CLINICAL REVIEW

Application Type	sNDA
Application Number	203565/S-016
Priority or Standard	Standard
Submit Date	January 29, 2021
Received Date	January 29, 2021
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Division/Office	DNH/OCHEN
Reviewer Name	Clinical: Hyon-Zu Lee, PharmD (Reviewer) Tanya Wroblewski, MD (Team Leader) Statistical: Lola Luo, PhD (Statistics) Yeh-Fong Chen, PhD (Team Leader) Thomas Gwise, PhD (Division Director)
Review Completion Date	See stamped date
Established/Proper Name	Ferric carboxymaltose injection
Trade Name	Injectafer
Applicant	American Regent, Inc.
Dosage Form	Injection
Applicant Proposed Dosing Regimen	No new dosing regimen is proposed.
Applicant Proposed Indications/Populations	For the treatment of iron deficiency anemia in pediatric patients ages 1 to 17 years: • who have intolerance to oral iron or have had unsatisfactory response to oral iron, or (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	For the treatment of iron deficiency anemia in pediatric patients ages 1 to 17 years: • who have intolerance to oral iron or have had unsatisfactory response to oral iron.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FCM	Ferric carboxymaltose
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Injectafer [ferric carboxymaltose (FCM) injection] is an iron replacement product approved in 2013 for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron; or who have non-dialysis dependent chronic kidney disease. Injectafer solution for intravenous use is currently available as 750 mg iron (as ferric carboxymaltose) in 15 ml; and 1000 mg iron in 20 ml single-dose vials.

The recommended dose regimen for adult patients weighing 50 kg (110 lb) or more is two doses of Injectafer 750 mg separated by at least 7 days for a total cumulative dose of 1500 mg of iron per course or alternatively, 15 mg/kg to a maximum of 1000 mg as a single dose. For adult patients weighing less than 50 kg (110 lb), the recommended dose regimen is two doses of Injectafer 15 mg/kg body weight separated by at least 7 days for a cumulative dose not to exceed (b) (4) mg of iron. Injectafer treatment may be repeated if iron deficiency anemia recurs. Injectafer is recommended to be administered either as an undiluted slow intravenous push (at a rate of approximately 100 mg per minute) or by infusion (over at least 15 minutes).

The current supplement proposes to expand the adult indication of Injectafer to pediatric patients ages 1 to 17 years.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sNDA contained primary safety and efficacy data from one randomized, active-controlled clinical study (1VIT17044) that compared Injectafer to oral iron (ferrous sulfate) in pediatric patients with iron deficiency anemia (IDA) who had inadequate response to any oral iron therapy; and a supportive single-arm, extension study (1VIT18045) that enrolled patients who had an unsatisfactory response to oral iron in study 1VIT17044. Study 1VIT17044 enrolled a total of 79 patients (Injectafer: 40 patients, ferrous sulfate: 39 patients); and study 1VIT18045 enrolled a total of 7 patients. In both studies, patients with IDA who had chronic kidney disease (CKD) were not enrolled.

In study 1VIT17044, the primary efficacy endpoint was the change in hemoglobin from baseline to Day 35. Study 1VIT17044 failed to demonstrate the superiority of Injectafer to oral iron. The least square mean change in hemoglobin from baseline to Day 35 (ANCOVA analysis, using the LOCF algorithm) was 2.2 g/dL (95% CI: 1.7, 2.8) in the Injectafer arm and 1.9 g/dL (95% CI: 1.4, 2.4) in the ferrous sulfate arm. The treatment difference at Day 35 (Injectafer minus ferrous sulfate) was 0.3 g/dL (95% CI: -0.3, 0.9), was not statistically significant (p = 0.3108).

Possible reasons for the failure to demonstrate the statistical significance of the primary

efficacy endpoint in the pediatric study (1VIT17044) include underestimation of the patient's tolerance to oral iron in the control arm or possibly failure to enroll sufficiently large number of patients. Ultimately, the failure of study 1VIT17044 could be attributed to inadequate statistical design. Although the study failed the primary endpoint, the course of iron deficiency anemia in a pediatric population is similar to IDA in an adult population.

The approval of Injectafer in adult patients with IDA in the non-CKD patient population was based on a randomized, active-controlled pivotal trial (study 1VIT09031) that evaluated the efficacy and safety of Injectafer in patients with IDA who had an unsatisfactory response to oral iron (Cohort 1) or who were intolerant to oral iron (Cohort 2). In Cohort 1, patients were randomized to Injectafer or oral iron; and in Cohort 2, to Injectafer or another IV iron per standard of care (SC). In Cohorts 1 and 2, a total of 495 patients (Injectafer: 244 patients, oral iron: 251 patients) and 482 patients (Injectafer: 245 patients, IV SC: 237 patients) were enrolled, respectively. In Cohort 1, the estimated difference in the mean change in hemoglobin from baseline and Day 35 (or time of intervention) between Injectafer and oral iron was 0.76 g/dL (95% CI: 0.59, 0.93) ($p<0.0001$). In Cohort 2, the estimated mean difference in hemoglobin between Injectafer and IV SC from baseline and Day 35 was 0.81 g/dL (95% CI: 0.61, 1.00) ($p<0.0001$). For further information regarding the efficacy results of study 1VIT09031, please refer the clinical review by Dr. Min Lu, dated June 6, 2012 and statistical review by Dr. Kyung Lee, dated June 28, 2012.

A pediatric indication statement may be based on adequate and well-controlled studies in adults provided that the Agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The extrapolation of efficacy is based on the following evidence-based assumptions:

1) The course of the disease in iron deficiency anemia is sufficiently similar in adults and children as the clinical and symptom markers (iron markers, ferritin, TSAT and hemoglobin, hematocrit) are the same for diagnosis for adults and pediatric patients. The continuity of the disease also spans across all ages.
2) The response to treatment for patients with IDA who are intolerant to oral iron or have unsatisfactory response to oral iron is sufficiently similar in adults and children as the same signs and symptoms are used for diagnosis and response assessment.
3) Adults and children have sufficiently similar exposure-response relationship and the pediatric dose to match the exposure can be determined. This was based on the results of Study 1VIT13036 (single arm study to characterize the PK and PD profile of IV FCM in pediatric subjects 1-17 years old with IDA), study reports from 1VIT17044, 1VIT18045, population PK/PD modelling of intravenous FCM in pediatric subjects with IDA and independent analysis to compare the PK and PD of pediatric subjects with that of adults conducted by the clinical pharmacology team. Please refer to the review Guoxian Shen, Ph.D. and Gene Williams Ph.D. from January 4, 2018, reviews by Christy John 5/30/2007

(NDA#22054), Bahru Habtemariam 6/21/2021 (NDA #203565 and Eliford Kitabi 04/23/2021 (NDA 203565,S-14) and Sudharshan Hariharan and Eliford Kitabi 10/29/2021 in DARRTs. .

4) The adult study, 1VIT09031, established the efficacy in adults based on change in hemoglobin from baseline and the efficacy from the adult population can be extrapolated to the pediatric population for IDA who are intolerant or have had an insufficient response to oral iron.

The Pediatric Research Equity Act (PREA) allows for extrapolation of efficacy data from adult population to pediatric population. Overall, the requirements for extrapolation of efficacy have been met. Study 1VIT17044 also fulfills PMR 2064-2.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

The benefit-risk assessment supports regular approval of Injectafer in pediatric patients (1 to 17 years of age) for the treatment of IDA who have intolerance to oral iron or have had unsatisfactory response to oral iron.

The efficacy evaluation of Injectafer for this indication was extrapolated from an adequate and well-controlled study in adults (i.e., study 1VIT09031), as described in Section 1.2. Conclusions on the Substantial Evidence of Effectiveness above.

The safety review was primarily based on a total of 78 pediatric patients (Injectafer: 40 patients, ferrous sulfate: 38 patients) who participated in study 1VIT17044. Patients in the Injectafer arm received 15 mg/kg to a maximum dose of 750 mg (whichever is smaller) on Days 0 and 7 for a maximum total dose of 1500 mg; and patients in the oral iron (ferrous sulfate) arm received age-dependent formulation and doses of oral ferrous sulfate daily for 28 days. The overall median total dose of Injectafer was 1500 mg (range: 0.5, 1500) [1 to <12 years: 672 mg (range: 264, 1500), 12 to ≤ 17: 1500 mg (range: 0.5, 1500). No deaths or SAEs were reported. A total of 3 patients (7.5%) in the Injectafer arm and none in the ferrous sulfate arm experienced grade 3 TEAEs. No grade 4 TEAEs were reported. The incidence of TEAEs was higher in the Injectafer arm compared to the ferrous sulfate arm (Injectafer: 35.0%, ferrous sulfate: 26.3%). In study 1VIT17044, the most frequently reported TEAEs (> 5%) in the Injectafer arm were hypophosphatemia, local administration reactions and rash. In study 1VIT18045, no deaths, SAEs, TEAEs or discontinuations due to TEAEs were reported.

Overall, the safety profile of Injectafer in the pediatric population was consistent with the current prescribing information. No new safety signals were observed. The benefit-risk assessment of Injectafer in pediatric patients (1 to 17 years of age) for the treatment of IDA who have intolerance to oral iron or have had unsatisfactory response to oral iron is favorable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Iron deficiency is the most common cause of anemia in children in the US. • Clinical findings of IDA in pediatric patients include pale skin, irritability, fatigue, tachycardia, cardiomegaly, pica in addition to	IDA may cause serious complications. Repletion with oral or IV iron is recommended for patients with IDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mood and neurocognitive disorders.	
Current Treatment Options	• INFeD, Dexferrum (iron dextran) • Ferrlecit (sodium ferric gluconate complex) • Venofer (iron sucrose)	Multiple IV therapies exist for the treatment of IDA in pediatric patients. However, currently only iron dextran is indicated for pediatric patients with IDA in whom oral iron administration is unsatisfactory or impossible. Injectafer provides an alternative treatment option.
Benefit	• Injectafer was approved for the treatment of adult patients with IDA who have intolerance to oral iron or have had unsatisfactory response to oral iron on July 25, 2013. • Efficacy was established in adults based on change from baseline in hemoglobin and iron parameters • The efficacy of Injectafer in pediatric patients (1 to 17 years of age) for the treatment of IDA who have intolerance to oral iron or have had unsatisfactory response to oral iron was extrapolated from an adequate and well-controlled study in adults.	Efficacy of Injectafer treatment is measured by improvement in hemoglobin and iron markers. The pediatric indication statement is based on adequate and well-controlled studies in adults and the Agency's conclusion that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients.
Risk and Risk Management	• The toxicities of Injectafer listed in the current Warnings and Precautions section of the prescribing information are hypersensitivity reactions, symptomatic hypophosphatemia and hypertension. No new safety signals were observed in the pediatric patients.	The risks of Injectafer in pediatric patients are manageable with adequate monitoring and recommendations in the label. No new concerning signals have emerged.

1.4. Patient Experience Data

Patient experience data was not included in this application.

2. Therapeutic Context

2.1. Analysis of Condition

Iron deficiency is the most common cause of anemia in children in the US. Common causes of iron deficiency in children include insufficient dietary intake with rapid growth, poor absorption due to abnormalities in the gastrointestinal tract and blood loss. Clinical findings of iron deficiency anemia in pediatric patients include pale skin, irritability, fatigue, tachycardia, cardiomegaly, pica in addition to mood and neurocognitive disorders (Özdemir 2015). Management of IDA in this patient population include investigation and elimination of the cause leading to iron deficiency, improvement of nutrition, education, and replacement with oral or IV iron therapy. Oral iron is the preferred treatment. However, there are certain conditions in which IV iron may be preferable, such as intolerance/refractoriness to oral iron; severe anemia (Hb< 7-8 g/dL); chronic blood loss difficult to manage with oral iron; use of erythropoiesis-stimulating agents in chronic kidney disease; anatomic or physiologic condition that interferes with oral iron absorption; or coexisting inflammatory state that interferes with iron homeostasis (Auerbach et al. 2016; Camaschella 2015; Rohrig et al. 2014). Intravenous iron products that are available in pediatric patients are summarized in Table 1. Availability of another IV iron product that can be safely administered in pediatric patients who need this option may be useful.

2.2. Analysis of Current Treatment Options

Currently available IV iron products for pediatric patients include INFeD, Ferrlecit and Venofer as summarized in the table below. Ferlecit and Venofer are indicated in pediatric patients with IDA and CKD; only iron dextran is indicated for pediatric patients with IDA in whom oral iron administration is unsatisfactory or impossible.

Table 1 Available Intravenous Iron Products in Pediatric Patients

Chemical name	INFeD, Dexferrum (iron dextran)	Ferrlecit (sodium ferric gluconate complex)	Venofer (iron sucrose)
Year of approval	1974	1999	2000
Indication	Documented iron deficiency in patients in whom oral	Iron deficiency anemia in adult patients and in	Iron deficiency anemia in patients with chronic

Chemical name	INFeD, Dexferrum (iron dextran)	Ferrlecit (sodium ferric gluconate complex)	Venofer (iron sucrose)
	iron administration is unsatisfactory or impossible	pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy	kidney disease
Safety	Box Warning for anaphylactic-type reactions	Warnings for hypersensitivity reactions	Warnings for hypersensitivity reactions
Population	Adults and pediatrics (>4 months of age)	Adults and pediatrics	Adults and pediatrics
Elemental iron per mL	50 mg/mL	12.5 mg/mL	20 mg/mL
Dose regimen	100 mg (2mL) may be given on a daily basis until the calculated total amount required has been reached. It is given undiluted at a slow gradual rate not to exceed 50 mg per minute. -Adults and Children over 15 kg (33 lbs): Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × LBW (kg) + (0.26 ×LBW) -Children 5-15 kg (11-33 lbs): Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × W (kg) + (0.26 ×W) Each mL contains 50 mg of elemental iron. -A test dose (0.5 mL) is required before the dosing.	Hemodialysis -Adult: 125 mg of elemental iron IV by slow injection (rate of up to 12.5mg/min) or infusion over 1 hour for a total cumulative total dose of 1000 mg over 8 sequential sessions dialysis. -Pediatrics: 0.12 mL/kg (1.5 mg/kg of elemental iron) diluted in 25 mL 0.9% sodium chloride and administered by IV infusion over 1 hour per dialysis session.	-Adult: Hemodialysis: 100 mg as slow IV injection or an infusion diluted in a 100mL of 0.9% NaCl over at least 15 minutes over 10 consecutive dialysis session for a total cumulative dose of 1,000 mg. Non-Dialysis Dependent CKD: 200 mg as slow IV injection or infusion on 5 occasions within the 14-day period for a total cumulative dose of 1,000 mg. There is limited experience with administration of an infusion of 500 mg diluted in 250 mL of 0.9% NaCl over a period of 3.5-4 hours on day 1 and day 14. Peritoneal Dialysis: 2 infusions of 300 mg over 1.5 hours 14 days apart followed by one

Chemical name	INFeD, Dexferrum (iron dextran)	Ferrlecit (sodium ferric gluconate complex)	Venofer (iron sucrose)
			400 mg infusion over 2.5 hours 14 days later for a total cumulative dose of 1,000 mg within a 28-day period. -Pediatrics (≥ 2 years): Hemodialysis for iron maintenance: 0.5 mg/kg (not to exceed 100 mg per dose), every two wks for 12 wks given undiluted by slow IV injection or infusion. Non-Dialysis or peritoneal dialysis dependent CKD who are on EPO for iron maintenance: 0.5 mg/kg (not to exceed 100 mg per dose), every 4 wks for 12 wks given undiluted by slow IV injection or infusion. - Treatment may be repeated if necessary. -The dosing for iron replacement treatment in pediatric patients with HDD-CKD, NDD-CKD or PDD-CKD has not been established.

