# 2. SYNOPSIS

## Protocol No. 1VIT14037

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| **Name of the Company:** Luitpold Pharmaceuticals, Inc. | **Individual Study Table Referring to Part of the Dossier** | **For National Authority Use (only)** |
| **Name of the Finished Product:** Injectafer® | **Volume:** | |
| **Name of the Active Ingredient:** Ferric carboxymaltose | **Page:** | |

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

**Principal Investigator:** Thirty-seven investigators randomized subjects.
**Study Center:** This study was conducted at 20 study centers in the United States and 17 study centers in Europe.

**Publications:** None

**Study Period:** 05 November 2015 [First Subject Screened]
02 January 2018 [Last Subject Completed]

**Phase of Development:** 3

**Objective:** The primary objective of this study was to evaluate the efficacy and safety of an intravenous (IV) Injectafer® in subjects with RLS.

**Methodology**: This was a Phase 3, double-blind, multi-center, randomized, placebo-controlled study that evaluated the efficacy and safety of Injectafer® in subjects with RLS. Subjects who satisfied the inclusion criteria and none of the exclusion criteria were eligible for participation in this approximately 12-month study. All subjects were stratified by augmentation (no augmentation, uncertain augmentation, definitive augmentation). Subjects were randomized in a 1:1 ratio within each stratum to receive either Injectafer® or IV placebo on Days 0 and 5.

All treated subjects were followed for efficacy and safety for 12 months. Subjects visited the clinic on Days 0 and 5 for treatment, and then on Days 14, 42, 168, and 365. In between the clinic visits, subjects were contacted remotely (phone) on Days 28, 84, 126, 210, 252, 294, and 336. The subject's participation in the study was for 1 year from Day 0.

- Subjects received either a 750 mg undiluted blinded dose of IV Injectafer® at 100 mg/minute or a blinded IV Placebo (15 mL of normal sterile saline) IV push at 2 mL/min on Days 0 and 5.

Subjects who did not have an intervention received additional blinded study drug treatment at the discretion of the Investigator after Day 42. An intervention was defined as either 1) an increase in dosage from the RLS medication at study entry, 2) the initiation of a new RLS medication, 3) the resumption of the previous medication prescribed for RLS, or 4) an increase in dosage from the RLS medication achieved at the end of the tapering period. Each subject received the same blinded study drug that was previously assigned: either a single blinded dose of Injectafer® or placebo (dosing as detailed above) on 2 independent days separated by 5 days. Dosing was to mirror the original treatment/follow-up period (dosing 5 days apart with safety follow-up visits, including laboratory assessments only 14 and 42 days after the first dose). No subject assessments were completed unless the dosing or follow-up days fell on an assessment day in the follow-up period. Eligible subjects were to have met the following requirements prior to receiving additional treatment:

- International Restless Legs Syndrome (IRLS) score ≥15
- Transferrin saturation <45% (confirmation could have been through a local laboratory)
- Ferritin <300 ng/mL (confirmation could have been through a local laboratory)

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

**Number of Subjects:**

| | Injectafer® | Placebo (normal sterile saline) |
|---|---|---|
| Planned | 100 | 100 |
| Randomized | 105 | 104 |
| Safety Population[a,b] | 107 | 101 |
| Full Analysis Set Population | 105 | 103 |

a Two subjects who were randomized to placebo were administered Injectafer® and were counted in the Injectafer® group in the Safety Population.
b One subject did not receive study drug and was excluded from the Safety and Full Analysis Set Populations.

**Diagnosis and Main Criteria for Inclusion:** Male or female subjects ≥18 years of age with RLS symptoms affirming diagnosis, including a score ≥15 on the IRLS at screening and on Day 0 prior to dosing.

