

12. Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Ray Chaudhuri K, Gonzalez Rodriguez V, Hogl B, et al Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurology 2011; Feb 27; 11:28. doi: 10.1186 /1471-2377-11-28. 11:28.

13. Nierenberg, MJ. Dopamine agonist withdrawal syndrome: implications for patient care. Drugs & Aging 2013; Aug; 30(8):587-92.
14. Garcia-Borreguero D, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013; 14:675-84.

15. Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. Lancet Neurol. 2005 Aug; 4(8): 465-75.

16. Frohlich AC, Eckeli AL, Bacelar A, Poyares D, Pachito DV, Stelzer FG, Coelho FMS, et al. Brazilian consensus on guidelines for diagnosis and treatment for restless legs syndrome. Arq Neuropsiquiatr 2015; 73(3):260-280.

17. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996; 19:205-213.

18. Trenkwalder C, Paulus W. Restless legs syndrome: pathophysiology, clinical presentation and management. Nature Reviews 2010; 6:337-346.

19. Ekbkom, K.A. Restless legs syndrome. Neurology 1960; 10:868-873.

20. Norlander, N.B. Restless Legs. Brit J Phys Med 1954;17: 160-162.

21. Silber M H Richardson J W Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. Mayo Clin. Proc. 2003; 78:52-54.

22. Earley, CJ, Allen, RP, Beard, JL, Conner, JR. Insight into the pathophysiology of restless legs syndrome. J. Neurosci. Res. 62:623-628, 2000.

23. Allen RP, Earley. MRI measurement of brain iron in patients with restless legs syndrome. Neurology. 2001. Jan 23, 56 (2):263-5.

24. Connor JR, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003; 61:304-9.

25. Connor JR, Wang XS, Patton SM, Menzies SL, Troncosco JC, Earley CJ, Allen RP. Decreased transferring receptor expression by neuromelantin cells in restless legs syndrome. Neurology 2004 May 11; 62(9):1563-7.

26. Ondo WG. Restless legs syndrome. Curr Neurol Neurosci Rep 2005; Jul; 5(4):266-74.

27. Hogl B, PoweW. Restless Legs Syndrome. Curr Opin Neurol 2005; Aug 18 (4):405-10.

28. Connor JR, Ponnuru P, Wang X, Patton SM, Allen RP, Earley CJ. Profile of altered brain iron acquisition in restless legs syndrome. Brain 2011; 134:959-68.

29. Silber MH, Becker PM, Earley C, Garcia-Borreguero D, Ondo WG. Willis-Ekbom Disease Foundation Revised consensus Statement on the Management of Restless Legs Syndrome. Mayo Clin Proc 2013; 88(9):977-86.

30. Earley CJ, et al. Altered brain iron homeostasis and dopaminergic function in restless legs syndrome (Willis-Ekbom Disease). Sleep Med 2014; 15:1288-1301.

31. Norlander, N.B. Therapy in restless legs. Acta Med Scand 1953; 145; 453-57.

32. Earley CJ, Heckler D, Allen RP The treatment of restless legs syndrome with intravenous iron dextran. Sleep Med. 2004 May; 5(3):231-35.

33. Early CJ, Heckler D, Allen RP. Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. Sleep Med. 2005 Jul; 6 (4):301-5.

34. Sloand JA, Shelly MA, Feigin A, Berstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. Am J Kidney Dis. 2004 Apr; 43(4):663-70.

35. Allen RP, Adler CH, Du W, Butcher A, Bregman DB, Earley CJ. Clinical efficacy and safety of IF ferric carboxymaltose (FCM) treatment of RLS: A multi-centred, placebo-controlled preliminary clinical trial. Sleep Medicine 2011Oct; 12(9):906-13.

36. O'Keefe ST, Gavin K, Lavan JN. Iron status and restless legs syndrome in the elderly. Age Ageing. 1994 May: 23 (3):200-3.

37. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichorn GR. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. Eur Neurol 2000, 43(2):70-5.

38. Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. Sleep Medicine 2009; 10(9); 973-975.

39. Trotti LM, Bhadriraju S, Becker LA. Iron for restless leg syndrome. Cochrane Database Syst Rev 2012 May16; 5:CD007834. doi: 10.1002/14651858.CD007834.pub2. Review.

