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CITIZEN PETITION

To Whom It May Concern:

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to (i) deny any Injectafer® (ferric carboxymaltose injection) ("Injectafer") supplemental New Drug Applications ("sNDAs") for any labeling changes based on the FAIR–HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless intended to add or strengthen a contraindication, warning, precaution, or adverse reaction; (ii) strengthen Injectafer warnings and precautions and its dosage and administration in relation to severe and symptomatic hypophosphatemia and its consequences; and (iii) require any potential future expanded or additional indication for Injectafer to be based on well-controlled clinical studies that specifically assess the risks of severe and symptomatic hypophosphatemia and its consequences for such intended use.

The FAIR-HF and CONFIRM-HF trials exhibit several significant deficiencies that should prevent the U.S. Food and Drug Administration ("FDA" or the "Agency") from being able to reach a favorable risk-benefit assessment as to the safety and effectiveness of Injectafer for use in patients with iron deficiency and heart failure with reduced ejection fraction based on these studies. The subsequent AFFIRM-AHF trial suffers from its own limitations that prevent this trial from being supportive of FAIR-HF and CONFIRM-HF. In addition, post-marketing adverse event reports, randomized clinical trials, systematic literature reviews, and a retrospective study demonstrate a strong association between Injectafer and hypophosphatemia, including its severe sequelae such as osteomalacia and fractures. The current Injectafer labeling is insufficient to address these risks and should be revised to include stronger warnings and additional patient monitoring information. As a result of the risks posed by the series of biochemical and hormonal changes induced by Injectafer, including hypophosphatemia, any studies of Injectafer in support of a label extension should sufficiently evaluate this risk, which has not been done to-date. The failure to adequately assess hypophosphatemia presents an unacceptable uncertainty in any risk-benefit assessment of Injectafer for any intended use.

Ultimately, the actions requested in this petition are intended to mitigate the potential for significant patient harm that could result from an expanded, and even current, use of Injectafer

without additional appropriate and well-controlled clinical investigations. We respectfully request that FDA consider the information presented in this petition and proceed with implementing the actions requested to help protect patient safety and ensure the rigorous requirements of the FDA approval process are applied and upheld.

A. Actions Requested

The undersigned hereby respectfully requests that FDA:

1. Deny any Injectafer sNDAs for any labeling changes based on the FAIR–HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless intended to add or strengthen a contraindication, warning, precaution, or adverse reaction.

2. Strengthen Injectafer warnings and precautions and its dosage and administration in relation to severe and symptomatic hypophosphatemia and its consequences.

3. Require any potential future expanded or additional indication for Injectafer to be based on well-controlled clinical studies that specifically assess the risks of severe and symptomatic hypophosphatemia and its consequences for such intended use.

B. Statement of Grounds

1. Legal and Factual Background

a) *New Drug Approval Process and Post-Marketing Safety*

The FDCA defines a "drug" as an article "intended for use" in the diagnosis, cure, mitigation, treatment, or prevention of disease, or an article (other than food) "intended to affect" the structure or any function of the body.[1] Based on its interpretation of this statutory provision, FDA regulates articles as "drugs" based upon the "objective intent" of the individual or entity responsible for the labeling and distribution of those articles in interstate commerce.[2] A "new drug" is defined as one whose composition has not been recognized by qualified experts as safe and effective for the intended use.[3] A drug becomes a "new drug" if it is recommended for use in a dose, method, or application different from that provided for in the approved labeling.[4] Thus, under FDA's construction of the statute, a drug that is intended for an unapproved use can be considered a "new drug" for that particular use, even if another use for that same drug has been FDA-approved. Prior to distribution or marketing, new drugs must be proven safe and effective via FDA approval processes before they can lawfully be introduced into interstate commerce.[5]

[1] 21 U.S.C. § 321(g)(1)(B)–(C).
[2] 21 C.F.R. § 201.128.
[3] 21 U.S.C. § 321(p).
[4] 21 C.F.R. § 310.3(h).
[5] *See* 21 C.F.R. § 201.128.