[Source: FDA compilation]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Injectafer was initially submitted by the trade name "Ferinject" (NDA 22054) on June 15, 2006. The proposed dose regimen was maximum single dose not to exceed 15 mg/kg per dose or 1000 mg as injection administered weekly with a maximum total cumulative dose of 2500 mg.

On July 9, 2007, a "Not Approvable Letter" was issued because the clinical data indicated that the proposed Ferinject dose regimen was accompanied with an unacceptable risk for death, serious adverse reactions and clinically important hypophosphatemia.

On September 12, 2007, the Applicant submitted a Complete Response (second cycle to NDA 22054) and the trade name was revised to "Injectafer" (which was accepted by FDA as an alternative to Ferinject). The proposed dose regimen was unchanged (1000 mg as a single maximum dose weekly until administration of the total calculated iron requirement or a maximum total cumulative dose of 2,500 mg is reached). The Agency issued a "Not Approvable Letter" on March 11, 2008 stating that the proposed dosage regimen may deliver an excessive iron dose during a single administration and recommended that the sponsor consider the development of an alternate dosage regimen that delivers a lower (single dose) amount of iron.

On September 30, 2011, the Applicant provided a response (third cycle) to the Complete Response letter dated March 11, 2008. The application was submitted as a new NDA (203565). The proposed dose regimen was revised to Injecftafer 15 mg/kg with the maximum individual dose of 750 mg and a total maximum cumulative dose of 1,500 mg over two infusions. A Complete Response letter was issued on July 23, 2012 due to deficiencies in manufacturing facility.

On January 30, 2013, the Applicant submitted a complete response (fourth cycle) to the July 23, 2012 action letter. Injectafer was granted approval on July 25, 2013 for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron; or who have non-dialysis dependent chronic kidney disease. The following pediatric postmarketing studies were required:

PMR 2064-1: Identify an optimal dose of Injectafer (ferric carboxymaltose injection) for the pediatric patient population. Conduct one or more pharmacokinetic (PK) and pharmacodynamic (PD) trials in pediatric patients aged 1 to <17 years with iron deficiency anemia sufficient to justify and to characterize the dose to be tested in a confirmatory clinical trial of safety and efficacy. Identify the most relevant PD endpoints to measure.

Final Protocol Submission: 07/2014
Trial Completion: 07/2016
Final Report Submission: 07/2017

PMR 2064-2 Determine the safety and efficacy of Injectafer (ferric carboxymaltose injection) in pediatric patients aged 1 to <17 years with iron deficiency anemia by conducting a randomized, active-controlled clinical trial.

Final Protocol Submission: 01/2017
Trial Completion: 01/2020
Final Report Submission: 01/2021

In 2018, the Applicant fulfilled PMR 2064-1 based on completed study 1VIT13036, a phase 2, open-label, non-randomized, multi-center, single arm study to characterize the pharmacokinetic and pharmacodynamic profile of FCM dosing in pediatric subjects with IDA after receiving either a 7.5 mg/kg or 15 mg/kg dose of FCM.

On August 25, 2020, an inadequate proposed pediatric study request (PPSR) letter was issued for the indication of IDA. The letter stated that the Applicant resubmit the PPSR requesting the following issues:

1. Although you amended Protocol 1VIT17044 to include pediatric patients with iron deficiency anemia and chronic kidney disease on hemodialysis, you have not provided information to demonstrate that the study accomplished sufficient enrollment of these patients (based on prevalence in the pediatric population) to address use of ferric carboxymaltose in this disease population. You should provide the underlying cause for the IDA in the enrolled subjects and rationale to support adequacy of the data from the patients studied to support assessment of use of ferric carboxymaltose in pediatric patients with iron deficiency anemia and chronic kidney disease on hemodialysis.

2. In your proposed Protocol 1VIT19046 pharmacokinetics/pharmacodynamics and safety study in pediatric patients age full-term to 12 months you have not provided sufficient data to support your proposed dosing for pediatric patients full-term to 3 months of age. While we agree that a study in the patient population age full-term to 12 months as you propose is appropriate, we do not find sufficient support for the dosing you propose for patients age full-term to <3 months. Typically dosing for infants is based upon pharmacokinetic (PK) and safety results in older pediatric populations.

The Applicant submitted the current submission (S-016) to provide the final clinical study report for studies associated with PMR 2064-2 and close out this PMR.

3.2. Summary of Presubmission/Submission Regulatory Activity

There were no pre-submission meetings or communications with regard to the current sNDA.

3.3. Foreign Regulatory Actions and Marketing History

Ferric carboxymaltose (FCM) was approved in Europe in 2007 for adults and pediatric patients ≥ 14 years of age. The trade name of FCM in Europe is “Ferinject”. It has also been reported that FCM is marketed in 75 countries, mainly “for treatment of iron deficiency when oral iron preparations are ineffective, cannot be used or there is a clinical need to deliver iron rapidly”.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Study 1VIT10744 is the pivotal trial in the current sNDA. Two clinical sites in the US were chosen for OSI inspections. The site selections were based on enrollment of large number of patients.

Table 2 Requested OSI Clinical Site Audits for the 1VIT17044 Trial

Site ID	Number of enrolled patients	Name of the PI	Location
207	18	Dihloren Peralta-Lee	South Florida Research Phase I-IV 4487 NW 36 Street, Miami Springs, FL 33166
225	11	Keila Hoover	Miami Clinical Research 7371 SW 24th Street, Miami FL 33155

The OSI inspection included review of IRB documentation, subject records, financial disclosures, investigational product controls, study monitoring, and validation of the data. The inspection involved review of all relevant records, such as informed consents, protocol and study protocol amendments, signed investigator agreements, IRB submissions and correspondence, clinical source data, concomitant (non-study) medications adverse event reporting, study test article accountability, and relevant study patient data listings including study endpoints.

Source records were evaluated for the study subjects randomized. The primary efficacy endpoint data were verified against the data line listings. No discrepancies in the study endpoint data were noted. There was no under-reporting of serious adverse events.

With regard to site #207, FDA noted that subjects (b) (6) did not have a recorded body weight for the Day 0 study visit. The previous P.I. (Maria Jaime, M.D.), enrolled majority of the study participants, before Dihloren Peralta-Lee, M.D. resumed the role as the current site principal lead (as of March 2020).

Review comment: The submission contained baseline weight for all 18 subjects enrolled at this site in the ADSL.xpt dataset.

With regard to site # 225, five out of eleven study subjects' documented history, of an inadequate response to any oral iron therapy were not documented adequately, until after the screening visit calendar date, according to the study protocol inclusion criteria #4. Specifically, the following study patients did not have fully recorded subject screening information at the

outset: (b) (6).

Review comment: The submission contained prior oral iron response information for all enrolled 11 subjects at this site in the ADSL.xpt dataset.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

OSI's overall assessment of findings and general recommendations for these sites were as follows:

> Two clinical investigator sites, Dihloren Peralta-Lee, M.D. and Keila Hoover, M.D., were inspected in support of NDA 203565 S-016.
>
> Based on these inspections, the conduct of the above pediatric studies appears to be adequate. The post-marketing requirement study data derived from the Dihloren Peralta-Lee, M.D. and Keila Hoover, M.D. clinical investigator sites are considered reliable.

This reviewer concludes that the overall compliance with GCP is acceptable.

For specifics regarding the OSI inspection, refer to the OSI review by Dr. Anthony Orencia, dated September 29, 2021.

4.2. Product Quality

No new information was provided.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Nonclinical Pharmacology/Toxicology

No new information was provided.

4.5. Clinical Pharmacology

Refer to Clinical Pharmacology review. See review by Anusha Ande, Jiajun Liu, Eliford Kitabi and Sudharshan Hariharan dated October 28, 2021.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The supplement contained an active-controlled clinical study (1VIT17044) and an extension study (1VIT18045).

Table 3 Clinical Studies Included in sNDA 203565/S-016

Trial ID	Design	Regimen	Primary Endpoint	No. of Subjects/ Sites	Status
1VIT17044	Phase 3, randomized, active controlled, safety and efficacy study of FCM vs oral iron in pediatric patients with IDA.	-FCM: 15 mg/kg to a maximum single dose of 750 mg (whichever was smaller) on Days 0 and 7 for a maximum total dose of 1500 mg. -Ferrous sulfate: subjects received an age-dependent formulation of oral ferrous sulfate daily for 28 days	Change in Hb from baseline to Day 35.	79 subjects (FCM: 40, ferrous sulfate: 39) -14 sites in 3 countries (USA, Ukraine and Poland)	Completed
1VIT18045	Single-arm, extension study of FCM in pediatric patients with IDA who had unsatisfactory response to oral iron in study 1VIT17044.	FCM: 15 mg/kg to a maximum single dose of 750 mg (whichever was smaller) on Days 0 and 7 for a maximum total dose of 1500 mg.	Change in Hb from baseline to Day 35.	-7 subjects -1 site in USA	Completed

[Source: FDA compilation]

5.2. Review Strategy

The clinical review was primarily based on the safety and efficacy data from study 1VIT17044 and included the following:

- Electronic submission of the clinical study report and other relevant portions of the sNDA
- Efficacy and safety data were audited or reproduced;
- Safety and efficacy data from study 1VIT18045;
- Regulatory history;
- Applicant's responses to FDA information requests;
- Existing labels; and
- Relevant published literature

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 1VIT17044

6.1.1. Study Design

Overview and Objective

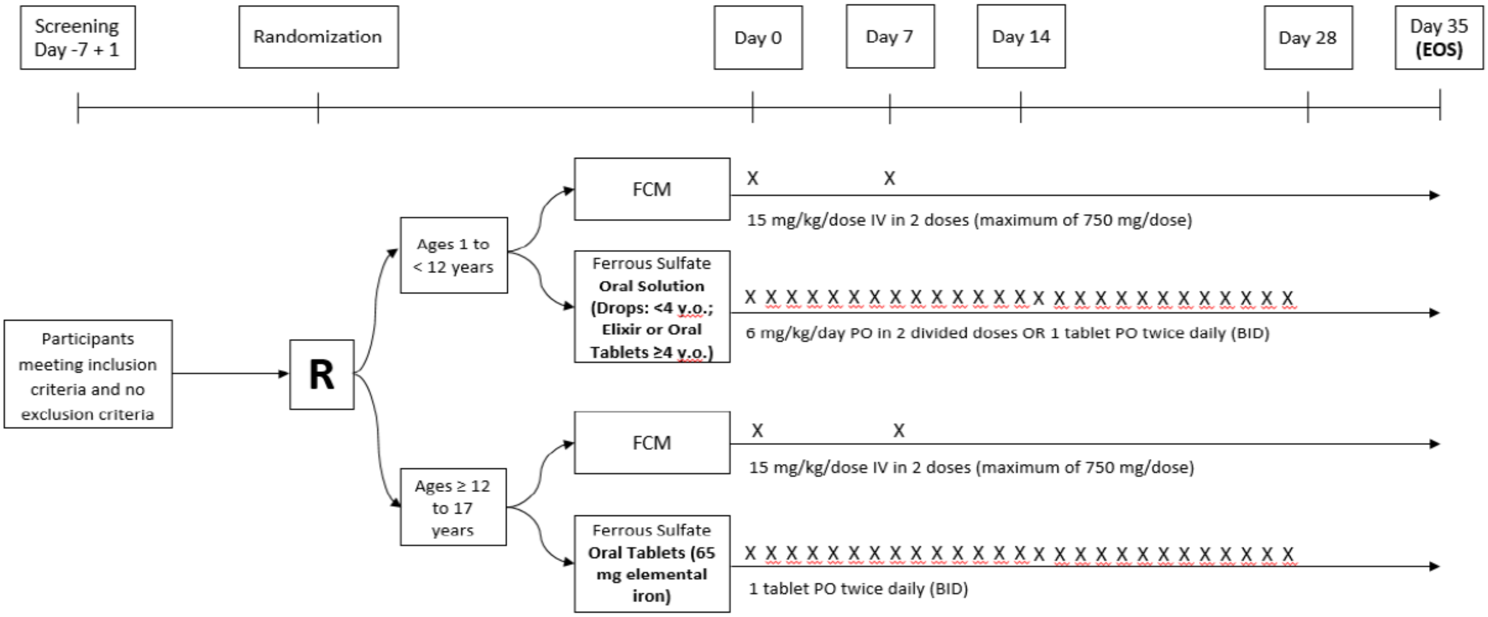
Trial ID and Title:
1VIT17044: A Multicenter, Multinational, Randomized, Active-Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia.

Study 1VIT17044 was a phase 3, multinational, randomized (1:1), active-controlled trial. The primary objective was to demonstrate the efficacy and safety of IV FCM compared to oral iron in pediatric patients with IDA who had an inadequate response to any oral iron therapy.

Trial Design

The figure below shows the overall trial design of study 1VIT17044.