40. Allen RP, Butcher A, Du W. Double-blind, placebo controlled multi-center evaluation of restless legs syndrome (RLS) treatment with a 1,000 mg of IV iron (ferric carboxymaltose - - FCM). Sleep 2009; 32(Abstract supplement):A294-A295.

41. Grote L, Leissner L, Hedner J, Ulfberg J. A randomized, double-blind, placebo-controlled, multi-center study of intravenous iron sucrose and placebo in the treatment of restless legs syndrome. Movement Disorders 2009; 24(10):1445-52.

42. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. A randomized, double-blind, placebo-controlled trial of iron in restless legs syndrome. European Neurology 2000; 43:70-5.

43. Earley CJ. Horska A, Mohamed MA, Barker PB, Beard JL, Allen RP. A randomized, double-blind, placebo-controlled trial of intravenous iron sucrose in restless legs syndrome. Sleep Medicine 2009; 10:206-11.

44. Pondal M. Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic J Neurol Neurosurg Psychiatry 2013 Feb; 84(2):130-5.

## Investigator Rated Global Impression – Global Improvement

1. Global Assessment of Effect (check one):

- 5 ☐ No effect
- 4 ☐ Mild effect
- 3 ☐ Moderate effect
- 2 ☐ Marked effect
- 1 ☐ Dramatic effect

2. Global Assessment of Improvement (check one):

- 7 ☐ Very much worse
- 6 ☐ Much worse
- 5 ☐ Minimally worse
- 4 ☐ No change
- 3 ☐ Minimal change
- 2 ☐ Much improved
- 1 ☐ Very much improved

Investigator Initials:_____

# International Restless Legs Syndrome Study Group Rating Scale (IRLS)

(Investigator Version 2.2)

Have the patient rate his/her symptoms for the following ten questions. The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.

In the past week…

(1) Overall, how would you rate the RLS discomfort in your legs or arms?

- [4] ☐ Very severe
- [3] ☐ Severe
- [2] ☐ Moderate
- [1] ☐ Mild
- [0] ☐ None

In the past week…

(2) Overall, how would you rate the need to move around because of your RLS symptoms?

- [4] ☐ Very severe
- [3] ☐ Severe
- [2] ☐ Moderate
- [1] ☐ Mild
- [0] ☐ None

In the past week…

(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?

- [4] ☐ No relief
- [3] ☐ Mild relief
- [2] ☐ Moderate relief
- [1] ☐ Either complete or almost complete relief
- [0] ☐ No RLS symptoms to be relieved

In the past week…

(4) How severe was your sleep disturbance due to your RLS symptoms?

- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week…

(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?

- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week…

(6) How severe was your RLS as a whole?

- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week…

(7) How often did you get RLS symptoms?

- [4]☐ Very often (This means 6 to 7 days a week)
- [3]☐ Often (This means 4 to 5 days a week)
- [2]☐ Sometimes (This means 2 to 3 days a week)
- [1]☐ Occasionally (This means 1 day a week)

[0]☐ Never

In the past week…

(8) When you had RLS symptoms, how severe were they on average?

[4]☐ Very severe (This means 8 hours or more per 24 hour day)

[3]☐ Severe (This means 3 to 8 hours per 24 hour day)

[2]☐ Moderate (This means 1 to 3 hours per 24 hour day)

[1]☐ Mild (This means less than 1 hour per 24 hour day)

[0]☐ None

In the past week…

(9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work life?

[4]☐ Very severe

[3]☐ Severe

[2]☐ Moderate

[1]☐ Mild

[0]☐ None

In the past week…

(10) How severe was your mood disturbance due to your RLS symptoms - for example angry, depressed, sad, anxious or irritable?

[4]☐ Very severe

[3]☐ Severe

[2]☐ Moderate

[1]☐ Mild

[0]☐ None

Pt NUM _____Date: _____ VISIT:

# Patient Global Impression

For the Past Week rate how much you feel your RLS symptoms have changed since you started the study

