1. STUDY SYNOPSIS

Protocol No. 1VIT13036

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: Ferric carboxymaltose	**Volume:**	
Name of the Active Ingredient: Ferric carboxymaltose	**Page:**	

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

Principal Investigator: Ten principal investigators enrolled subjects.
Study Center: This study was conducted at 8 sites in Poland and 2 sites in Russia.

Publications: None

Study Period: 19 February 2015 [First Subject Screened]
22 January 2017 [Last Subject Completed]

Phase of Development: 2

Objective: The primary objectives of this study were to characterize the pharmacokinetics and determine appropriate dosing and safety of ferric carboxymaltose [FCM] for the pediatric population suffering from iron-deficiency with anemia.

Methodology: This is a Phase II, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamics profile of FCM dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of FCM. Eligible subjects were enrolled sequentially in Cohort 1 (FCM at 7.5 mg/kg with a maximum single dose of 750 mg) and Cohort 2 (FCM at 15 mg/kg with a maximum single dose of 750 mg). Subjects visited the clinic on Day 0 for treatment; all treated subjects were followed for safety for 35 days. Pharmacokinetic and pharmacodynamics parameters were assessed prior to dosing and at 1, 2, 6, 12, 24, 48, and 72 hours post-dose. The subject's duration of participation in the study was for approximately 35 Days from Day 0.

Number of Subjects:

	Cohort 1	Cohort 2
Planned	16	16
Enrolled	16	19
Treated	16	19
Safety Population	16	19
Pharmacokinetic and Pharmacodynamic Population	16	19

Diagnosis and Main Criteria for Inclusion: Male or female subjects 1 to 17 years of age (6 to 17 years of age in Russia only) who gave written Informed Consent/Assent along with parent or guardian's written Informed Consent with a diagnosis of IDA who had a screening transferrin saturation (TSAT) <20% and a screening hemoglobin of <11 g/dL. For subjects who were receiving an erythropoietin stimulating agent (ESA), a stable dose was required for >8 weeks prior to screening. The ESA type, route, frequency, and dose were to remain unchanged throughout the study.

Test Product: FCM
Dose: 7.5 mg/kg or 15 mg/kg (to a maximum of 750 mg) was administered on Day 0.
Mode of Administration: Undiluted intravenous at 100 mg/minute
Batch Number: 320111B
Duration of Treatment: 1-day Treatment Phase with follow-up to Day 35.

Criteria for Evaluations:
Primary: The primary efficacy variable was the change from baseline to each scheduled visit for hemoglobin, ferritin, and TSAT.
Safety: Safety endpoints included:

- Proportion of subjects reporting treatment-emergent adverse events, overall and related, by system organ class and preferred term
- Subjects reporting treatment-emergent serious adverse events, overall and related
- Mean change from baseline to each scheduled visit for clinical laboratory values
- Incidence of treatment-emergent potentially clinically significant (PCS) clinical laboratory values
- Vital signs were summarized for dosing day, each visit, and each treatment group. The change in vital signs from baseline to each scheduled visit was summarized for each treatment group and stratified by age groups: 1 - <6 years and 6 to 17 years

Statistical Methods: The safety population included all subjects who received FCM. All safety analyses were performed with the Safety Population.
The Pharmacokinetics and Pharmacodynamics Population included all subjects in the Safety Population who had evaluable iron profiles and no protocol violation that could affect the Pharmacokinetics and Pharmacodynamics of FCM. All efficacy analyses were performed with the Pharmacokinetics and Pharmacodynamics Population.

Efficacy Analysis: Hemoglobin, ferritin, and TSAT levels were summarized for each visit, and for each treatment group. In addition, the change from baseline to each visit was summarized for each treatment group.