In general, approval for a new indication must be supported by "substantial evidence" that the drug is effective for such use. The FDCA defines substantial evidence to mean:

> [E]vidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.[6]

FDA generally requires two randomized, adequate, and well-controlled clinical trials. The FDCA, however, provides FDA the ability to consider "one adequate and well-controlled clinical investigation and confirmatory evidence."[7] In addition to ensuring that a drug is effective, FDA must also ensure that it is safe. In fact, FDA is required to implement "a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs."[8] Thus, to support approval, a drug's benefits must outweigh its risks.

FDA has recently described this risk-benefit assessment in a draft guidance released in September 2021, entitled "Benefit-Risk Assessment for New Drug and Biological Products".[9] As a general matter, such an assessment is an "informed judgment as to whether the benefits (with their uncertainties) of the drug outweigh the risks (with their uncertainties and approaches to managing risks)" under the drug's conditions for use.[10] In addition to the content submitted in an sNDA, FDA considers a variety of other factors, such as the nature and severity of the condition, the benefits and risks of available therapies for such condition, and risk management tools that may be necessary to ensure a drug's benefits outweigh its risks.

Notably, this "assessment becomes *more challenging* in cases where the potential for serious safety risks is identified or expected to exist," and requires a determination that the drug's benefits and risk are "sufficiently characterized" and that the benefits outweigh the risks.[11] Such determination requires a comprehensive evaluation of "available evidence, *recognition of the data gaps, and careful consideration of a complex set of factors, including the severity of the condition, the patient population, and the current treatment landscape*."[12] Even where a drug presents serious risks, FDA can still approve it where, for example, there is a clearly demonstrated "*direct and meaningful benefit* on *the most important clinical outcomes*."[13] FDA,

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[6] 21 U.S.C. § 355(d).
[7] *Id.*
[8] *Id.*
[9] FDA, Draft Guidance for Industry, *Benefit-Risk Assessment for New Drug and Biological Products* (Sept. 2021) [hereinafter "Benefit-Risk Guidance"], *available at:* https://www.fda.gov/media/152544/download.
[10] *Id.* at 3–4.
[11] *Id.* at 4 (emphasis added).
[12] *Id.* (emphasis added).
[13] *Id.* (emphasis added).

however, is likely to have "a lower tolerance for potential serious risks or toxicities" when there are treatment options with lesser risks for the targeted condition.[14]

Depending on the particular therapeutic context and treatment landscape, FDA may accept a certain level of uncertainties in its risk-benefit assessment. For example, FDA may accept greater uncertainty for drugs intended to treat a serious disease or conditions with unmet needs or to treat rare diseases. Conversely, FDA would likely not accept much uncertainty for drugs intended to treat non-serious conditions for which there are other treatments. Uncertainties that can affect FDA's risk-benefit assessments, include, without limitation, aspects of study design, such as "population, endpoints, duration, data sources, and any differences between the clinical study and real-world use" and "proposed risk management strategies, such as patient monitoring, which have not been studied in clinical trials."[15]

Even when FDA determines that a drug has a favorable risk-benefit profile at the time of approval, it can mandate safety-related labeling changes upon becoming aware of new safety information that the Agency believes should be required in the labeling under Section 504(o)(4) of the FDCA.[16] The FDCA defines "new safety information" to mean "information derived from a clinical trial, an adverse event report, a postapproval study . . . or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 355(k) of this title; or other scientific data deemed appropriate by [FDA] about [among other things] a serious risk or an unexpected serious risk associated with use of the drug that [FDA] has become aware of (that may be based on a new analysis of existing information) since the drug was approved."[17] A "serious risk" means a risk of an adverse drug experience that results in, among other things, death, an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.[18] FDA's position is that the "new safety information" statutory definition is "broad to enable FDA to require application holders to add information about serious risks to the labeling of a drug when the Agency determines that such information should be included."[19] Where FDA requires safety-related labeling changes, other labeling changes may also be required to ensure consistency throughout the labeling.[20]