1 = Very much improved

2= Much improved

3 = Minimally improved

4 = No Change

5 = Minimally worse

6 = Much worse

7= Very much worse

## Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes……..…1

16-30 minutes……..2

31-45 minutes……..3

46-60 minutes……..4

More than 60 minutes …….5

---

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number

of hours per night: ☐☐

---

**How often during the <u>past 4 weeks</u> did you…**

(Circle One Number On Each Line)

| | All of the Time ▼ | Most of the Time ▼ | A Good Bit of the Time ▼ | Some of the Time ▼ | A Little of the Time ▼ | None of the Time ▼ |
|---|---|---|---|---|---|---|
| 3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)? | 1 | 2 | 3 | 4 | 5 | 6 |
| 4. get enough sleep to feel rested upon waking in the morning? | 1 | 2 | 3 | 4 | 5 | 6 |
| 5. awaken short of breath or with a headache? | 1 | 2 | 3 | 4 | 5 | 6 |
| 6. feel drowsy or sleepy during the day? | 1 | 2 | 3 | 4 | 5 | 6 |
| 7. have trouble falling asleep? | 1 | 2 | 3 | 4 | 5 | 6 |
| 8. awaken during your sleep time and have trouble falling asleep again? | 1 | 2 | 3 | 4 | 5 | 6 |
| 9. have trouble staying awake during the day? | 1 | 2 | 3 | 4 | 5 | 6 |
| 10. snore during your sleep? | 1 | 2 | 3 | 4 | 5 | 6 |
| 11. take naps (5 minutes or longer) during the day? | 1 | 2 | 3 | 4 | 5 | 6 |
| 12. get the amount of sleep you needed? | 1 | 2 | 3 | 4 | 5 | 6 |



Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), <u>Measuring functioning and well-being: The Medical Outcomes Study approach</u> (pp. 235-259), Durham, NC: Duke University Press.

# Cambridge- Hopkins Restless Legs Syndrome

## Short Form 2 DIAGNOSITC QUESTIONNAIRE (CH-RLSq13)

*Answer the questions as completely as you can. Please **circle** the one best answer to each question* thus: (•)

| | |
|---|---|
| 1. Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down? | • Yes<br>• No |
| 2. Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down? | • Yes<br>• No |

*If you answered YES to either question 1 or 2 continue Question 3. If you answered NO to BOTH stop here*

## The following is about these feelings

| | |
|---|---|
| 3. Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active? | • Resting<br>• Active |
| 4. Do these feelings usually *start* when you are resting (either sitting or lying down)? | • Yes<br>• No |
| 5. If you get up or move around when you have these feelings do these feelings get any better while you actually keep moving? | • Yes • No<br>• Don't know |
| 6. Which times of day are these feelings in your legs **most** likely to occur? *(Please circle one or more than one)* | • Morning • Mid-day<br>• Afternoon • Evening<br>• Night<br>• About equal at all times |
| 7. Which times of day are these feelings in your legs **least** likely to occur? *(Please circle one or more than one)* | • Morning • Mid-day<br>• Afternoon • Evening<br>• Night<br>• About equal at all times |
| 8. Will simply changing leg position by itself *once* without continuing to move usually relieve these feelings? | • Usually relieves<br>• Does *not* usually relieve<br>• Don't know |

| | |
|---|---|
| 9. Are these feelings *ever* due to muscle cramps? | • Yes • No<br>• Don't know |
| 9b. If so, are they *always* due to muscle cramps? | • Yes • No<br>• Don't know |
| 10. Do these feelings occur *only* when sitting or only when lying down? | • Neither<br>• Only when sitting<br>• Only when lying down<br>• Both when sitting and . when lying down. |
| 11. When you actually experience the feelings in your legs, how *distressing* are they? | • Not at all distressing<br>• A little bit<br>• Moderately<br>• Extremely distressing |
| 12. In the past 12 months, how often did you experience these feelings in your legs? (please circle only one answer) | • Every day<br>• 4-5 days per wk<br>• 2-3 days per wk<br>• 1 day per wk<br>• 2 days per month<br>• 1 day per month or less<br>• Never |
| 13. Approximately how old were you when you first noticed these feelings in your legs?(*please write age)* | ☐☐ Yrs |

**NAME:** _____ **DATE:** _____

1. **In the past <u>week</u>, on average, what time did your RLS symptoms usually start: _____ AM / PM**

2. **During the past <u>week</u>, how satisfied did you feel with the treatment for RLS,**

| Not Satisfied at all | | | | | | | | | Very Satisfied | Don't know |
|---|---|---|---|---|---|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |

3. **During the past <u>week</u>, how would you rate the Intensity of the sensation or Discomfort you experienced when your RLS symptoms did occur,**

| Minimal Discomfort | | | | | | | | | Quite Severe | Don't know |
|---|---|---|---|---|---|---|---|---|---|---|
| ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |

| **In the past <u>week</u>, how often did you:** | **Never** | **<1/week** | **1-2/week** | **3-4/week** | **5+/week** | **Don't know** |
|---|---|---|---|---|---|---|
| **4. …have trouble falling asleep within 30 minutes because of your RLS symptoms?** | ○ | ○ | ○ | ○ | ○ | ○ |
| **5. …wake up several times at night?** | ○ | ○ | ○ | ○ | ○ | ○ |
| **6. … have trouble getting back to sleep because of your RLS symptoms?** | ○ | ○ | ○ | ○ | ○ | ○ |
| **7. … have RLS symptoms when you awakened for the day?** | ○ | ○ | ○ | ○ | ○ | ○ |
| **8. …need to take more medication for the RLS symptoms?** | ○ | ○ | ○ | ○ | ○ | ○ |
| **9. …find that your RLS medications just did not seem to work as well?** | ○ | ○ | ○ | ○ | ○ | ○ |
| **10. … find that the RLS symptoms were starting earlier than usual?** | ○ | ○ | ○ | ○ | ○ | ○ |
| **11. …have RLS symptoms in other parts of the body other than your legs?** | ○ | ○ | ○ | ○ | ○ | ○ |

**12. Overall, in the past <u>week</u>, was your typical night's sleep…?**

Very sound or restful ○ Sound or restful ○ Average quality ○ Restless ○ Very restless ○ Don't know ○

**13. On average, in the past <u>week</u>, how many hours of sleep did you get each night?**

More than 7 ○ More than 6, up to 7 ○ More than 5, up to 6 ○ 5 or fewer ○ Don't know ○

**14. List your current RLS medications and total daily dose:**

# The Hopkins-Hening RLS
# Diagnostic Interview

Subject Name: _____ ID #: _____ DOB: _____

Interviewer: _____ Date: _____ Time: _____

## Final Diagnosis:

Definite RLS; Probable RLS; Possible RLS;

Secondary Definite; Secondary Possible; Cause: _____

Not-RLS; Diagnosis Unknown

Circle if subject reports growing pains: ____ Yes ____ No

**General Note** – The final standard for answering questions is the judgment of the interviewer. As a result, answers may be revised if later questions make it clear that an earlier answer was inaccurate. When revising answers, document why this was done (e.g. questions on sleep indicate there are leg discomforts, etc.). If an interviewee mentions multiple different feelings, be clear which is indicated by any given answer. Remember, to be diagnosed with RLS, all relevant criteria must be satisfied by a single feeling. Where it is not indicated to skip ahead, continue the interview with the next question.

Revised 17mar2008

1. Have you ever had unpleasant or uncomfortable feelings in your legs that occurred **mainly while you were either sitting or lying down**?

**Yes** **No**

**If NO, go to 3**

2. Are these feelings **painful** rather than just **uncomfortable?** **Yes** **No**

3. Have you ever felt the **need or urge to move** your legs that occurred **mainly while you were sitting or lying down**?

**Yes** **No**

If **NO** to both questions #**1** and #**3**, go to #**15**. ⟶

3a. Do both the urge to move and the unpleasant sensations occur at the same time?

**Yes** **No**

If **NO**, there may be two different symptoms and this should be explored and clarified. Remember – all criteria must be satisfied by a single symptom.

3b) How would you describe these feelings or sensations?

_____

_____

3c. Do these feelings in your legs ever become **overwhelming** to the point that you cannot resist moving your legs?

**Yes** **No**

3d. How would you feel if you developed this feeling and were in a situation where you couldn't move? (Note: Can Give Examples)

_____

_____

3e. Do these feelings only occur when your legs are in specific positions, such as crossed or bent a particular way?

**Yes** **No**

If **YES**, explain _____

3f. When you have these feelings, how long do they last before they have gone away so that you can sit or lie down for an hour or more without having the feelings?

This means that the person does not have to continue moving to relieve the feelings.

_____

If answer is 5 minutes or less, explain how consistent with RLS

4. Have you ever experienced a muscle cramp in the legs?

**Yes** **No**

**If YES, go to 4a**

**If NO, go to 5**

4a. Were these feelings you described earlier muscle cramps in the legs?