Figure 1 1VIT17044: Study Design



[Source: 1VIT17044 protocol]

Patients were to be randomized in a 1:1 ratio to either Group A (FCM) or Group B (oral iron). Randomization was to be stratified by baseline hemoglobin (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years). Patients randomized to the FCM group were to receive a dose of FCM at 15 mg/kg to a maximum single dose of 750 mg (whichever is smaller) on Days 0 and 7 for a maximum total dose of 1500 mg. FCM was to be administered as either an undiluted IV push at a rate of 100 mg (2 mL)/minute or infused over 15 minutes (in no more than 250 mL of normal saline).

Review comment: The Applicant states that the 15 mg/kg dose (maximum of 750 mg) was selected based on the safety and efficacy results of the Applicant's phase 2 dose-finding PK/PD study (1VIT13036) in which cohorts received single, weight-based dose of FCM at either 7.5 mg/kg or 15 mg/kg. However, patients in the above phase 2 study received a single dose of 15 mg/kg (with a maximum of 750 mg per dose) which is less than the total maximum cumulative FCM dose of 1500 mg (2 doses of 150 mg/kg with a maximum of 750 mg per dose) administered in study 1VIT17044. Based on prior review of FCM, the incidence and severity of FCM toxicity generally increase with higher cumulative dose.

Patients in the oral iron group were to receive an age-dependent formulation of oral ferrous sulfate daily for 28 days as follows:

- Patients <12 years of age were to receive 6 mg (elemental iron)/kg/day divided into two daily doses; and patients ≥12 were to receive two daily doses of oral tablet (65 mg of

elemental iron/tablet/dose).

- Infants and children (ages 1 to < 4 years) were to receive oral ferrous sulfate drops (15 mg elemental iron/mL), while children (ages ≥4 to <12 years) had the option to receive oral ferrous sulfate elixir (44 mg elemental iron/5 mL) or oral ferrous sulfate tablets. Adolescents (ages ≥12 to 17 years) were to receive an oral ferrous sulfate tablet twice a day (BID).
- The maximum daily dose for all participants was 130 mg of elemental iron.

Patients who experience adverse reactions due to the oral iron during the treatment phase could have the weight-based dose of ferrous sulfate reduced from 6 mg/kg to 3 mg/kg. If the patient was receiving tablets, the dose was to be reduced from one tablet taken twice daily to one tablet per day.

Review comment: According to Özdemir 2015, the most commonly used total daily dose of oral elemental iron for the treatment of IDA in pediatric patients ranges between 3-6 mg/kg/day divided into one to 3 doses. The Applicant selected a total daily dose of 6 mg/kg/day divided into two doses (maximum daily dose of 130 mg of elemental iron) for all ages based on the common practice of medicine in pediatric hematology in the US. According to Powers et al. 2015, of the 1217 pediatric hematologist who participated in a survey, most prescribed ferrous sulfate (84%) for the treatment of IDA at the dose of 6 mg/kg/day (62%) divided in two daily doses (68%). Therefore, the dose regimen of oral ferrous sulfate is acceptable.

Concomitant intervention was defined as follows:

- Blood transfusion.
- Use of IV or oral iron outside of protocol.
- Increase in erythropoietin for any reason (Day 0 thru Day 35).
- Change in inflammatory bowel disease (IBD) treatment

All patients were to return for efficacy and safety evaluations, including adverse events and laboratory assessments, on Days 7, 14, 28, and 35. Additional pharmacokinetic sampling and analyses were to be performed for patients receiving FCM on Days 0 and 7.

From the time of consent until the start of treatment with study drug, patients were not to receive any form of supplemental iron outside of the study (intravenous or blood transfusion iron from 4 weeks prior to consent or oral iron including multivitamins with iron). No prophylactic medications were to be administered prior to FCM administration without prior approval.

If a patient was receiving an ESA, a stable (+-20%) dose was required for at least 8 weeks prior to consent. The ESA type, route, frequency and dose were to remain unchanged throughout the study unless the dose were to be decreased or held per the prescribing information. Once

decreased or held it was not to be increased or restarted unless it was deemed necessary. If the latter event occurred, the subject was to continue on study for safety analysis.

If a patient was receiving treatment for IBD, therapy was to remain stable for at least 8 weeks prior to consent and remain stable throughout the duration of the study.

Eligibility Criteria:

Key Inclusion Criteria:

1. Male or female patients 1 to 17 years of age with assent to participation and the parent or guardian is willing and able to sign the informed consent.
2. Screening hemoglobin <11 g/dL.
3. Screening ferritin ≤ 300 ng/mL and TSAT <30%.
4. Documented history of an inadequate response to any oral iron therapy for at least 8 weeks (56 days) prior to randomization.
5. If receiving an ESA: stable ESA therapy (+/- 20% of current dose) for at least 8 weeks prior to screening visit and no ESA dosing or product changes anticipated for the length of the trial.
6. If undergoing treatment for IBD must be on stable therapy for at least 8 weeks.

Key Exclusion Criteria:

1. Known history of hypersensitivity reaction to any component of FCM.
2. Previous randomization and treatment in this study or any other clinical study of FCM.
3. History of acquired iron overload, hemochromatosis, or other iron accumulation disorders.
4. Significant severe diseases of the liver, hematopoietic system, cardiovascular system, psychiatric disorder, or other conditions which may place a subject at added risk.
5. Any existing non-viral infection.
6. Known history of positive hepatitis B antigen (HBsAg) or hepatitis C viral antibody (HCV) with evidence of active hepatitis.
7. Known history of positive HIV-1/HIV-2 antibodies (anti-HIV).
8. Anemia due to reasons other than iron deficiency (e.g., hemoglobinopathy and vitamin B12 or folic acid deficiency) that have not been corrected.
9. Intravenous iron and /or blood transfusion in the 4 weeks prior to consent.
10. Administration and / or use of an investigational product (drug or device) within 30 days of screening.
11. Alcohol or drug abuse within the past six months.
12. Female participant who is pregnant or lactating, or sexually active female of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.

Schedule of Events:

Table 4 1VIT17044: Schedule of Assessments

Visit Day	Screening (Day -7 + 1)	Day 0	Day 7	Day 14	Day 28	Day 35
Informed Consent / Assent	X					
Medical History	X					
Physical Exam		X				X
Inclusion/Exclusion Criteria	X	X				
IRT	X	X				X
Vital Signs	X	X	X	X	X	X
Weight	X	X				
Height	X					
Temperature		X	X			
Hematology, Chemistry and Iron Indices[1]	X	X	X	X	X	X
Serum Pregnancy Test	X					X
Concomitant Medications	X	X	X	X	X	X
IBD Treatment / ESA Stability (if applicable)	X	X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X
Randomization		X				
Injectafer® Dosing		X	X			
Pharmacokinetic Sampling[2]		X	X			
Oral Iron Dosing		X	X	X	X	
Oral Iron Dispensing		X	X	X		
Oral Iron Compliance Assessment			X	X	X	

[Source: 1VIT17044 protocol]

When administering FCM, heart rate and blood pressure were to be assessed pre-, immediately

(within 5 minutes) post, and 30 minutes post administration. Patients were to be discharged from the site only if there were no significant signs or symptoms 30 minutes after the administration was completed.

The patient was to be monitored for at least 30 minutes for serious acute reactions as hypersensitivity or bioactive (labile) iron reactions to non-dextran IV iron products have been reported. The reactions include hypotension, loss of consciousness, bronchospasm with dyspnea, shortness of breath, and seizures.

In the event a serious acute reaction was seen, the site was to have the capability to provide appropriate resuscitation measures which include IV NS, IV epinephrine, steroids and/or antihistamines.

Study Endpoints

The primary endpoint was the change in hemoglobin (Hb) from baseline to Day 35. Baseline Hb was defined as the last Hb obtained before randomization.

The secondary endpoints included the following:

- Change in ferritin from baseline to Day 35
- Change in TSAT from baseline to Day 35
- Changes from baseline in Hb, ferritin, TSAT, and reticulocyte hemoglobin content.
- Pharmacokinetic assessments

Statistical Analysis Plan

Randomization schema:
Eligible participants were randomized in a 1:1 ratio to receiver either

- Group A: IV FCM (Injectafer)
- Group B: oral iron (oral solution drops, elixir or oral tablets)

Blinding:
The study was open label, but the study statisticians were blinded to study drug assignment prior to dataset lock.

Sample Size Consideration:
A total of 60 participants (30 per treatment group) were required to detect an expected difference in Hb of 1.0 g/dL (common standard deviation = 1.16 g/dL) at two-sided alpha of 0.05 with 90% statistical power. Given the presence of missing data, approximately 72 participants should be randomized.

Statistical Hypothesis:

$$H_0: \mu_T = \mu_C$$
$$H_A: \mu_T \neq \mu_C$$

where μ_T = the mean change in Hb from baseline to Day 35 in the Injectafer treatment arm; μ_c= the mean change in Hb from baseline to Day 35 in the oral ferrous sulfate (iron) treatment arm.

This was a superiority study. The efficacy of Injectafer would be demonstrated if the p-value from the pre-specify statistical test that compares the change in Hb from baseline to Day 35 between the two treatment arms was less than 0.05.

Analysis Population:
The Intent-to-Treat (ITT) population: all randomized participants. Participants were evaluated according to the treatment to which they were randomized. It was the primary population for efficacy analyses.

The modified Intent-to-Treat (mITT) population: all participants in the ITT population who received at least one dose of study drug, had a baseline Hb measurement, and at least one corresponding post-baseline measurement. It was used as sensitivity analyses.

Handling of Missing Data
Participants who withdrew from the study for any reason were included in the analyses regardless of time on study.

For statistical inferential analyses, missing data were imputed using last observation carried forward (LOCF) method for Hb and other efficacy endpoints. For example, for the primary endpoint, Hb, when Day 35 data was missing (subject had discontinued before Day 35, or measurement not taken at Day 35 though subject was not discontinued), Day 28 result would be carried forward. If the post-baseline value of the first scheduled visit was missing, the worst value obtained from the same time point of all subjects in ITT population would be used for both treatment groups. The worst value was defined as the lowest value for Hb, ferritin, TSAT and reticulocyte hemoglobin content.

Sensitivity analysis was conducted to assess the impact of missing values on inferences based on primary efficacy endpoints and missing data was handled by using missing at random (MAR) in mixed effect model repeat measurement (MMRM) model.

Primary Efficacy Analysis: Change in Hb from Baseline to Day 35
Treatment group difference for change in Hb was assessed with the analysis of

covariance (ANCOVA), with treatment and randomization strata (Hb and age categories) as fixed factors and baseline value of Hb as a covariate. Baseline Hb was defined as the last Hb obtained before randomization. Missing value were imputed using LOCF.

Review Comment: imputing missing values using LOCF method is generally considered not appropriate because it provides biased estimates. A multiple imputation method with appropriate assumption for the underlying missing data mechanism should be used. In this case, sensitivity analysis is important to assess the robustness of the results.

Sensitivity Analysis:
A MMRM model was conducted to provide an analysis under the assumption that data were MAR. The change in Hb from baseline to Day 35 visit was the dependent variable. Treatment group, visit, and treatment group by visit interaction were fixed effects. Subjects within treatment group were random effects. Baseline Hb (<10, ≥10 g/dL) and age (1 to <12 and ≥12 to 17 years) were covariates. An unstructured covariance matrix was used to allow for unequal variances between visits. If the interaction term was not significant, it would be dropped from the model. No imputation of missing data other than that inherent in the MMRM model were performed.

Subgroups:

The following subgroups using LOCF were examined for the primary efficacy endpoint (i.e., change in Hb from baseline to Day 35):

- Baseline Hb (<10, ≥10 g/dL)
- Age (1 to <12, ≥ 12 to 17 years)

Treatment group difference for change in Hb by subgroup was assessed via the analysis of covariance (ANCOVA), with treatment and randomization strata (Hb and age categories) as fixed factors and baseline value of Hb as a covariate. Missing value were imputed using LOCF as specified for the primary endpoint.

Secondary Efficacy Analysis:
Change from baseline to Day 35 in ferritin, TSAT were summarized descriptively because they are considered exploratory analyses.

Multiplicity Adjustment:
There was a single primary comparison. Therefore, sensitivity analysis and/or secondary endpoints analyses were not adjusted for multiple comparisons.

Interim Analysis:
The study had a Data Safety Monitoring Board (DSMB) whose primary objective was safety evaluation. No formal interim analyses of efficacy were planned for this study.

Protocol Amendments

The clinical trial landmarks and protocol amendments are summarized in the table below.

Table 5 1VIT17044: Key Landmarks and Key Protocol Amendments

Date	Landmarks
April 20, 2017	Original protocol
September 14, 2017	(b) (4)
January 31, 2019	First subject enrollment date
March 13, 2019	Amendment 2: -The name of the Applicant was changed from Luitpold Pharmaceuticals to American Regent. - Allowed children (≥4 to <12 years of age) the option to receive either ferrous sulfate elixir or ferrous sulfate tablets. - Revised the exclusion criteria to allow enrollment of patients with chronic kidney disease on hemodialysis.
September 26, 2019	Administrative revisions
June 22, 2020	Last subject follow-up date
January 25, 2021	Date of study report

[Source: FDA compilation from sNDA submission]

6.1.2. Study Results

Compliance with Good Clinical Practices

Study 1VIT17044 was conducted in compliance with ethical principles of the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, all applicable local regulatory authorities'

requirements, and the US Food and Drug Administration (FDA) Code of Federal Regulations (CFR), 21 CFR Part 50 & 312. The study protocol and all amendments, the informed consents, and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Informed consent was obtained from each subject prior to commencement of the treatment.

Financial Disclosure

The sNDA submission contained FDA financial certification form 3454 signed by Marsha Simon, Director of Clinical Regulatory Affairs, dated January 28, 2021. The Applicant certified to the following statement:

"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

The submission contained lists of clinical investigators that participated in study 1VIT17044 (12 principal/28 sub-investigators) and study 1VIT18045 (2 principal/2 subject-investigators).

None of the clinical investigators were full or part-time employees of the Applicant for the covered clinical studies.

Patient Disposition

In study 1VIT17044, a total of 79 patients were randomized (Injectafer: 40, ferrous sulfate: 39) from 14 sites across 3 countries. In the ITT population, 44% of patients were enrolled from US and Ukraine, respectively, and 9% from Poland.