[14] *Id.* at 5.
[15] *Id.* at 10–11.
[16] 21 U.S.C. § 355(o)(4).
[17] 21 U.S.C. § 355-1(b)(3).
[18] 21 U.S.C. § 355-1(b)(4)–(5).
[19] FDA, Guidance for Industry, *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* (Jul. 2013) at 4, *available at:* https://www.fda.gov/media/116594/download.
[20] *Id.* at 5.

b) *Iron Deficiency in Adults with Heart Failure with Reduced Ejection Fraction (NYHA class II-III)*

Iron deficiency is a common condition that affects greater than 15% of the world's population.[21] Symptoms of iron deficiency include fatigue, headache, thinning hair, pale skin, angular cheilitis, dyspnea, nail changes, and restless leg syndrome.[22] The prevalence of iron deficiency in symptomatic heart failure is approximately 50%.[23] Heart failure prevalence in the United States has been estimated to be 2.5% based on self-reported data.[24] Approximately half of those have heart failure with reduced ejection fraction.[25] Typically, patients with heart failure have other cardiovascular risks and conditions. For example, approximately 75% have high blood pressure, 40% have type 2 diabetes mellitus, and 30-60% have coronary heart disease.[26] Many heart failure patients also have various degrees of reduced renal function.[27] In age- and risk factor-adjusted models, incident heart failure conferred a fivefold increased risk of death.[28] As such, these patients constitute a vulnerable patient population.

c) *Injectafer*

FDA initially approved Injectafer on July 25, 2013 under New Drug Application ("NDA") 203565. The current NDA holder is American Regent, Inc. ("American Regent"). Injectafer is marketed globally by Vifor Pharma under the brand name Ferinject®.[29] Vifor Pharma also served as the sponsor for the FAIR-HF, CONFIRM-HF, and AFFIRM-AHF trials. Injectafer is an iron replacement product currently indicated for the treatment of iron deficiency anemia in: (i) adults and pediatric patients 1 year of age and older who have either intolerance to oral iron or an unsatisfactory response to oral iron; and (ii) adult patients who have non-dialysis dependent chronic kidney disease. Injectafer is administered intravenously as an undiluted slow intravenous push or by infusion. Injectafer utilizes weight-based dosing regimens. For patients weighing 50 kg or more, Injectafer can be administered: (i) in two 750 mg doses at least 7 days apart; or (ii) in an alternative single dose at 15 mg/kg body weight up to 1,000 mg. For patients

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[21] Benedikt Schaefer et al., *Hypophosphatemia after intravenous iron therapy: Comprehensive review of clinical findings and recommendations for management*, BONE, no. 154, Jan. 2022, at 1. [hereinafter "Schaefer et al. Bone 2022"] (attached as Exhibit A).

[22] *Id.*

[23] IJsbrand T. Klip et al., *Iron deficiency in chronic heart failure: An international pooled analysis*, 165 AM. HEART. J. 575, 575 (2013) (attached as Exhibit B).

[24] Emelia J. Benjamin et al., *Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association*, 137 CIRCULATION e67, e422 (2018) (attached as Exhibit C).

[25] Clyde W. Yancy et al., *2013 ACCF/AHA Guideline for the Management of Heart Failure*, 62 J. AM. COLL. CARDIOLOGY e147, e155 (2013) (attached as Exhibit D).

[26] Amy Groenewegen et al., *Epidemiology of heart failure*, 22 EUR. J. HEART FAILURE 1342, 1348 (2020). [hereinafter "Groenewegen et al."] (attached as Exhibit E).