**Test Product:** Injectafer®

**Dose:** 750 mg on Day 0 and Day 5

**Mode of Administration:** Undiluted IV at 100 mg/minute

**Lot Numbers:** 403201, 512701

**Reference Therapy:** Placebo

**Dose:** 15 mL on Day 0 and Day 5

**Mode of Administration:** IV at 2 mL/min

**Lot Number:** Not available

**Duration of Treatment:** 2 single-day treatments (Days 0 and 5), with follow-up to Day 365

**Criteria for Evaluations:**

**Primary:** The co-primary efficacy variables were IRLS total score change from baseline to Day 42 and the proportion of subjects rated as much or very much improved per the Clinical Global Impression (CGI) performed by the Investigator (CGI-I) on Day 42.

**Secondary:** The major secondary efficacy endpoints in ranked order of testing included:

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

**Other**: Other efficacy endpoints that were tested included:

- Proportion of responders based on CGI-I/CGI-S at each time point
- IRLS, RLS-QLI, MOS Sleep Scale, and Fatigue Linear Analog Scale change from baseline at each time point
- CGI-I and CGI-S scores at each time point
- Augmentation assessment by Investigator change between baseline, Day 42, Day 168 and end of study (Day 365)
- Proportion of subjects requiring intervention for RLS
- Time from Day 5 to the next dose of study drug

**Safety:** Safety endpoints included:

- Incidence of treatment-emergent adverse events (TEAEs) and incidence of serious adverse events (SAEs)
- Laboratory assessments
- Vital signs
- Physical examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)

**Statistical Methods:**

**Efficacy Analysis:**

In general, continuous variables were summarized by number of subjects, mean, standard deviation, median, minimum, and maximum values. Categorical variables were summarized by number and percentage of subjects in each category. If applicable, hypothesis testing was carried out at the 2-sided $\alpha$=0.05 level unless otherwise specified; 2-sided 95% confidence intervals were presented, where specified. An interim analysis of efficacy took place after 200 subjects had completed Day 84.

Primary Endpoints

The actual values of IRLS total score on baseline and Day 42, and the change from baseline to Day 42 were summarized via descriptive statistics by treatment group. Treatment group difference for change in IRLS total score was assessed using analysis of covariance (ANCOVA), with region (United States [US], Europe [EUR]), baseline RLS medication-related augmentation, and treatment as fixed factors and baseline IRLS total score as a covariate. Missing values were imputed using Last Observation Carried Forward (LOCF).

Responders were defined as subjects rated as much or very much improved with the CGI-I on Day 42. The number (percentage) of CGI-I responders was summarized by treatment group. Treatment differences for proportions were assessed using logistic regression with treatment, region (US, EUR), and baseline RLS medication-related augmentation as fixed factors, and baseline IRLS total score as a covariate. Missing values were imputed using LOCF.

To assess the robustness of the primary efficacy analysis, sensitivity analyses were performed.

**Efficacy Analysis (Continued):**

A mixed model repeated measures (MMRM) model was conducted to provide an analysis under the assumption that data were missing at random. The MMRM model included changes in IRLS total score from baseline to Days 5, 28, and 42 as the dependent variables; baseline RLS medication-related augmentation, treatment group, visit, treatment group by visit interaction, and regions (US, EUR) as fixed effects; subjects within treatment group as random effects; and baseline IRLS total score as a covariate.

A logistic regression model was used to assess the treatment group difference as a proportion of subjects rated as much or very much improved with the CGI-I on Day 42. The model had treatment, region (US, EUR), and baseline RLS medication-related augmentation as fixed factors, and baseline IRLS total score as a covariate. If the Day 42 data were missing, no imputation was performed. Subjects with missing data were excluded from the statistical testing. The odds ratio for treatment comparison and associated 95% confidence intervals and p-values were presented.

The same logistic regression model as the primary analysis was used to assess the treatment group difference in proportion of subjects rated as much or very much improved with the CGI-I on Day 42.

The Cochran-Mantel-Haenszel (CMH) test was used to assess the treatment group differences as proportion of responders (i.e., subjects rated as much or very much improved) with the CGI-I on Day 42, using baseline RLS medication-related augmentation and region (US, EUR) as the stratification factors. Subjects with missing data were imputed as "non-responder."