Table 6 1VIT17044: Patient Enrollment by Country (ITT Population)

	Injectafer (n=40)	Ferrous sulfate (n=39)	Total (n=79)
USA	15 (37.5%)	20 (51.3%)	35 (44.3%)
Ukraine	19 (47.5%)	16 (41.0%)	35 (44.3%)
Poland	6 (15.0%)	3 (7.7%)	9 (11.4%)

[Source: ADSL.xpt]

Of the 79 randomized patients, 1 patient in the ferrous sulfate arm did not receive study treatment. Therefore, the safety population consisted of 78 patients (Injectafer: 40, ferrous

sulfate: 38). The majority (96%) of patients completed the study. A total of 3 patients (Injectafer: 1, ferrous sulfate: 2) discontinued prematurely from the study.

Table 7 1VIT17044: Analysis Population and Patient Disposition

	Injectafer (n=40)	Ferrous sulfate (n=39)	Total (n=79)
Randomized (ITT) population	40 (100%)	39 (100%)	79 (100%)
Safety population	40 (100%)	38 (97.4%)	78 (98.7%)
Subjects completed the study	39 (97.5%)	37 (94.9%)	76 (96.2%)
Subjects discontinued from study	1 (2.5%)	2 (5.1%)	3 (3.8%)
Primary reason for discontinuation			
Other*	1 (2.5%)	2 (5.1%)	3 (3.8%)

*Ferrous sulfate arm: Patient was randomized but did not receive study medications (1 patient); office was shut down due to COVID-19 (1 patient). Injectafer arm: Not able to administer study drug at Day 0 Visit (could not use the supplied needles) and the patient had to be re-screened and re-randomized (1 patient).
[Source: ADSL.xpt]

Protocol Violations/Deviations

Overall, a total of 33 patients (41.8%) had a protocol deviation. Majority of the protocol deviations (40.5%) were considered minor deviations which were mostly "study visit out of window" (22.8%) and "Study procedures non-compliance" (8.9%). One patient in the ferrous sulfate had a major protocol deviation. This patient did not receive study treatment.

Table 8 1VIT17044: Protocol Deviations (ITT Population)

	Injectafer (n=40)	Ferrous sulfate (n=39)	Total (n=79)
All patients with protocol deviation	18 (45.0%)	15 (38.5%)	33 (41.8%)
Patients with major protocol deviation	0	1 (2.6%)	1 (1.3%)
Inclusion/exclusion criteria	0	1 (2.6%)	1 (1.3%)
Patients with minor protocol deviation	18 (45.3%)	14 (35.9%)	32 (40.5%)
Study visit out of window	7 (17.5%)	11 (28.2%)	18 (22.8%)
Study procedures non-compliance	6 (15.0%)	1 (2.6%)	7 (8.9%)
Other (related to laboratory testing)	4 (10.0%)	1 (2.6%)	5 (6.3%)
Inclusion/exclusion criteria	2 (5.0%)	3 (7.7%)	5 (6.3%)
Study drug non-compliance	1 (2.5%)	0	1 (1.3%)
Unable to test all PK samples	2 (5.0%)	0	2 (2.5%)

[Source: ADDV.xpt]

Demographic Characteristics

In study 1VIT17044, patient demographics were generally balanced between the treatment

arms. There were more females (79.7%) than males (20.3%). The median age was 14 years (range, 1 to 17) and most patients were White (87.3%). Approximately one-third (34.2%) of patients were Hispanic/Latino.

Table 9 1VIT17044: Patient Baseline Demographics (ITT Population)

	Injectafer (n=40)	Ferrous sulfate (n=39)	Total (n=79)
Age (years)			
Mean (SD)	12.5 (4.84)	12.8 (4.35)	12.6 (4.57)
Median	14.5	14.0	14.0
Range	1, 17	1, 17	1, 17
Age group (years)			
≥ 12 to ≤ 17	30 (75.0%)	31 (79.5%)	61 (77.2%)
≥ 1 to < 12	10 (25.0%)	8 (20.5%)	18 (22.8%)
Gender			
Female	33 (82.5%)	30 (76.9%)	63 (79.7%)
Male	7 (17.5%)	9 (23.1%)	16 (20.3%)
Race			
White	35 (87.5%)	34 (87.2%)	69 (87.3%)
African American	5 (12.5%)	4 (10.3%)	9 (11.4%)
Asian	0	0	0
Other	0	1 (2.6%)	1 (1.3%)
Ethnicity			
Not Hispanic/Latino	30 (75.0%)	22 (56.4%)	52 (65.8%)
Hispanic/Latino	10 (25.0%)	17 (43.6%)	27 (34.2%)
Weight (kg)			
Median	53	51	52
Range	9, 79	12, 97	9, 97

[Source: ADSL.xpt]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics were also generally balanced between the arms in study 1VIT17044. The most commonly reported (>10%) medical history by System Organ Class (SOC) were blood and lymphatic system disorders (100%), reproductive system and breast disorders (15.4%), gastrointestinal disorders (14.1%) and skin and subcutaneous tissue disorders (11.5%).

Table 10 1VIT17044: Medical History by System Organ Class in ≥ 5% of Patients (Safety Population)

	Injectafer (n=40)	Ferrous sulfate (n=38)	Total (n=78)
All	40 (100%)	38 (100%)	78 (100%)
Blood and lymphatic system disorders	40 (100%)	38 (100%)	78 (100%)
Reproductive system and breast disorders	7 (17.5%)	5 (13.2%)	12 (15.4%)
Gastrointestinal disorders	7 (17.5%)	4 (10.5%)	11 (14.1%)
Skin and subcutaneous tissue disorders	6 (15.0%)	3 (7.9%)	9 (11.5%)
Eye disorders	3 (7.5%)	1 (2.6%)	4 (5.1%)
Congenital, familial and genetic disorders	2 (5.0%)	2 (5.3%)	4 (5.1%)
Respiratory, thoracic and mediastinal disorder	2 (5.0%)	4 (10.5%)	6 (7.7%)
Hepatobiliary disorders	2 (5.0%)	0	2 (2.6%)
Immune system disorders	1 (2.5%)	3 (7.9%)	4 (5.1%)
Infections and infestations	1 (2.5%)	2 (5.3%)	3 (3.8%)
Psychiatric disorders	1 (2.5%)	2 (5.3%)	3 (3.8%)
Metabolism and nutrition disorders	1 (2.5%)	2 (5.3%)	3 (3.8%)
Investigations	0	2 (5.3%)	2 (2.6%)

[Source: ADMH.xpt]

Baseline hemoglobin was 9.5 g/dL (range, 5.6 to 11.7) and most patients (92%) did not have an adequate hemoglobin response to oral iron.

Table 11 1VIT17044: Baseline Disease Characteristics (ITT Population)

	Injectafer (n=40)	Ferrous sulfate (n=39)	Total (n=79)
Hemoglobin (g/dL)			
Median	9.5	9.3	9.5
Range	6.0, 11.1	5.6, 11.7	5.6, 11.7
Hemoglobin category			
<10 g/dL	33 (82.5%)	24 (61.5%)	57 (72.2%)
≥ 10 g/dL	7 (17.5%)	15 (38.5%)	22 (27.8%)
Transferrin saturation (%)			
Mean	7.3	9.7	8.4
Median	4.0	6.0	5.0
Range	2, 29	2, 33	2, 33
Ferritin (ng/mL)			
Mean	7.9	15.0	11.4
Median	3.4	5.7	3.9

Range	1.3, 75.6	1.4, 93.1	1.3, 93.1
IV iron intolerance			
No	40 (100%)	39 (100%)	79 (100%)
Yes	0	0	0
Oral Iron Tolerance Response			
Did not have an adequate hemoglobin response	35 (87.5%)	38 (97.4%)	73 (92.4%)
Iron parameters did not normalize	20 (50.0%)	13 (33.3%)	33 (41.8%)
Other CBC parameters did not normalize	19 (47.5%)	12 (30.8%)	31 (39.2%)
Other	2 (5.0%)	0	2 (2.5%)

[Source: ADSL.xpt]

With regard to the etiology of iron deficiency anemia, the most common reasons (>10%) were due to mixed etiologies (100%), insufficient dietary iron intake (48%), multifactorial (30%) and heavy uterine bleeding (11%).

Table 12 1VIT17044: Iron Deficiency Anemia Etiology (ITT Population)

	Injectafer (n=40)	Ferrous sulfate (n=39)	Total (n=79)
All	40 (100%)	39 (100%)	79 (100%)
IDA of mixed etiologies	40 (100%)	39 (100%)	79 (100%)
Insufficient dietary iron intake	17 (42.5%)	21 (53.8%)	38 (48.1%)
Multifactorial	13 (32.5%)	11 (28.2%)	24 (30.4%)
Heavy uterine bleeding	4 (10.0%)	5 (12.8%)	9 (11.4%)
Gastrointestinal related	5 (12.5%)	1 (2.6%)	6 (7.6%)
Other	2 (5.0%)	0	2 (2.5%)
Celiac disease	2 (5.0%)	0	2 (2.5%)
IBD	1 (2.5%)	1 (2.6%)	2 (2.5%)
Malabsorption	0	0	0
GI bleeding	0	0	0
Other*	1 (2.5%)	1 (2.6%)	2 (2.5%)
Chronic kidney disease	0	0	0

*Irregular menstruation.
[Source: ADMH.xpt and CSR]

Review comment: Although study 1VIT17044 was amended to include patients with IDA and CKD, none were enrolled in the study.

On July 12, 2021, the Applicant submitted an addendum to S-016. The submission contained a post-hoc assessment of renal function for patients in study 1VIT17044. Based on this

assessment, the Applicant found 5 patients in study 1VIT17044 who had baseline estimated glomerular filtration rate (eGFR) values below 60 mL/min/1.73 m^2 (4 patients had baseline eGFR < 60 mL/min/1.73 m^2 and 1 patient < 45 mL/min/1.73 m^2). According to the Applicant, these 5 patients were originally categorized as having IDA etiologies of "Insufficient Dietary Iron Intake". Based on this post-hoc assessment, 60 patients (76%) in the study 1VIT17044 were found to have baseline eGFR values of ≥90 mL/min/1.73m^2, of whom 33 patients (83%) were in the Injectafer arm and 27 patients (69%) were in the ferrous sulfate arm.

However, according to 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines to define the diagnostic criteria and classification of pediatric CKD, CKD is defined as the presence of structural or functional kidney damage that persists over a minimum of three months. Functional damage is typically characterized by a sustained reduction of eGFR, a persistent elevation of urinary protein excretion, or both. The diagnosis of pediatric CKD is based on fulfilling one of the following criteria:

- *GFR of less than 60 mL/min per 1.73 m^2 for greater than three months with implications for health regardless of whether other CKD markers are present.*

- *GFR greater than 60 mL/min per 1.73 m^2 that is accompanied by evidence of structural damage or other markers of kidney function abnormalities, including proteinuria, albuminuria, renal tubular disorders, or pathologic abnormalities detected by histology or inferred by imaging. This category also includes patients with functioning kidney transplants.*

The Applicant has provided assessment of eGFR values at a single time point with no other information sufficient for diagnosis of CKD.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:
In the Injectafer arm, all except 1 patient received the two doses of 15 mg/kg (to a maximum of 750 mg). The median single and cumulative total doses of Injectafer were 750 mg (range, 0.5 mg to 750 mg) and 1500 mg (range, 0.5 mg to 1500 mg), respectively. A total of 16 patients 40%) received Injectafer by IV push and 24 patients (60%) by IV infusion.

Table 13 1VIT17044: Injectafer Total Cumulative Dose by Age Group (Safety Population)

	1 to <12 years (n=10)	12 to ≤ 17 (n=30)	Total (n=40)
Dose (mg)			
Mean (SD)	719 (416)	1402 (289)	1231 (438)
Median (Q1, Q3)	672 (339, 1008)	1500 (1470, 1500)	1500 (1101, 1500)
Range	264, 1500	0.5, 1500	0.5, 1500

Administration			
IV push	6 (60%)	10 (33%)	16 (40%)
IV infusion	4 (40%)	20 (67%)	24 (60%)

[Source: CSR]

In the ferrous sulfate arm, the reported mean (SD) percent compliance was 99.42% (2.22) (range, 88.6 to 100). The mean (SD) and median total doses of ferrous sulfate were 3352 mg (709) and 3640 mg (range, 845 to 4160), respectively.

Prior and Concomitant Medications:
Majority of patients (97%) reported prior medications. The most common prior drug class was iron preparations (87%) which included ferrous sulfate (32%).

A total of 18 patients (23%) reported concomitant medications. The most frequently reported concomitant drug class was antihistamines (8%). The most common concomitant medication was salbutamol sulfate (5%).

Efficacy Results – Primary Endpoint

Primary Endpoint: Change in Hb from Baseline to Day 35:

An increase in Hb from baseline to Day 35 was comparable between both treatment arms. When adjusted for treatment and randomization strata (Hb and age categories) and baseline Hb, the least square mean change in Hb from baseline to Day 35 was 2.2 g/dL in the Injectafer and 1.9 g/dL in the ferrous sulfate arm. The treatment difference at Day 35 (Injectafer - ferrous sulfate) of 0.3 g/dL (95% CI: -0.3, 0.9), using the LOCF algorithm, was not statistically significant (p = 0.3108).

An MMRM model was conducted under the assumption that data were MAR as a sensitivity analysis. The treatment difference between the Injectafer and ferrous sulfate arms was not statistically significant (0.5 g/dL [95% CI: -0.2, 1.2], p = 0.1684).

Review Comment: From these results, the study failed to show the superior efficacy of Injectafer in treating pediatric patients with IDA over ferrous sulfate even though the observed mean change in Hb from baseline to Day 35 in the Injectafer arm was numerically larger than that of the ferrous sulfate arm.