Safety Analysis: No formal hypothesis testing was planned for this study. Only descriptive, summary statistics were planned for assessment of dosing and safety.
Medical/surgical histories were summarized separately for the treatment groups. Body system and condition/surgery were coded with the Medical Dictionary for Regulatory Activities terminology.
The adverse event profile was characterized with severity as graded by Version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events and relationship to study drug. Relationship to study drug was categorized as related (possibly or probably related) and unrelated (none or unlikely). Adverse events with unknown severity or relationship were counted as unknown.
Subjects who reported the same preferred term on multiple occasions were 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 reported multiple preferred terms for a system organ class, the subject was counted only once for that system organ class.
Changes in clinical laboratory findings and vital signs from baseline to each scheduled study visit were summarized descriptively with the mean, median, standard deviation, minimum value, and maximum value. The number and percentage of subjects with PCS clinical laboratory values and vital signs were summarized for each treatment group.
Treatment-emergent PCS laboratory tests were defined as those tests for which the baseline value was normal and the post-baseline value was abnormal (i.e., met Grade 3 or Grade 4 toxicity criteria from the National Cancer Institute Common Terminology Criteria for Adverse Events). Subjects with PCS values were identified.. Vital signs were summarized for dosing day, each visit, and each treatment group. The change in vital signs from baseline to each scheduled visit was summarized for each treatment group and stratified by age groups: 1 - <6 years and 6 to 17 years.

SUMMARY – CONCLUSIONS

Efficacy Results:

Key efficacy conclusions include:

- Clinically important mean increases in hemoglobin from baseline to Day 35 were observed in both cohorts. The mean increase from baseline to Day 35 was larger in Cohort 2 (2.8 g/dL) than Cohort 1 (1.9 mg/kg). Hemoglobin values peaked on Day 35 for both cohorts.
- For both cohorts, when compared to the respective mean screening values, the mean ferritin and TSAT values were increased at 72 hours post-dose, Day 14, Day 28, and Day 35 and peaked at 72 hours post-dose; mean changes in ferritin and TSAT were consistently greater in Cohort 2 compared with Cohort 1 during the study.

Safety Results:

During the study, at least 1 treatment-emergent adverse event was experienced by 56.3% of subjects in Cohort 1 and 63.2% of subjects in Cohort 2. The most common treatment-emergent adverse events were pyrexia and rash (2 subjects each [12.5%]) in Cohort 1 and rhinorrhea and urticaria (3 subjects each [15.8%]) and hyperthermia and upper respiratory tract infection (2 subjects each [10.5%]) in Cohort 2.
Three subjects (18.8%) in Cohort 1 and 6 subjects (31.6%) in Cohort 2 experienced treatment-emergent adverse events considered related to study drug. The only treatment-emergent adverse event considered related to study drug that was experienced by >1 subject was urticaria (3 subjects [15.8%] in Cohort 2).
The majority of subjects who had treatment-emergent adverse events had events that were Grade 1 or Grade 2 in severity.
No subject died during this study.
Two subjects in Cohort 1 experienced serious treatment-emergent adverse events (1 subject with upper respiratory tract infection [Grade 2] and 1 subject with sinusitis [Grade 3]). The events were not considered to be related to study drug.
All subjects received the planned single dose of FCM; therefore, there were no reports of treatment-emergent adverse events leading to discontinuation of FCM. None of the subjects discontinued from the study.
No subject had a PCS laboratory value.
Mean changes from pre-treatment sitting systolic and diastolic blood pressure were greater in Cohort 1 compared to Cohort 2 immediately post-treatment and at 30 minutes post-treatment. These mean changes were larger in subjects aged 1 to <6 years compared to mean changes for subjects aged 6 to 17 years. No consistent dose relationships across age groups in blood pressure and heart rate were observed.

Conclusions:

In conclusion, clinically important mean increases in hemoglobin from baseline to Day 35 were dose-related. Treatment of IDA with FCM was also associated with dose-related mean increases in ferritin and TSAT values. Ferric carboxymaltose was generally well-tolerated at both dose levels with similar adverse event profiles in both cohorts.