**Yes** **No**

**If YES, go to 4b**

**If NO, go to 5**

4b. Were the feelings you described earlier **always** muscle cramps in the legs?

**Yes** **No**

If **YES, Conclude the interview, subject is NOT RLS**
If **NO,** continue or revisit 1 and 3

If NO, the subject has two different feelings – a cramp is one and something else is the other – since cramps are not RLS, you need to go back to 1 and be sure and indicate that all answers correspond to this other feeling.

5. If you had these feelings and you got up to walk -- **while you are actually walking around**, do you get any relief from these feelings?

The answer to this question does not require complete relief, but only some relief.
**NOTE**: If any suspicion of confusion, indicate that this is before sitting or lying down again.

**Yes** **No** **Don't Know**

5a. If you move your legs, do you get any relief from these feelings, **even temporarily**?

**Yes** **No**

5b. What do you do to get relief from these feelings (this question is to be answered by behaviors and not by medications taken)?

_____

_____

5c. If you move your leg once to a new position, but don't continue to move or do anything else, will that single change of position be enough to relieve the feelings?

**Yes** **No**

**If YES, explain**_____

6. Do these feelings ever start when you are walking?

**Yes** **No**

**If YES, explain**_____

7. Do these feelings occur more often when you are sitting or more often when you are lying down?

More sitting _____ About the same _____ More lying _____

- If more **sitting** – GO TO 7a
- If more **lying or about the same** – GO TO 8

7a. Would it be true to say that you have these feelings almost exclusively when you are sitting? That is, do these feelings occur 90% or more of the time they occur when you are sitting?

**Yes** **No**

7b. Do these feelings ever occur while you are lying down?

**Yes** **No**

8. Are these feelings in your legs **worse at night or in the evening** than other times of the day?

**Yes** **No**

* Note: Ask **8a only** if **8** is **NO** and symptoms are severe, daily, and consistent with RLS.

8a. Was there ever a time in your life when these feelings were worse at night than other times of the day?

**Yes** **No**

9. Approximately, how old were you when you first noticed these feelings in your legs?

_____ years old

10. Are you presently on medication for these feelings? **Yes** **No**

**If YES, go to 10a.**

**If NO, go to 11**

10a. Please respond to the following questions the way you think you would be if you were **not** on any treatment at this time.

10b. Please respond to the following questions for the period of time during which you had these feelings.

**** Note to interviewer:** Select tense appropriate to patient's symptoms: either present or past

11. How many days in the month do (did) you have these feelings? _____

11a. For how many years has it been occurring (did it occur) at least this frequently?

_____

11b. At what time of day do (did) these feelings **usually** start?

_____during sleep _____at bedtime

_____after 6 p.m., but before bedtime _____before 6 p.m. _____before noon

**Note to interviewer:** The answers to questions 13 and 14 should reflect the interviewer's judgment that the medications or medical problems detailed are at least possibly the cause of the RLS symptoms. Enough information should be entered to allow a reviewer to determine if this judgment is correct, especially the time course of the medication use or medical problem.

12. Are you aware of any medications or medical problems which might be causing (have caused) these feelings? (Answer YES indicates interviewer believes problem has caused RLS)

**Yes** **No**

12a. **(<u>If yes</u>)** What is the medication or medical problem?

_____

For all medical problems, identify when they started, before or after the feelings began, and whether they have continued while the feelings continued.

_____

_____

_____

13. Do the sensations in your legs disrupt your sleep or cause you to loss sleep?
**Yes** **No**

## Investigator Rated Global Impression – Global Improvement

1. Global Assessment of Effect (check one):

- 5 ☐ No effect
- 4 ☐ Mild effect
- 3 ☐ Moderate effect
- 2 ☐ Marked effect
- 1 ☐ Dramatic effect

2. Global Assessment of Improvement (check one):

- 7 ☐ Very much worse
- 6 ☐ Much worse
- 5 ☐ Minimally worse
- 4 ☐ No change
- 3 ☐ Minimal change
- 2 ☐ Much improved
- 1 ☐ Very much improved

Investigator Initials:_____

# International Restless Legs Syndrome Study Group Rating Scale (IRLS)

(Investigator Version 2.2)

Have the patient rate his/her symptoms for the following ten questions. The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions. The examiner should mark the patient's answers on the form.