Table 14 1VIT17044: Summary of Observed Hb (g/dL) (ITT Population)

Hemoglobin (g/dL)	Injectafer (N=40)	Ferrous Sulfate (N=39)
Baseline		
N	40	39
Mean (SD)	9.1 (1.12)	9.4 (1.34)
Median (Min, Max)	9.5 (6.0. 11.1)	9.3 (5.6, 11.7)
Day 35		
N	34	36
Mean (SD)	12.3 (1.19)	11.7 (1.37)
Median (Min, Max)	12.6 (9.3, 14.4)	12.1 (7.8, 14.0)
Change from Baseline to Day 35		
N	34	36
Mean (SD)	3.3 (1.66)	2.4 (1.82)
Median (Min, Max)	3.5 (-0.6, 6.7)	2.4 (-1.5, 7.1)

Source: Reviewer's analysis

Table 15 1VIT17044: Difference in Change in Hb from Baseline to Day 35 (ITT Population)

Hemoglobin (g/dL)	Injectafer (N=40)	Ferrous Sulfate (N=39)
Change from Baseline to Day 35 (ANCOVA analysis, LOCF)		
N	40	39
LS mean (95% CI)	2.2 (1.7, 2.8)	1.9 (1.4, 2.4)
LS mean difference (95% CI)	0.3 (-0.3, 0.9)	
p-value	0.3108	
Change from Baseline to Day 35 (MMRM analysis)		
N	34	36
LS mean (95% CI)	3.0 (2.5, 3.5)	2.5 (2.0, 3.0)
LS mean difference (95% CI)	0.5 (-0.2, 1.2)	
p-value	0.1684	

Source: Reviewer's analysis

Review Comment: For the primary analysis using the ANCOVA model, the missing values at Day 35 were explicitly imputed using LOCF method. For the sensitivity analysis using the MMRM model, the missing values at Day 35 were not explicitly imputed.

Supportive Analysis: Change in Hb from Baseline Over Time

Both treatment arms had similar mean (SD) Hb levels at baseline, with 9.1 (1.12) g/dL for the Injectafer arm and 9.4 (1.34) g/dL for the ferrous sulfate arm. There appeared to be a steady increase in mean Hb levels from baseline in both arms until Day 28. Mean change from baseline Hb levels for participants who received ferrous sulfate reached a plateau of 2.4 (1.77)

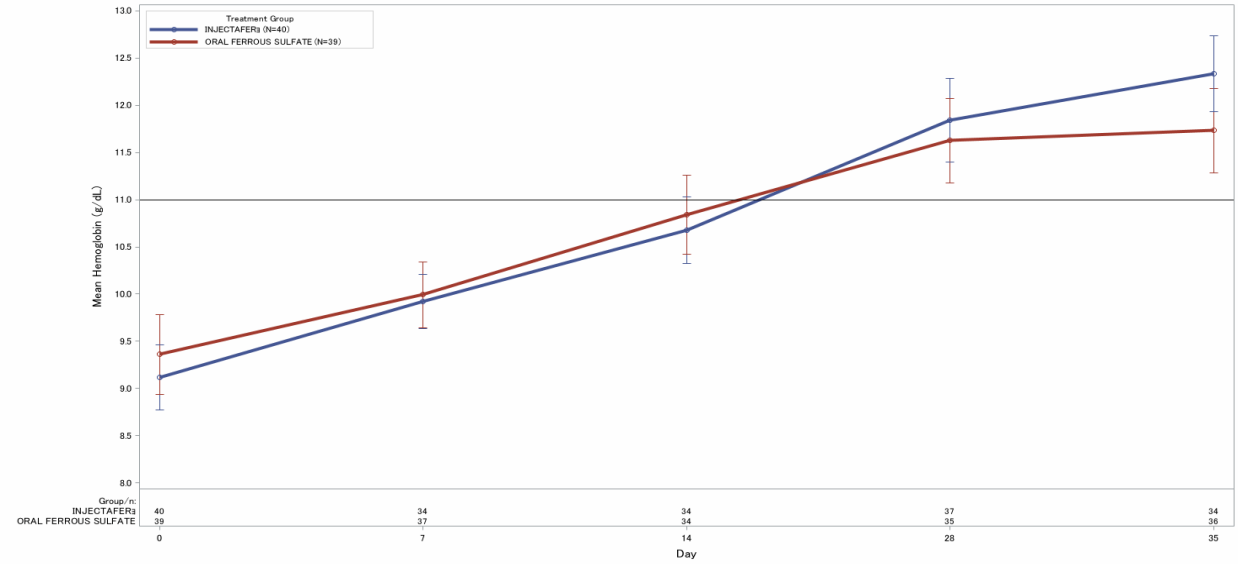
g/dL at Day 28 and 2.4 (1.82) g/dL at Day 35. Hb levels for participants who received Injectafer rose after Day 28, with a mean (SD) Hgb of 2.7 (1.72) g/dL at Day 28 and 3.3 (1.66) g/dL at Day 35 (table and figure below).

Table 16 1VIT17044: Change in Hb (g/dL) from Baseline to Each Visit (ITT Population)

Hemoglobin (g/dL)	Injectafer (N=40)	Ferrous Sulfate (N=39)
Baseline		
N	40	39
Mean (SD)	9.1 (1.12)	9.4 (1.34)
Median (Min, Max)	9.5 (6.0, 11.1)	9.3 (5.6, 11.7)
Change from Baseline to Day 7		
N	34	37
Mean (SD)	0.7 (0.68)	0.6 (0.68)
Median (Min, Max)	0.8 (-0.6, 2.2)	0.6 (-0.8, 2.0)
Change from Baseline to Day 14		
N	34	34
Mean (SD)	1.6 (1.30)	1.4 (1.50)
Median (Min, Max)	1.8 (-1.0, 4.2)	1.5 (-3.3, 4.7)
Change from Baseline to Day 28		
N	37	35
Mean (SD)	2.7 (1.72)	2.4 (1.77)
Median (Min, Max)	2.8 (-0.9, 6.6)	2.3 (-2.2, 7.0)
Change from Baseline to Day 35		
N	34	36
Mean (SD)	3.3 (1.66)	2.4 (1.82)
Median (Min, Max)	3.5 (-0.6, 6.7)	2.4 (-1.5, 7.1)

Source: Reviewer's analysis

Figure 2 1VIT17044: Mean (±SD) Hemoglobin Over time (ITT population)

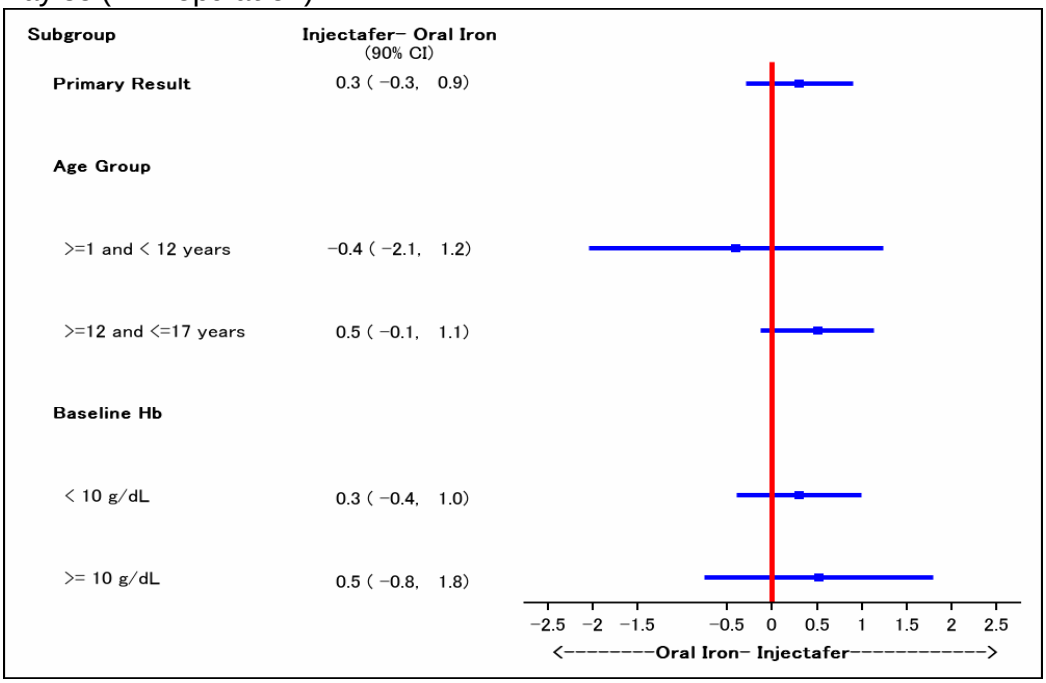


Source: Reviewer's Analysis

Subgroup Analysis:

Subgroup analyses by age group and baseline Hb were assessed (figure below). The results from these subgroup analyses agreed with the primary analysis result.

Figure 3 1VIT17044: Subgroup Analyses for the Difference of Change in Hb from Baseline to Day 35 (ITT Population)



Source: Reviewer's Analysis

Data Quality and Integrity

The quality and integrity of the submitted data generally appeared adequate. No issues were identified.

Efficacy Results – Secondary and other relevant endpoints

Since there were no pre-specified methods for the adjustment of multiplicity to control the family wise Type I error rate, the results from the secondary endpoints should be considered exploratory only.

Change in Ferritin from Baseline to Day 35:

An increase in ferritin from baseline to Day 35 appeared to be higher in the Injectafer arm than the ferrous sulfate arm.

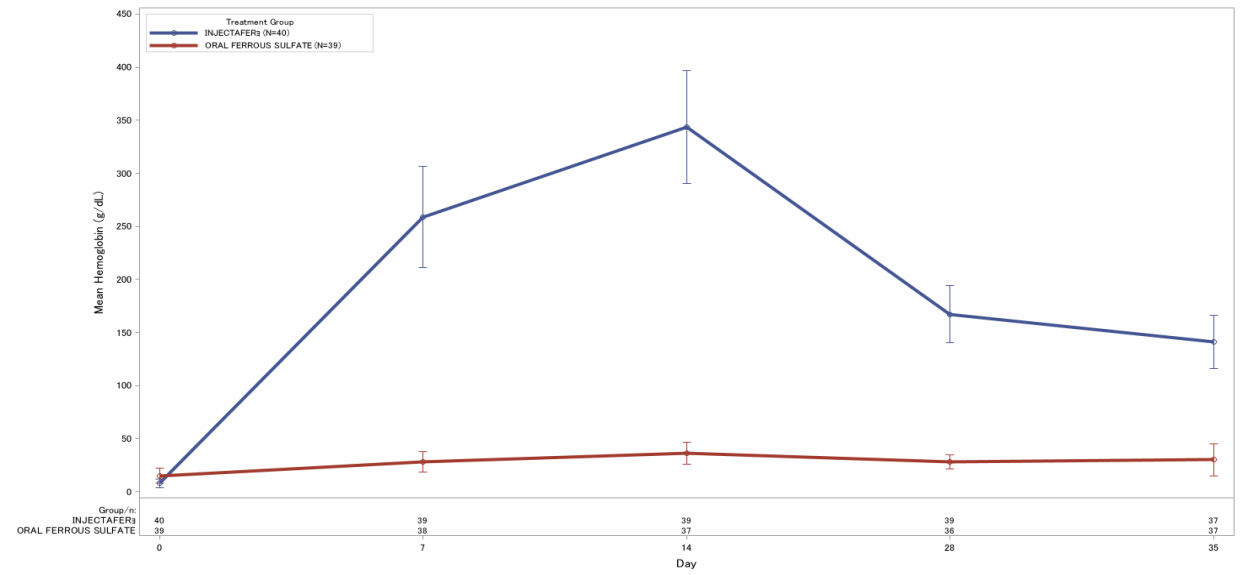
Table 17 1VIT17044: Summary of Observed Ferritin (ng/mL) (ITT Population)

Ferritin (ng/mL)	Injectafer (N=40)	Ferrous Sulfate (N=39)
Baseline		
N	40	39
Mean (SD)	7.9 (13.37)	15.0 (22.63)
Median (Min, Max)	3.4 (1.3, 75.6)	5.7 (1.4, 93.1)
Day 35		
N	37	37
Mean (SD)	141.0 (77.93)	30.3 (46.75)
Median (Min, Max)	140.5 (6.8, 343.6)	15.8 (3.5, 250.3)
Change from Baseline to Day 35		
N	37	37
Mean (SD)	133.4 (76.32)	14.7 (40.58)
Median (Min, Max)	129.1 (1.4, 334.9)	8.2 (-35.0, 236.4)

Source: Reviewer's analysis

Change in Ferritin Over Time:
Results for ferritin levels were highly variable in the Injectafer arm. Mean values showed a dramatic increase from baseline to Day 14 and a large decline from Day 14 to Day 35. In the ferrous sulfate arm, the ferritin levels appeared low and steady throughout the 35 days.

Figure 4 1VIT17044: Mean (±Sd) Ferritin Over Time (ITT population)



Source: Reviewer's analysis

Change in Percent Transferrin Saturation (TSAT) from Baseline to Day 35:
An increase in percent TSAT from baseline to Day 35 in the Injectafer arm was approximately 3 times of that in the ferrous sulfate arm.