[27] Joerg C. Schefold et al., *Heart failure and kidney dysfunction: epidemiology, mechanisms and management*, 1 NAT'L REV. NEPHROLOGY 610, 610 (2016) (attached as Exhibit F).

[28] Groenewegen et al. at 1349.

[29] For ease of reference, this petition generally uses the defined term "Injectafer" throughout. Where appropriate, however, this petition may refer to Injectafer by its established name, ferric carboxymaltose, or European brand name, Ferinject.

weighing less than 50 kg, Injectafer can be administered in two doses at least 7 days apart at 15 mg/kg body weight.[30]

Injectafer is contraindicated in patients with a history of hypersensitivity to Injectafer or its components. Warnings and precautions for Injectafer include hypersensitivity reactions, hypertension, and laboratory test alterations. Injectafer also has a warning and precaution and instructions for repeat treatment monitoring assessments pertaining to hypophosphatemia as discussed below. The most common adverse reactions in adults are nausea, hypertension, flushing, injection site reactions, erythema, hypophosphatemia, and dizziness. The most common adverse reactions in pediatric patients are hypophosphatemia, injection site reactions, rash, headache, and vomiting.[31]

This petition is primarily concerned with three completed—yet deficient—clinical trials for Injectafer known as FAIR-HF, CONFIRM-HF, and AFFIRM-AHF. FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) enrolled ambulatory patients with stable chronic heart failure of New York Heart Association ("NYHA") Class II or III, a left ventricular ejection fraction ("LVEF") of 40% or less (for patients in NYHA Class II) or 45% or less (for patients in NYHA Class III), a hemoglobin level at the screening visit between 95 and 135 g per liter, and iron deficiency from June 25, 2007 to December 31, 2008. It was a multi-center, double-blind, randomized, placebo-controlled parallel group study. The primary endpoints of FAIR-HF were self-reported Patient Global Assessment ("PGA") score and NYHA Class, both measured at just Week 24. The study enrolled a small number of patients, totaling just 459, that were randomized 2:1 to Injectafer (n=304) and placebo (n=155). Of note, 79% percent of the sites in FAIR-HF were located in Eastern Europe, a region known for clinical trial integrity issues. Specifically, out of a total of 75 sites, 27 were in Russia, 16 in Ukraine, 7 in Poland, 5 in the Czech Republic, and 4 in Romania.[32]

The results of FAIR-HF found that the self-reported PGA score at Week 24 was improved in the Injectafer group, with 50% of patients reporting that they were much or moderately improved, as compared with 28% of patients in the placebo group (odds ratio for being in a better rank, 2.51; 95% confidence interval ["CI"], 1.75 to 3.61; $P < 0.001$). Similarly, the NYHA functional class at Week 24, after adjustment for the baseline value was improved in the Injectafer group, with 47% having a NYHA functional Class I or II, as compared with 30% in the placebo group (odds ratio for improvement by one class, 2.40; 95% CI, 1.55 to 3.71; $P < 0.001$). Limitations of this trial include the use of the self-reported PGA score because it is a crude 7-step score where the patient is asked about his/her medical condition since starting in the trial and is not commonly used in cardiology where specific health-related quality of life instruments have been developed, such as the Kansas City Cardiomyopathy Questionnaire and Minnesota Living with Heart Failure Questionnaire. Another limitation is that dosing was low and did not reflect contemporary use of high-dose intravenous ("IV") iron. In fact, the manuscript authors acknowledge that "[w]e required that iron was given in doses of 200 mg per

[30] Injectafer Full Prescribing Information (Nov. 2021), *available at:* https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/203565Orig1s016_CORRECTED_lbl.pdf.
[31] *Id.*
[32] Stefan D. Anker et al., *Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency*, 361 NEW ENG. J. MED. 2436, 2438, Supp'l App'x (2009) (attached as Exhibit G).

application and that the dosing frequency was weekly during the correction phase and monthly during the maintenance phase. The results of our study are applicable only to this dosing regimen."[33]