In the past week…

(1) Overall, how would you rate the RLS discomfort in your legs or arms?

- [4] ☐ Very severe
- [3] ☐ Severe
- [2] ☐ Moderate
- [1] ☐ Mild
- [0] ☐ None

In the past week…

(2) Overall, how would you rate the need to move around because of your RLS symptoms?

- [4] ☐ Very severe
- [3] ☐ Severe
- [2] ☐ Moderate
- [1] ☐ Mild
- [0] ☐ None

In the past week…

(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?

- [4] ☐ No relief
- [3] ☐ Mild relief
- [2] ☐ Moderate relief
- [1] ☐ Either complete or almost complete relief
- [0] ☐ No RLS symptoms to be relieved

In the past week…

(4) How severe was your sleep disturbance due to your RLS symptoms?

- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week…

(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?

- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week…

(6) How severe was your RLS as a whole?

- [4]☐ Very severe
- [3]☐ Severe
- [2]☐ Moderate
- [1]☐ Mild
- [0]☐ None

In the past week…

(7) How often did you get RLS symptoms?

- [4]☐ Very often (This means 6 to 7 days a week)
- [3]☐ Often (This means 4 to 5 days a week)
- [2]☐ Sometimes (This means 2 to 3 days a week)
- [1]☐ Occasionally (This means 1 day a week)

[0]☐ Never

In the past week…

(8) When you had RLS symptoms, how severe were they on average?

[4]☐ Very severe (This means 8 hours or more per 24 hour day)

[3]☐ Severe (This means 3 to 8 hours per 24 hour day)

[2]☐ Moderate (This means 1 to 3 hours per 24 hour day)

[1]☐ Mild (This means less than 1 hour per 24 hour day)

[0]☐ None

In the past week…

(9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work life?

[4]☐ Very severe

[3]☐ Severe

[2]☐ Moderate

[1]☐ Mild

[0]☐ None

In the past week…

(10) How severe was your mood disturbance due to your RLS symptoms - for example angry, depressed, sad, anxious or irritable?

[4]☐ Very severe

[3]☐ Severe

[2]☐ Moderate

[1]☐ Mild

[0]☐ None

## Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes……..…1

16-30 minutes……..2

31-45 minutes……..3

46-60 minutes……..4

More than 60 minutes …….5

---

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number

of hours per night: ☐☐

---

**How often during the <u>past 4 weeks</u> did you…**

(Circle One Number On Each Line)

| | All of the Time ▼ | Most of the Time ▼ | A Good Bit of the Time ▼ | Some of the Time ▼ | A Little of the Time ▼ | None of the Time ▼ |
|---|---|---|---|---|---|---|
| 3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)? | 1 | 2 | 3 | 4 | 5 | 6 |
| 4. get enough sleep to feel rested upon waking in the morning? | 1 | 2 | 3 | 4 | 5 | 6 |
| 5. awaken short of breath or with a headache? | 1 | 2 | 3 | 4 | 5 | 6 |
| 6. feel drowsy or sleepy during the day? | 1 | 2 | 3 | 4 | 5 | 6 |
| 7. have trouble falling asleep? | 1 | 2 | 3 | 4 | 5 | 6 |
| 8. awaken during your sleep time and have trouble falling asleep again? | 1 | 2 | 3 | 4 | 5 | 6 |
| 9. have trouble staying awake during the day? | 1 | 2 | 3 | 4 | 5 | 6 |
| 10. snore during your sleep? | 1 | 2 | 3 | 4 | 5 | 6 |
| 11. take naps (5 minutes or longer) during the day? | 1 | 2 | 3 | 4 | 5 | 6 |
| 12. get the amount of sleep you needed? | 1 | 2 | 3 | 4 | 5 | 6 |



Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), <u>Measuring functioning and well-being: The Medical Outcomes Study approach</u> (pp. 235-259), Durham, NC: Duke University Press.

Pt NUM _____Date: _____ VISIT:

# Patient Global Impression

For the Past Week rate how much you feel your RLS symptoms have changed since you started the study

1 = Very much improved

2= Much improved

3 = Minimally improved

4 = No Change

5 = Minimally worse

6 = Much worse

7= Very much worse