Table 18 1VIT17044: Summary of Observed Transferrin Saturation (%) (ITT Population)

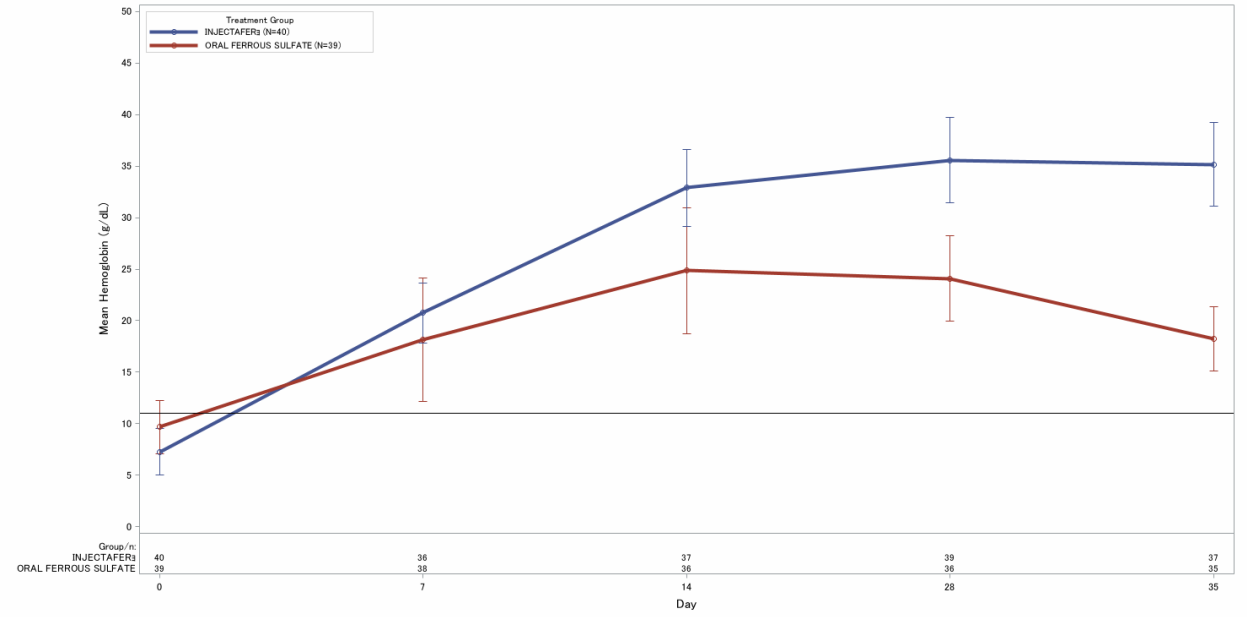
Transferrin Saturation (%)	Injectafer (N=40)	Ferrous Sulfate (N=39)
Baseline		
N	40	39
Mean (SD)	7.3 (7.36)	9.7 (8.30)
Median (Min, Max)	4.0 (2.0, 29.0)	6.0 (2.0, 33.0)
Day 35		
N	37	35
Mean (SD)	35.2 (12.60)	18.2 (9.48)
Median (Min, Max)	35.0 (14.0, 62.0)	17.0 (3.0, 40.0)
Change from Baseline to Day 35		
N	37	35
Mean (SD)	27.7 (13.43)	8.8 (7.07)
Median (Min, Max)	29.0 (0, 58.0)	8.0 (-2.0, 24.0)

Source: Reviewer's analysis

Change in Percent TSAT Over Time:

Participants from the ferrous sulfate arm started with a slightly higher percent TSAT than the Injectafer arm at baseline. However, for Injectafer treated participants, the increase in percent TSAT from baseline appeared to be durable and was maintained to Day 35. For the ferrous sulfate arm, there was no clear trend.

Figure 5 1VIT17044: Mean (±SD) Percent Transferrin Saturation Over Time (ITT population)



Source: Reviewer's analysis

Efficacy Conclusion:

Study 1VIT17044 failed to show the superior efficacy of Injectafer to ferrous sulfate in change of Hb from baseline to Day 35. Sensitivity analyses and subgroup analyses seemed to support the primary analysis result. Secondary endpoints, change from baseline to Day 35 in ferritin and percent TSAT, appeared to show some benefit of Injectafer compared to ferrous sulfate. However, since there were not any pre-specified multiplicity adjustment methods, results from these secondary endpoints should be considered exploratory only.

Clinical Reviewer Comment:

Study 1VIT17044 failed to demonstrate the superiority of the primary efficacy endpoint possibly due to flaws in the statistical design. However, considering the pathophysiology of the disease is sufficiently similar between adults and children, it is reasonable to extrapolate the efficacy results from adequate and well-controlled studies in adults. For results of the pivotal studies in adults, see the clinical review (of NDA 203565) by Dr. Min Lu, dated June 6, 2012 and statistical review by Dr. Kyung Lee, dated June 28, 2012. In addition, although the results of the secondary endpoints should be considered exploratory, the increase in ferritin and TSAT showed some benefit of Injectafer compared to ferrous sulfate.

6.2. Study 1VIT18045

6.2.1. Study Design

Overview and Objective

Trial ID and Title:
1VIT18045: Evaluating the Efficacy and Safety of Intravenous Ferric Carboxymaltose in Pediatric Patients with Iron Deficiency Anemia and an Unsatisfactory Response to Oral Iron under Study Protocol 1VIT17044.

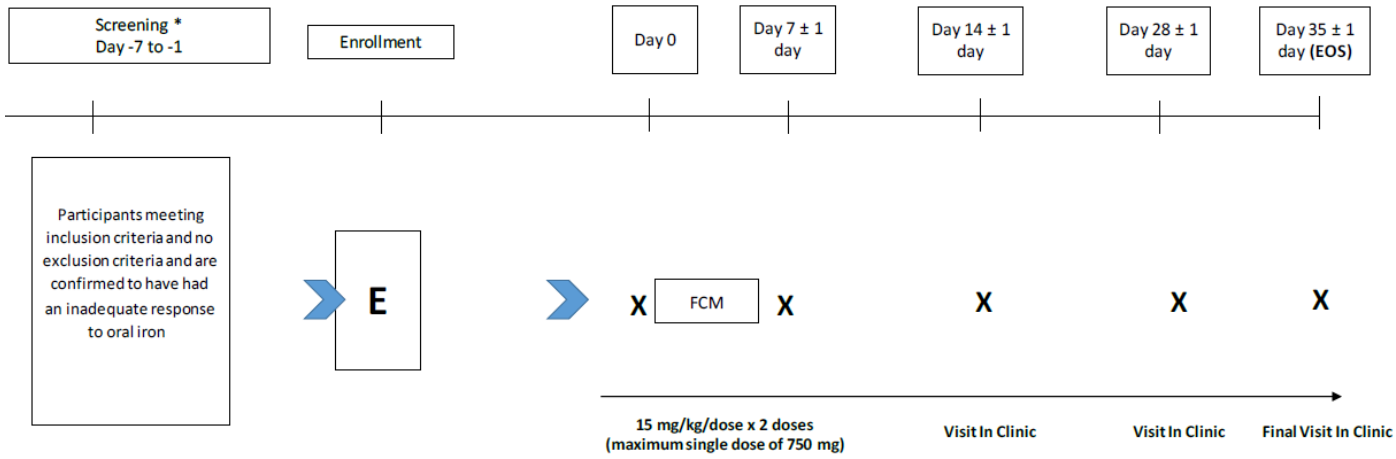
Study 1VIT18045 was a single-arm, open-label, multi-national study that evaluated the efficacy and safety of a one course treatment with FCM in subjects who had an unsatisfactory response to oral iron in study 1VIT17044. The primary objective was to allow patients who were randomized to receive oral iron in study 1VIT17044 and who had an unsatisfactory response to oral iron; or those that required a concomitant intervention [defined as blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason (Day 0 thru Day 35 of study protocol 1VIT17044), change in inflammatory bowel disease (IBD) treatment] to receive one course of FCM.

Trial Design

Study 1VIT18045 was a rollover trial for study 1VIT17044. To qualify for study 1VIT18045, patients were to have an end-of-study visit on Day 35 of study 1VIT17044. Patients then were to be screened and have a baseline evaluation. Enrolled patients to study 1VIT18045 were to receive one course of FCM [i.e., two doses of FCM 15 mg/kg (maximum single dose of 750 mg, whichever is smaller), separated by 7 days (on Days 0 and 7) for a maximum cumulative dose of 1500 mg]. FCM were to be administered as either an undiluted IV push at a rate of 100 mg (2 mL)/minute or infused (in no more than 250 mL of normal saline) over 15 minutes.

An unsatisfactory response (non-responder) to oral iron treatment was defined as an increase of hemoglobin < 1g/dL from baseline.

Figure 6 1VIT18045: Study Design



* Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening

[Source: 1VIT18045 protocol]

Eligibility Criteria:

Key Inclusion Criteria:

1. Unsatisfactory response to oral iron or those that required a concomitant intervention, (defined as blood transfusion, use of IV or oral iron outside of protocol, increase in erythropoietin for any reason [Day 0 thru Day 35 of study protocol 1VIT17044], change in IBD treatment).
2. Hgb <11 g/dL.
3. Ferritin ≤300 ng/dL and TSAT <30%.

Key Exclusion Criteria:

1. Known history of hypersensitivity reaction to any component of FCM.
2. History of acquired iron overload, hemochromatosis, or other iron accumulation disorders.
3. History of significant diseases of the liver, hematopoietic system, cardiovascular system, psychiatric disorder, or other conditions which, in the opinion of the investigator, may place a subject at added risk for participation in the study.
4. Any existing non-viral infection.
5. Known history of positive HBsAg or HCV with evidence of active hepatitis.
6. Known history of positive HIV-1/HIV-2 antibodies (anti-HIV).
7. Anemia due to reasons other than iron deficiency (e.g., hemoglobinopathy and vitamin B12 or folic acid deficiency) that has not been corrected.
8. Administration and/or use of an investigational product (drug or device) within 30 days of screening.
9. Alcohol or drug abuse within the past six months.

10. Female participant who is pregnant or lactating, or sexually active females who are of childbearing potential not willing to use an acceptable form of contraceptive precautions during the study.

Schedule of Events:

Table 19 1VIT18045: Schedule of Assessments

Procedures	Screening[1] Day -7 to -1	Enrollment Visit 1, Day 0	Study Visit 2 Day 7 ± 1 day	Study Visit 3 Day 14 ± 1 day	Study Visit 4 Day 28 ± 1 day	Study Visit 5 Day 35 ± 1 day
Informed Consent / Assent	X					
Medical History	X					
Physical Exam		X				X
Inclusion/Exclusion Criteria	X	X				
Interactive Response Technology (IRT)	X	X				X
Vital Signs	X	X	X	X	X	X
Weight	X	X				
Height	X					
Temperature		X	X			
Blood sampling for Hematology, Chemistry and Iron Indices (5.5 mL) [1]	X	X	X	X	X	X
Blood sampling for Serum Pregnancy Test (1.5 mL), if applicable	X					X
Concomitant Medications	X	X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X
FCM Dosing		X	X			

Note that there will be a 7 ± 1 day waiting period between 1VIT17044 end of study and extension screening.
[Source: 1VIT18045 protocol]

Study Endpoints

The primary endpoint was the change in Hgb from baseline to Day 35.

Secondary efficacy endpoints included the following:

- Change in ferritin from baseline to Day 35
- Change in percent TSAT from baseline to Day 35

Statistical Analysis Plan

Randomization and Sample Size Consideration:
This was a non-randomized, single arm study. There were no sample size estimations for this study. The current study was a rollover from study 1VIT17044. There would be a maximum of 36 participants from study 1VIT17044 who had an unsatisfactory response (i.e., an increase in Hb of < 1g/dL from baseline) to oral iron or required an intervention.

Analysis Population:
Safety population: All enrolled subjects who were treated. All primary and secondary efficacy analyses were based on the safety population.

Statistical Methods:

Primary Endpoint:
The primary efficacy endpoint was the change in Hb from baseline to day 35. The observed value of Hb at baseline, Day 35, and change from baseline to Day 35 were summarized via descriptive statistics.

Secondary Endpoints:
Change in ferritin and percent TSAT from baseline to Day 35 were analyzed similarly to the primary endpoint.

Missing Data Handling Method:
For the summaries of the data, only observed values were reported.

Multiplicity Adjustment:
Not applicable.

Interim Analysis:
No formal interim analysis was planned.

6.2.2. Study Results

Compliance with Good Clinical Practices

Study 1VIT18045 was reviewed and approved by the Independent Ethics Committees or Institutional Review Boards and conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki. Written informed consent was obtained from each subject prior to performance of study-specific procedures.

Patient Disposition

A total of 7 patients rolled over from study 1VIT17044 and all 7 patients received 2 doses of Injectafer (administered as IV push) on Days 0 and 7 in the extension study 1VIT18045. The median cumulative dose of Injectafer was 1500 mg (range: 600, 1500). All 7 patients completed study 1VIT18045; no patients discontinued prematurely from the study.

Table 20 1VIT18045: Subject Disposition by Treatment Group (all subjects)

	Injectafer N (%)
Subjects in the safety population	7 (100)
Subjects who completed the study	7 (100)
Subject who discontinued from study	0

Source: Reviewer's analysis

No protocol deviations were reported in study 1VIT18045.

Demographic and Disease Characteristics

In study 1VIT18045, the median age was 13 years (range, 3 to 18), 71% of patients were female and all patients were White.

The median hemoglobin at baseline was 10.6 g/dL (range, 9.1 to 11.6). All 7 patients had IDA. The IDA etiology for 4 patients (57.1%) was insufficient dietary iron intake; and 3 patients (42.9%) was heavy uterine bleeding.

Table 21 1VIT18045: Baseline Demographics and Disease Characteristics (Safety Population)

	Injectafer (n=7)
Age (years)	
Mean (SD)	12.3 (5.71)
Median	13
Range	3, 18*
Age group (years)	
≥ 12 to ≤ 17	5 (71.4%)
≥ 1 to < 12	2 (28.6%)
Gender	
Female	5 (71.4%)
Male	2 (28.6%)
Race	
White	7 (100%)
Ethnicity	
Hispanic/Latino	7 (100%)
Weight (kg)	
Median	56
Range	20, 74
Hemoglobin (g/dL)	
Median	10.6

Range	9.1, 11.6
Hemoglobin category	
<10 g/dL	2 (28.6%)
≥ 10 g/dL	5 (71.4%)
IV iron intolerance	
No	7 (100%)
Yes	0

* Subject was 17 years of age when enrolled in the 1VIT17044 lead in study and turned 18 years of age just prior to enrolling in the 1VIT18045 extension study.
[Source: ADSL.xpt]

Efficacy Results – Primary Endpoint

The observed mean (SD) change from baseline in Hb at Day 35 was 0.7 (1.19) g/dL (table below). Since the sample size is very small and there was no pre-specified statistical hypothesis, the result is considered exploratory only.

Table 22 1VIT18045: Change in Hb (g/dL) from Baseline to Day 35 (Safety Population)

	Injectafer (N =7)
Baseline	
N	7
Mean (SD)	10.4 (0.96)
Min, Max	9.1, 11.6
Day 35	
N	7
Mean (SD)	11.1 (0.90)
Min, Max	10.3, 12.4
Day 35 Change from Baseline	
N	7
Mean (SD)	0.7 (1.19)
Min, Max	-0.9, 2.2

Source: Reviewer's analysis

Efficacy Results – Secondary and other relevant endpoints

Change in Ferritin from Baseline to Day 35:
The observed mean (SD) change from baseline in ferritin at Day 35 was 188.9 (128.94) ng/mL.