CONFIRM-HF (Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) enrolled stable ambulatory heart failure patients in NYHA Class II or III, with LVEF ≤ 45%, elevated natriuretic peptides (brain natriuretic peptide > 100 pg/mL and/or N-terminal-pro-brain natriuretic peptide > 400 pg/mL), presence of iron deficiency (defined as serum ferritin level < 100 ng/mL, or between 100 and 300 ng/mL if transferrin saturation < 20%) and hemoglobin < 15 g/dL from September 2011 to February 2013. It was a multi-center, double-blind, randomized, placebo-controlled parallel group study. The primary endpoint was change in 6-minute walk test ("6MWT") distance from baseline to Week 24. The study enrolled a small number of patients, totaling of 304, that were randomized 1:1 to Injectafer (n=152) and placebo (n=152). 86% of all patients were recruited in Eastern Europe, specifically Russia (n=161), Poland (n=50) and Ukraine (n=50). This equated to patients recruited from Russia constituting 53% of all patients.[34]

The results of CONFIRM-HF found an increase in 6MWT distance by 18 ± 8 m in the Injectafer group at Week 24, whereas in the placebo group there was a decrease in 6MWT distance by 16 ± 8 m (both least squares mean ± standard error). It resulted in a significant difference in changes in 6MWT distance at Week 24 in Injectafer vs. placebo of 33 ± 11 m (least squares mean ± standard error), P = 0.002. Limitations of this trial include use of the 6MWT which provides less objective information than other endpoints, such as cardiopulmonary exercise testing with an assessment of peak oxygen consumption ("VO_2").[35]

AFFIRM-AHF (A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure) enrolled patients from March 21, 2017 to July 30, 2019. It was a multi-center, double-blind, randomized, placebo-controlled parallel group study. The primary endpoint was a composite endpoint of recurrent heart failure hospitalizations and cardiovascular death up to 52 weeks after randomization. AFFIRM-AHF enrolled 1,132 patients that were randomized 1:1 to Injectafer or placebo. All patients were hospitalized for acute heart failure and had concomitant iron deficiency and an LVEF ≤ 50%.[36] In contrast, patients in FAIR-HF and CONFIRM-HF were required to be ambulatory patients with LVEF ≤ 40% or 45%. Acutely hospitalized heart failure patients represent a different patient population and disease state than stable ambulatory patients.

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[33] *Id.* at 2446.
[34] Piotr Ponikowski et al., *Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency*, 36 EUR. HEART J. 657, 658, Suppl. App'x (2015). [hereinafter "Ponikowski et al."] (attached as Exhibit H).
[35] *Id.* at 657.
[36] Piotr Ponikowski et al., *Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial*, 398 LANCET 1895, 1895, Suppl. App'x (2020) (attached as Exhibit I).

293 primary events (57.2 per 100 patient-years) occurred in 558 patients in the Injectafer group and 372 (72.5 per 100 patient-years) occurred in 550 patients in the placebo group (rate ratio=0.79; 95% CI 0.62–1.01; P=0.059). Hence, the trial did not meet its primary endpoint. Several secondary endpoints were tested in a non-hierarchical fashion, including the individual components of the primary composite endpoint. There was no difference in cardiovascular death between the two groups: 77 [14%] of 558 in the Injectafer group vs 78 [14%] in the placebo group (hazard ratio=0.96; 95% CI 0.70–1.32; P=0.81). Total heart failure hospitalizations was significantly different 217 (31.72 per 100 patient-years) in the Injectafer group and 294 (43.15 per 100 patient-years), (rate ratio=0.74; 95% CI 0.58–0.94; P=0.013). Limitations of this trial include: (i) for evaluation of major cardiovascular efficacy and safety endpoints, the total exposure time in the trial was limited due to the combination of short duration of 52 weeks and a modest sample size; and (ii) the trial was not appropriately designed to investigate potential effects on serum phosphate or markers for bone turnover.[37] Regarding this second limitation, AFFIRM-AHF did not measure serum phosphate at the time point where serum phosphate would be the lowest (*i.e.*, approximately 14 days after infusion) and did not measure parameters like alkaline phosphatase, bone specific alkaline phosphatase, procollagen type 1 N-terminal propeptide, or carboxy-terminal collagen crosslinks for effects on biochemical biomarkers of mineral and bone homeostasis. In addition, this trial did not include design elements to consider individual patients who may have experienced more pronounced drops in serum phosphate because it only assessed serum phosphate as mean change from baseline.