The co-primary endpoints were summarized descriptively by region, baseline augmentation, sex, race, and age (<65 years, ≥65 years).

**Safety Analysis:**

Adverse events were coded by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. The verbatim term was included in the adverse event listings.

A TEAE was defined as an adverse event that occurred or worsened on or after the first dose of study drug. Only TEAEs were included in summary tables. All adverse events, treatment-emergent or otherwise, were presented in subject data listings.

The incidence of TEAEs was summarized as the number (percentage) of subjects with TEAEs within SOC and PT by treatment group. Subjects who reported the same PT on multiple occasions were counted once for the PT, under the highest severity (severe > moderate > mild) when summarized by severity and under the closest relationship (probably related > possibly related > unlikely related > none) to study drug/RLS treatment tapering when summarized by relationship. If a subject reported multiple PTs for an SOC, the subject was counted only once for that SOC. Treatment related adverse events were defined as those events recorded on the electronic case report form (eCRF) as 'probably related' or 'possibly related'; others were not related adverse events.

Laboratory assessments included hematology, clinical chemistry, iron indices, and phosphorus. All laboratory parameters were presented in conventional units. Quantitative results (including actual value, change from baseline to each smallest value after baseline, largest value after baseline, and end of study) were summarized using descriptive statistics by treatment for each laboratory test group. Laboratory test results were assigned a low (L), normal (N), or high (H) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Shifts from baseline to the smallest value after baseline, largest value after baseline, and end of study in LNH classification for each parameter in hematology and clinical chemistry were summarized by treatment group. The number and percentage of subjects with treatment-emergent potentially clinically significant (PCS) laboratory values at any time after baseline were summarized by treatment.

Vital signs included sitting body temperature, blood pressure, and heart rate. All vital signs were presented in standard units. Frequency and percentage of subjects with values considered PCS occurring at any time postbaseline in dosing days were summarized by visit (and time point) and by treatment.

The C-SSRS questionnaire was completed at Screening, Baseline, and Days 42, 168, and 365. The number (percentage) of subjects with a "yes" response was summarized and listed for each question and each visit by treatment group.

**Efficacy Results:**

Co-primary Endpoints

The co-primary efficacy endpoints in this study were change from baseline on Day 42 with respect to IRLS total score and proportion of responders (defined as subjects rated as much or very much improved) with the CGI-I on Day 42. Because statistical significance was not reached for the difference between the Injectafer® and placebo groups with respect to proportion of responders with the CGI-I on Day 42, the primary endpoint was not met in this study.

- Based on the LOCF, ANCOVA analysis, a statistically significant difference between the Injectafer® and placebo groups was observed for least squares (LS) mean change from baseline to Day 42 in the IRLS total score (-8.0 and -4.8, respectively, p=0.0043).
- Based on the LOCF, logistic regression analysis, no statistically significant difference between the Injectafer® and placebo groups was observed with respect to proportions of subjects achieving response based on the CGI-I on Day 42 (36.2% and 28.2%, respectively, p=0.2162).

Secondary Endpoints

The major secondary efficacy endpoints were tested in a hierarchical order; that is, statistical significance for major secondary efficacy endpoints was to be declared only if the co-primary efficacy tests (IRLS and CGI-I Day 42) were statistically significant. Because statistical significance was not reached for 1 of the co-primary endpoints (CGI-I responder rate on Day 42), statistical significance for secondary endpoints (CGI-S scores on Day 42; RLS-QLI, MOS Sleep Scale, Fatigue Linear Analog Scale change from baseline to Day 42; time off pre-enrollment prescribed RLS medications) was not declared.

**Safety Results:**

During the study, at least 1 TEAE was experienced by 67.3% of the subjects in the Injectafer® group and 40.6% of the subjects in the placebo group. The most common TEAEs were nausea (10 subjects [9.3%]), hypophosphatemia (8 subjects [7.5%]), and dizziness (8 subjects [7.5%]) in the Injectafer® group and headache (6 subjects [5.9%]) in the placebo group.