Table 23 1VIT18045: Change in Ferritin from Baseline to Day 35 (Safety Population)

	Injectafer (N =7)
Baseline	
N	7
Mean (SD)	61.5 (47.66)
Min, Max	7.1, 132.9
Day 35	
N	7
Mean (SD)	250.3 (106.50)
Min, Max	141.8, 408.5
Day 35 Change from Baseline	
N	7
Mean (SD)	188.9 (128.94)
Min, Max	40.5, 381.0

Source: Reviewer's analysis

Change in Percent Transferrin Saturation (TSAT) from Baseline to Day 35:

The observed mean (SD) change from baseline in percent TSAT at Day 35 was 11.7% (10.13).

Table 24 1VIT18045: Change in TSAT from Baseline to Day 35 (Safety Population)

	Injectafer (N =7)
Baseline	
N	7
Mean (SD)	25.0 (12.99)
Min, Max	13, 48
Day 35	
N	7
Mean (SD)	36.7 (5.50)
Min, Max	28, 46
Day 35 Change from Baseline	
N	7
Mean (SD)	11.7 (10.13)
Min, Max	-2, 24

Source: Reviewer's analysis

Efficacy Conclusion:
The observed mean change from baseline in Hb at Day 35 was 0.7 g/dL. The mean change from baseline to Day 35 for ferritin was 188.9 ng/mL and for percent TSAT was 11.7% (10.13). Due to the very small study sample size, it is difficult to draw any statistical conclusion based on these results.

7. Review of Safety

7.1. Safety Review Approach

Safety review was primarily based on study 1VIT17044. Safety data from study 1VIT18045 were also reviewed.

Also see section 5.2 of this review.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Injectafer was approved in 2013 for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron; or who have non-dialysis dependent chronic kidney disease. According to the Developmental Safety Update Report (DSUR) of January 1, 2021, a total of 9,477 subjects (including patients, healthy volunteers and pregnant women in their second to third trimester) received treatment with Injectafer in clinical trials.

With regard to the clinical studies of Injectafer in pediatrics conducted by the Applicant, the safety database consists of a total of 82 subjects (study 1VIT17044: 40 subjects, study 1VIT18045: 7 subjects, study 1VIT13036: 35 subjects). In studies 1VIT17044 and 1VIT18045, a total of 47 subjects received two doses of Injectafer, separated by 7 days.

Study 1VIT13036 was a multi-center, open-label, single arm study to characterize the pharmacokinetics and pharmacodynamics of Injectafer in pediatric subjects 1 – 17 years old with IDA. A total of 35 patients received single Injectafer doses of either 7.5 mg/kg or 15 mg/kg in this study. Data from study 1VIT13036 were reviewed by Dr. Robie-Suh (see review signed off on 11/29/2017). It was concluded that the results do not suggest any new safety signal for the population studied.

In addition to the above studies, the Applicant states that a retrospective observation study of Ferinject was conducted in 35 pediatric patients (study FER-PAED-2010-001). In study FER-PAED-2010-001, the reported mean number and total dose were 2.2 and 911 mg, respectively. No efficacy analyses were performed. A total of 2 subjects reported adverse reactions (1 mild urticaria and 1 mild oedema). Both events occurred on the first day of treatment with FCM but did not reoccur on subsequent dosing. No deaths, SAEs, or severe AEs were reported.

In addition, the Applicant provided the results of literature search of FCM in pediatric patients. A total of seven published studies reported exposure to FCM in a total of 983 pediatric patients

(see Table 25).

Table 25 Seven Published Studies of Iron Deficiency Anemia with Ferric Carboxymaltose in Pediatric Patients

Publication (Author, Year)	Population Number	Age range (years)	Adverse Events
Laass, 2014	72	1-17	3 subjects reported mild adverse drug reactions related to FCM; two of these were considered to be potentially related to long duration of administration and to high volume of saline solution for dilution.
Mantadakis, 2017	15	8-17	Not reported
Tan, 2017	51	1-13	No adverse outcomes were documented
Valério de Azevedo, 2017	10	1-17	Minor adverse reactions were reported in only 2 patients in the FCM group: minor headaches (one patient) and fever (one patient).
Papadopoulos, 2018	35	3-17	2 patients who received FCM developed rash after completing their first infusion. Both reactions were mild.
Kirk, 2019	656	1-17	Not reported

Ozsahin, 2020	144	1-17	4 subjects suffered immediate events possibly associated with FCM (urticaria, nausea, headache, and discomfort), which were all mild and had resolved before the patients were dismissed from the day clinic.

[Source: Applicant's submission on April 29, 2021]

The efficacy and safety of FCM was also assessed in pediatric patients (<18 years of age) with IDA in a retrospective study (by Sasankan et al, 2020) of gastroenterology patients (October 2015 to October 2017) at a children's hospital. Data were analyzed on 61 pediatric patients. The median age was 14 years, 32 (52%) were male, 26 (42%) were <14 years old, and 7 (11.5%) were <5 years old. Seventeen patients (28%) were switched from oral iron supplements to FCM. The median dose of FCM delivered was 19 mg/kg. The median Hb increased from 108 g/L to 126 g/L at 1-month post-infusion ($p<0.001$). It was reported that a total of 48 (94%) patients had anemia correction after receiving FCM. Two patients (3%) reported AEs (skin bruising and staining). It was concluded that treatment with FCM appeared to be effective in correcting IDA in children across a wide range of gastrointestinal indications and all ages.

7.2.2. Relevant characteristics of the safety population:

As stated, safety review of the sNDA was primarily based on study 1VIT17044. The baseline demographics and disease characteristics of the safety population in study 1VIT17044 were similar to the ITT population (see Table 9, Table 11 and Table 12).

7.2.3. Adequacy of the safety database:

Injectafer was approved in 2013 for treatment of IDA in adult patients; the safety database of Injectafer in adult patients is adequate. However, there is limited clinical experience in the pediatric patient population. The Applicant's safety database of Injectafer in pediatric patients available in the NDA consists of a total of 82 subjects as described in section 8.2.1 and is acceptable for the pediatric population for IDA.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of data was adequate to allow safety evaluation. No major concerns regarding data integrity were identified during the safety review.

7.3.2. Categorization of Adverse Events

In study 1VIT17044, AEs were reported using the verbatim term and coding using MedDRA terminology version 22.0. Mapping of the verbatim AE terms to MedDRA Preferred Term and System Organ Class (SOC) was acceptable. The intensity of AEs was graded according to the National Cancer Institute Common Technology Criteria for Adverse Events (NCI-CTCAE) criteria (version 5) except for abnormal laboratory values. The Applicant used the scale defined in DAIDS (Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 (March 2017) to identify abnormal clinical laboratory values.

7.3.3. Routine Clinical Tests

In studies 1VIT17044 and 1VIT18045, vital signs, hematology and chemistry laboratory parameters, and iron indices were obtained during screening, Days 0, 7, 14, 28 and 35. Refer to Table 4 and Table 19 of this review.

7.4. Safety Results

Table 26 summarizes the overall safety results of study 1VIT17044. The overall incidence of TEAEs was higher in the Injectafer arm (35%) compared to the ferrous sulfate arm (26.3%). No deaths or SAEs were reported in the study. Most of the TEAEs were mild [grade 1 (Injectafer: 25%, ferrous sulfate: 21%)] in severity.

Table 26 1VIT17044: Overall Summary of Safety (Safety Population)

	Injectafer (n=40)	Ferrous sulfate (n=38)
Deaths	0	0
TESAEs	0	0
TEAEs	14 (35.0%)	10 (26.3%)
TEAEs considered related to study treatment	7 (17.5%)	5 (13.2%)
Mild (grade 1)	10 (25.0%)	8 (21.1%)
Moderate (grade 2)	1 (2.5%)	2 (5.3%)
Severe (all grade 3)	3 (7.5%)	0
TEAEs leading to any study drug discontinuation	1 (2.5%)	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

In study 1VIT18045, no deaths, SAEs, TEAEs or discontinuations due to TEAEs were reported.

7.4.1. Deaths

No deaths were reported in studies 1VIT17044 and 1VIT18045.

7.4.2. Serious Adverse Events

No SAEs were reported in studies 1VIT17044 and 1VIT18045.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In study 1VIT17044, one patient (2.5%) in the Injectafer arm discontinued study treatment due to a TEAE of injection site pain that was grade 2 (moderate) in severity. No other patient discontinued study treatment due to a TEAE.

In study 1VIT18045, no patient discontinued study treatment due to a TEAE.

7.4.4. Significant Adverse Events

During study 1VIT17044, a total of 3 patients (7.5%) in the Injectafer arm reported severe (grade 3) TEAEs [hypophosphatemia (2 patients); and urticaria (1 patient)].

In study 1VIT18045, no patient experienced severe (grade 3) TEAE.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 27 summarizes the TEAEs that occurred in ≥ 1 patient in the Injectafer arm in study 1VIT17044. The overall incidence of TEAEs was higher in the Injectafer arm (35%) compared to the ferrous sulfate arm (26.3%). The most frequently reported TEAEs (> 5%) in the Injectafer arm were hypophosphatemia, local administration reactions and rash.

Table 27 1VIT17044: Treatment-Emergent Adverse Events that Occurred in **≥** 1 Patient in the Injectafer Arm (Safety Population)

FMQ	Injectafer (n=40)	Ferrous sulfate (n=38)
All	14 (35.0%)	10 (26.3%)
Hypophosphatemia	5 (12.5%)	0
Local administration reactions	3 (7.5%)	0
Rash	3 (7.5%)	0
Headache	2 (5.0%)	1 (2.6%)
Vomiting	2 (5.0%)	1 (2.6%)

Urticaria	2 (5.0%)	0
Nasopharyngitis	1 (2.5%)	2 (5.3%)
Flushing	1 (2.5%)	0
Gastrointestinal infection	1 (2.5%)	0
Liver function test increased	1 (2.5%)	0
Platelet count decreased	1 (2.5%)	0
White blood cell count decreased	1 (2.5%)	0

*Grouped Terms by FDA Medical Query (FMQ).
Local administration reactions include infusion site hematoma, infusion site hypoesthesia and injection site pain.
Hypophosphatemia includes hypophosphatemia and blood phosphorus decreased.
Rash includes Boston exanthema and urticaria.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

Treatment-Emergent AEs that were considered study treatment related occurred in 17.5% and 13.2% of patients in the Injectafer and ferrous sulfate arms, respectively. The most commonly reported TEAEs considered related to study treatment in the Injectafer arm (≥ 5%) were hypophosphatemia and urticaria while all study treatment related TEAEs in the ferrous sulfate arm were in the gastrointestinal disorders System Organ Class (SOC); constipation (n=5), upper abdominal pain (n=1), vomiting (n=1) and tooth discoloration (n=1).

Table 28 1VIT17044: TEAEs Assessed as Drug-Related (Safety Population)

FMQ	Injectafer (n=40)	Ferrous sulfate (n=38)
All	7 (17.5%)	5 (13.2%)
Hypophosphatemia	5 (12.5%)	0
Urticaria	2 (5.0%)	0
Flushing	1 (2.5%)	0
Liver function test increased	1 (2.5%)	0
Constipation	0	5 (13.2%)
Abdominal pain upper	0	1 (2.6%)
Tooth discoloration	0	1 (2.6%)
Vomiting	0	1 (2.6%)

*Grouped Terms by FDA Medical Query (FMQ).
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

In study 1VIT18045, no TEAEs were reported.

7.4.6. Laboratory Findings

Iron indices:
In study 1VIT17044, the median increase in ferritin (129.6 ng/mL vs. 8.3 ng/mL), serum iron (64 mcg/dL vs. 21.5 mcg/dL) and transferrin saturation (29% vs. 8.5%) was greater in the Injectafer arm compared to the ferrous sulfate arm at Day 35.

Table 29 1VIT17044: Median Changes from Baseline to End of Study (Day 35) in Hemoglobin and Iron Indices (Safety Population)

	Injectafer (n=40)	Ferrous sulfate (n=38)
Ferritin (ng/mL)		
Median	129.6	8.3
Range	0, 378.8	-35.0, 236.4
Serum iron (mcg/dL)		
Median	64.0	21.5
Range	-8, 145	-6, 247
Total iron binding capacity (mcg/dL)		
Median	-119.0	-52.5
Range	-210, 13	-151, 38
Transferrin saturation (%)		
Median	29.0	8.5
Range	0, 58	-7, 70
Reticulocyte Hemoglobin (pg)		
Median	8.35	5.2
Range	-1.8, 14.3	-0.9, 10.1

[Source: ADLB.xpt]

Hematology and Chemistry:
The median increase in hemoglobin from baseline to Day 35 was similar between the two arms (Injectafer: 3.1 g/dL, ferrous sulfate: 2.35 g/dL) while greater decrease in median platelet count was observed in the Injectafer arm compared to the ferrous sulfate arm (-70.5 x 10^3/mcL vs. -37.0 x 10^3/mcL).

Table 30 1VIT17044: Median Changes from Baseline to End of Study (Day 35) in Hematology and Chemistry Values (Safety Population)

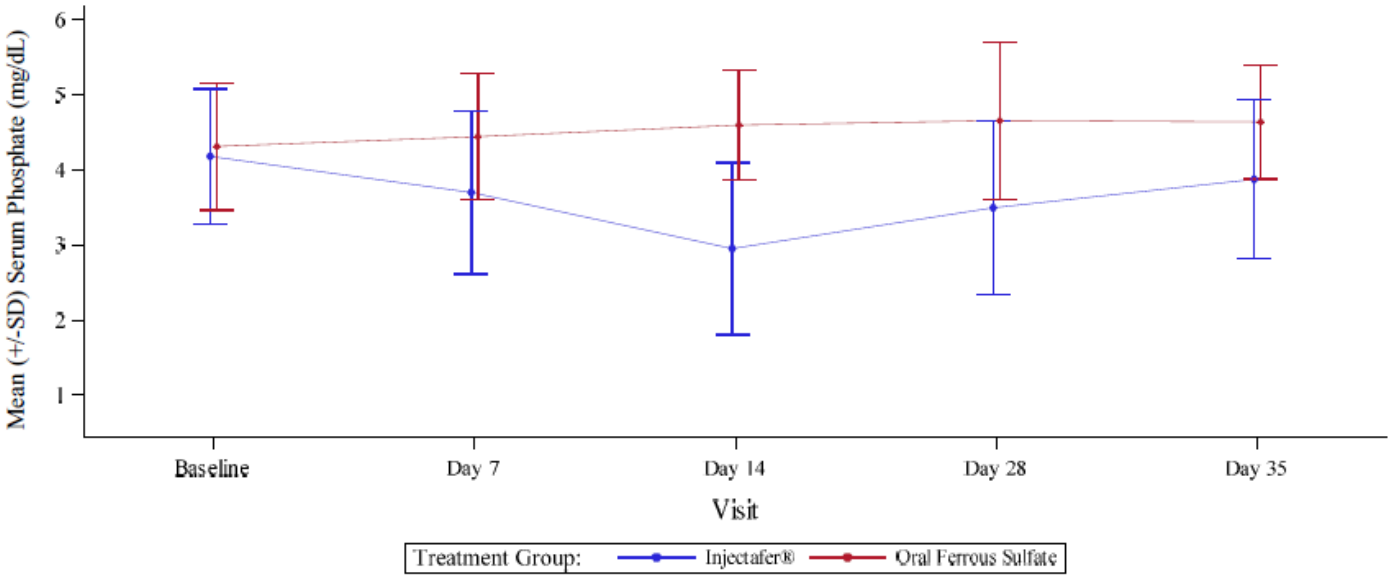
	Injectafer (n=40)	Ferrous sulfate (n=38)
Hemoglobin (g/dL)		
Median	3.1	2.35

	Injectafer (n=40)	Ferrous sulfate (n=38)
Range	-0.9, 6.7	-1.5, 7.1
Neutrophils (10^3/mcL)		
Median	-0.26	0.125
Range	-2.51, 3.46	-2.84, 4.96
Platelets (10^3/mcL)		
Median	-70.5	-37.0
Range	-346, 61	-303, 208
ALT (U/L)		
Median	1.0	1.0
Range	=9, 52	-33, 41
Bilirubin (mg/dL)		
Median	0	0
Range	-0.5, 0.5	-0.3, 0.8
Creatinine (mg/dL)		
Median	0	0
Range	-0.1, 0.1	-0.3, 0.4
Calcium (mg/dL)		
Median	0.2	0
Range	-0.6, 20.	-1.0, 1.2
Potassium (mEg/L)		
Median	-0.10	-0.15
Range	-2.1, 0.5	-1.1, 1.0
Sodium		
Median	0	0
Range	12, 9	-10, 11
Phosphate (mg/dL)		
Median	0	0.3
Range	-2.5, 1.2	-1.3, 2.0

[Source: CSR]

The median values for chemistry values were generally similar between the two arms. However, as noted in the section 8.4.5, hypophosphatemia occurred in 12.5% of patients in the Injectafer arm versus none in the ferrous sulfate arm. The mean serum phosphate levels in the Injectafer arm decreased from baseline to Day 14, rising just below the baseline value at Day 35 [-0.27 (0.845)]; while the phosphate levels in the ferrous sulfate arm were stable.

Figure 7 1VIT17044: Mean (±SD) Serum Phosphate Over Time (Safety Population)



[Source: CSR]

7.4.7. Vital Signs

Overall, there were no clinically relevant changes from baseline for vital signs (systolic and diastolic blood pressure, heart rate or temperature) in study 1VIT17044.

7.4.8. Electrocardiograms (ECGs)

Routine electrocardiograms (ECGs) were not required in studies 1VIT17044 and 1VIT18045. The ECG analyses were not conducted.

7.4.9. QT

The Applicant has not conducted QT or QTc prolongation studies.

7.4.10. Immunogenicity

This section is not applicable.

7.5. Analysis of Submission-Specific Safety Issues

Study 1VIT17044:
Based on the previous clinical experience with Injectafer, AEs of special interest include the following: hypophosphatemia, hypersensitivity or anaphylactoid reactions, injection/infusion site reactions, hemosiderosis and cardiovascular events. In the Injectafer arm,

hypophosphatemia, hypersensitivity/anaphylactoid reactions and injection/infusion site reactions were reported in 12.5%, 7.5% and 7.5% of patients, respectively. One patient experienced flushing. No cases of hemosiderosis were reported.

In the Injectafer arm, most of the AEs of special interest were grade 1 in intensity. Grade 3 (severe) events were reported for hypophosphatemia (n=2) and urticaria (n=1); and one patient had grade 2 (moderate) injection site pain. All except one patient (who experienced mild hypophosphatemia) recovered from these AEs.

Table 31 1VIT17044: TEAEs of Special Interest (Safety Population)

	Injectafer (n=40)	Ferrous Sulfate (n=38)
All	9 (22.5%)	1 (2.6%)
Hypophosphatemia	5 (12.5%)	0
Hypersensitivity or anaphylactoid reactions	3 (7.5%)	1 (2.6%)
Urticaria	2 (5.0%)	0
Flushing	1 (2.5%)	0
Erythema	0	1 (2.6%)
Injection/infusion site reactions	3 (7.5%)	0
Cardiovascular	1 (2.5%)	0
Flushing	1 (2.5%)	0
Hemosiderosis	0	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

7.6. Safety Analyses by Demographic Subgroups

Overall, the incidences of TEAEs were higher in the ≥ 1 to < 12 age group compared to the ≥ 12 to ≤ 17 age group in both the Injectafer arm (50% vs. 30%) and ferrous sulfate arm (37.5% vs. 23.3%); while by gender, the incidences of TEAEs were higher in males compared to females in both the Injectafer arm (42.9% vs. 33.3%) and ferrous sulfate arm (33.3% vs. 241%) with low numbers of events and small number of patients in the subgroups as summarized in the tables below. Therefore, these results should be interpreted with caution.

Table 32 1VIT17044: Overall Summary of Safety by Age Group (Safety Population)

	Injectafer (n=40)		Ferrous sulfate (n=38)	
	≥ 1 to < 12 (n=10)	≥ 12 to ≤ 17 (n=30)	≥ 1 to < 12 (n=8)	≥ 12 to ≤ 17 (n=30)
Deaths	0	0	0	0
TESAEs	0	0	0	0
TEAEs	5 (50.0%)	9 (30.0%)	3 (37.5%)	7 (23.3%)
Grade 3 or 4 TEAEs	0	3 (10%)	0	0
TEAEs leading to any study drug discontinuation	0	1 (3.3%)	0	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

Table 33 1VIT17044: Overall Summary of Safety by Gender (Safety Population)

	Injectafer (n=40)		Ferrous sulfate (n=38)	
	Female (n=33)	Male (n=7)	Female (n=29)	Male (n=9)
Deaths	0	0	0	0
TESAEs	0	0	0	0
TEAEs	11 (33.3%)	3 (42.9%)	7 (24.1%)	3 (33.3%)
Grade 3 or 4 TEAEs	3 (9.1%)	0	0	0
TEAEs leading to any study drug discontinuation	1 (3.0%)	0	0	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

7.7. Specific Safety Studies/Clinical Trials

This section is not applicable.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted.

7.8.2. Human Reproduction and Pregnancy

The current Injectafer label contains the following in the pregnancy subsection of the Use in Specific Populations section:

> Fetal/Neonatal adverse reactions:
> Severe adverse reactions including circulatory failure (severe hypotension, shock including in the context of anaphylactic reaction) may occur in pregnant women with parenteral iron products (such as Injectafer) which may cause fetal bradycardia, especially during the second and third trimester.

The Division of Pediatric and Maternal Health (DPMH) conducted a review of fetal AEs reported in pregnant women exposed to FCM (see review by Dr. Jean Limpert, dated March 29, 2021). The following contents are excerpted from Dr. Limpert' review:

> Cases of possible hypersensitivity reactions and multiple corresponding fetal adverse events including fetal bradycardia (n=1), fetal distress (n=2), uterine contractions (n=1), emergency cesarean section (n=4), and premature infant (n=2) were reported. All of these cases were reported outside of the United States. In each of these cases, the role of IV FCM cannot be excluded due to the temporal association and the reported events. In six cases, the pregnancy outcome is not known. In three cases, healthy full-term infant was delivered.
>
> Based on the Applicant's cumulative review for the period of (b) (6) , a total of 38 fetal death/stillbirth (including cases of abortions) were identified. Of the 38 cases, two cases were reported in the United States and the rest were reported internationally. A total of four cases (all reported outside of the United States) included symptoms of a maternal hypersensitivity reaction and fetal death for which the role of IV FCM could not be excluded.
>
> In addition, there were additional reports of maternal exposure to FCM with a possible temporal association to fetal death without documented maternal hypersensitivity reactions. Three cases do not report maternal symptoms but have a close temporal relationship (< 1 day) of fetal death for which parenteral FCM cannot be excluded. In addition, there are three cases that have a temporal relationship of fetal death (within one week) for which parenteral FCM cannot be excluded. Finally, there are two more cases that are possibly related to parenteral FCM that have a temporal relationship of 10-11 days and another case that is plausibly related without an exact temporal relationship reported. All of these cases were reported outside of the United States.
>
> While confounders of maternal medical problems and maternal medications are noted above, and some cases lack pertinent details, it is the accumulation of cases of fetal deaths with plausible temporal association rather than any one single case that raises the level of concern. It is possible there could be an uncharacterized toxicity of IV FCM.

It is notable that with the exception of six cases, all of these cases occurred in the European Union, New Zealand, or Australia. While both Injectafer and Ferinject are IV FCM, it is not clear if there could be minor differences that could potentially account for the imbalance of cases (e.g., inactive ingredients, differences in manufacturing process). It is also possible that these two products have different frequencies of use in the United States versus other countries that may account for this imbalance.

7.8.3. Pediatrics and Assessment of Effects on Growth

Assessments of effects on growth were not conducted.

7.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No case of overdose was included in the submission. In studies 1VIT17044 and 1VIT18045, no patient was identified with TEAE indicative of potential of drug abuse, withdrawal or rebound effects.

7.9. Safety in the Postmarket Setting

7.9.1. Safety Concerns Identified Through Postmarket Experience

According to the Developmental Safety Update Report of January 1, 2021, a total of 9,477 subjects received Injectafer in the development program. No new safety signals were reported from postmarket experience.

7.10. Integrated Assessment of Safety

The safety evaluation of Injectafer in pediatric patients with IDA was primarily based on a total of 78 patients (Injectafer: 40 patients, ferrous sulfate: 38 patients) who participated in study 1VIT17044. Patients in the Injectafer arm received a dose of 15 mg/kg to a maximum single dose of 750 mg (whichever is smaller) on Days 0 and 7 for a maximum total dose of 1500 mg. Patients in the ferrous sulfate arm received an age-dependent formulation of oral ferrous sulfate daily for 28 days. The overall median total dose of Injectafer was 1500 mg (range: 0.5, 1500) [1 to <12 years: 672 mg (range: 264, 1500), 12 to ≤ 17: 1500 mg (range: 0.5, 1500). The safety findings of study 1VIT17044 were as follows:

- No deaths or SAEs were reported.
- One patient (2.5%) in the Injectafer arm had a grade 2 injection site pain that resulted in discontinuation of the study treatment. No patients in the ferrous sulfate arm experienced a TEAE that resulted in the study treatment discontinuation.
- A total of 3 patients (7.5%) in the Injectafer arm and none in the ferrous sulfate arm experienced grade 3 TEAEs. No grade 4 TEAEs were reported.
- The incidence of TEAEs was higher in the Injectafer arm compared to the ferrous sulfate arm (Injectafer: 35.0%, ferrous sulfate: 26.3%). The most frequently reported TEAEs

(> 5%) in the Injectafer arm were hypophosphatemia, local administration reactions and rash.
- The incidence of TEAEs considered related to study treatment occurred in 17.5% and 13.2% of patients in the Injectafer and ferrous sulfate arms, respectively. The most frequently reported treatment related TEAEs in the Injectafer arm (≥ 5%) were hypophosphatemia and urticaria.

Supportive safety results from study 1VIT18045 did not reveal new safety signals.

8. Advisory Committee Meeting and Other External Consultations

Advisory committee or any other external consultations were not required for this sNDA.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The following are recommended major changes to the Injectafer prescribing information based on this review:

- 1 INDICATIONS AND USAGE: Revise the pediatric indication to treatment of IDA in pediatric patients ages 1 to 17 years who have intolerance to oral iron or have had unsatisfactory response to oral iron.

- 2 DOSAGE AND ADMINISTRATION: Revise that the Injectafer single-dose treatment is recommended only for adult patients.

- 6 ADVERSE REACTIONS: Add brief description of study 1VIT17044 and a table summarizing the incidences of adverse reactions observed in study 1VIT17044.

- 8 USE IN SPECIFIC POPULATIONS: Add that the safety and effectiveness of Injectafer for IDA in pediatric patients aged ≥ 1 year who have intolerance to oral iron or have had unsatisfactory response to oral iron have been established by evidence from adequate and well-controlled studies of Injectafer in adults with additional pharmacodynamic and safety data in pediatric patients.

- 12 CLINICAL PHARMACOLOGY: Add summary of pediatric pharmacokinetic data.

- 14 CLINICAL STUDIES: Deleted [redacted] (b) (4)

10.Risk Evaluation and Mitigation Strategies (REMS)

REMS is not required for this sNDA.

11.Postmarketing Requirements and Commitments

No clinical PMCs or PMRs are necessary for this sNDA.

12.Appendices

12.1. References

1. Laass MW, et al.. Effectiveness and safety of ferric carboxymaltose treatment in children and adolescents with inflammatory bowel disease and other gastrointestinal diseases. BMC Gastroenterol. 2014; 14: 184.
2. Carman N, et al. Ferric carboxymaltose in the treatment of iron deficiency in pediatric inflammatory bowel disease. Transl Pediatr. 2019 Jan; 8(1): 28–34.
3. Ozsahin H, et al. Intravenous ferric carboxymaltose for iron deficiency anemia or iron deficiency without anemia after poor response to oral iron treatment: Benefits and risks in a cohort of 144 children and adolescents. Pediatr Blood Cancer. 2020;67:e28614.
4. Powers JM, McCavit TL, Buchanan GR. Management of iron deficiency anemia: a survey of pediatric hematology/oncology specialists. Pediatr Blood Cancer. 2015;62(5):842-6.
5. Recommendations to prevent and control iron deficiency in the United States: centers for disease control and prevention. MMWR Recomm Rep. 1998;47: 1-29.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 1VIT17044

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Sponsor employees (including both full-time and part-time		

employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 1VIT18045

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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