Thirty-seven subjects (34.6%) in the Injectafer® group and 7 subjects (6.9%) in the placebo group experienced at least 1 TEAE considered to be related to study drug. Nausea (7 subjects [6.5%]), feeling hot (6 subjects [5.6%]), and hypophosphatemia (6 subjects [5.6%]) were the most common TEAEs considered related to study drug in the Injectafer® group; headache (3 subjects [3.0%]) was the most common TEAE considered related to study drug in the placebo group.

One subject (0.9%) in the Injectafer® group died during the study. This subject experienced an SAE of colon cancer stage IV that led to death and was unrelated to study drug.

A similar percentage of subjects in the Injectafer® and placebo groups experienced SAEs (5.6% and 4.0%, respectively). One subject in the Injectafer® group experienced an SAE of hypophosphatemia that was considered to be probably related to study drug.

One subject (0.9%) in the Injectafer® group experienced TEAEs of blood pressure increased, feeling hot, and tinnitus that led to discontinuation of study drug and were considered probably related to study drug. One subject (0.9%) in the Injectafer® group experienced an SAE of colon cancer stage IV that led to discontinuation from the study, was considered to be not related to study drug, and not related to tapering of RLS treatment. One subject (1.0%) in the placebo group experienced an SAE of hemorrhagic stroke that led to discontinuation from the study and was considered to be not related to study drug and not related to tapering of RLS treatment.

Four subjects (3.7%) in the Injectafer® group experienced RLS treatment tapering-related TEAEs of lethargy, neuropathy peripheral, muscle spasms, and insomnia (1 subject [0.9%] each), and 2 subjects (2.0%) in the placebo group experienced RLS treatment tapering-related TEAEs of pain in extremity and fall (1 subject [1.0%] each).

The majority of subjects with TEAEs had events that were mild or moderate in severity. A greater percentage of subjects in the Injectafer® group (20.6%) experienced severe TEAEs compared with the placebo group (8.9%). The most common severe TEAEs experienced by subjects in the Injectafer® group were hypophosphatemia (6.5%) and blood phosphorus decreased (2.8%). Severe TEAEs experienced by subjects in the placebo group were reported by 1 subject (1.0%) each.

Fourteen subjects (13.1%) in the Injectafer® group and 4 subjects (4.0%) in the placebo group experienced treatment-emergent hypersensitivity reactions. The most common treatment-emergent hypersensitivity reaction experienced by subjects in the Injectafer® group was flushing (6 subjects [5.6%]) and in the placebo group was pruritis (2 subjects [2.0%]).

Seventy-five subjects (76.5%) in the Injectafer® group and 1 subject (1.0%) in the placebo group had a PCS low phosphorus value. Among subjects in the Injectafer® group who had a normal phosphorus value at baseline, the mean number of days from baseline to first PCS phosphorus value was similar among subjects with grade 2 (19.9 days), grade 3 (20.0 days), and grade 4 (25.4 days) PCS phosphorus values. The mean number of days to return to normal phosphorus values increased with increasing grade: 55.2 days (grade 2), 115.9 days (grade 3), and 124.1 days (grade 4).

No clinically important safety findings were observed with respect to vital signs or the C-SSRS questionnaire responses.

**Conclusions:**

The co-primary efficacy endpoints in this study were change from baseline on Day 42 with respect to IRLS total score and proportion of responders (defined as subjects rated as much or very much improved) with the CGI-I on Day 42. Because statistical significance was not reached for the difference between the Injectafer® and placebo groups with respect to proportion of responders with the CGI-I on Day 42, the primary endpoint was not met in this study. Injectafer® and placebo had generally similar safety profiles except for substantially more PCS low phosphorous values in the Injectafer® treatment group compared with the placebo treatment group.