d) *Hypophosphatemia*

Hypophosphatemia is a condition where patients have low serum phosphate levels caused by increased urinary phosphate excretion. Although hypophosphatemia can be asymptomatic, it presents the potential for severe and long-lasting complications. Persistent hypophosphatemia can cause debilitating diseases, such as myopathy, osteomalacia, and fractures. The most common symptoms of hypophosphatemia include general weakness, fatigue, bone and muscle pain, and osteomalacia with fractures. Other possible symptoms of hypophosphatemia include respiratory symptoms, nausea, vomiting, and diarrhea.[38]

Despite the potential serious consequences of hypophosphatemia, it is inconsistently identified and graded in clinical trials, including trials of Injectafer sponsored by American Regent and Vifor Pharma. Systematic literature reviews have found "(1) inconsistent inclusion of serum phosphate and hypophosphatemia as end-points of interest in studies of [IV iron] within [iron deficiency anemia], (2) a lack of a standard approach and timeline for measurement of phosphate levels, and (3) significant variability in the reporting, definitions and follow-up of any hypophosphatemia observed. These findings indicate that there is a clear need for additional rigorous and standardized research into hypophosphatemia as a clinical consequence of [IV iron] administration."[39] Further, until there are consistent definitions and measurement of hypophosphatemia and systematic inclusion of detailed reporting of serum phosphate in trials

[37] *Id.*
[38] Schaefer et al. Bone 2022 (attached as Exhibit A).
[39] John A. Glaspy et al., *Hypophosphatemia Associated with Intravenous Iron Therapies for Iron Deficiency Anemia: A Systematic Literature Review*, 16 THERAPEUTICS AND CLINICAL RISK MGMT. 245, 255 (2020). [hereinafter "Glaspy et al. 2020"] (attached as Exhibit J).

and clinical practice, "it may continue to be difficult to fully understand the severity and magnitude of treatment-emergent hypophosphatemia. The studies analyzed within this review may have underestimated the occurrence of hypophosphatemia and its . . . clinical consequences due to the short duration of dosing regimens and follow-up evaluation used within study protocols."[40] Ultimately, despite documented serious consequences of hypophosphatemia, particularly as associated with Injectafer, "current trials neither consistently nor adequately assess the frequency and severity of treatment-emergent hypophosphatemia and may underestimate its prevalence."[41]

On February 19, 2020, FDA approved an sNDA for Injectafer that, among other things, added safety and dosage and administration information to the U.S. Full Prescribing Information ("USPI") related to hypophosphatemia.[42] Specifically, the USPI was updated as follows: (i) a warning and precaution was added for symptomatic hypophosphatemia that identifies a history of gastrointestinal disorders associated with malabsorption of fat-soluble vitamins or phosphate, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, vitamin D deficiency and malnutrition as possible risk factors; (ii) the dosage and administration section was amended to recommend monitoring of serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of Injectafer treatment with similar language reflected in the hypophosphatemia warning and precaution; and (iii) the post-marketing experience section was revised to include hypophosphatemia as an adverse reaction that had been reported from the post-marketing spontaneous reports with Injectafer.[43] With the exception of additional adverse events of hypophosphatemia reported in clinical trials added to the USPI after this sNDA approval, these changes remain the primary language related to hypophosphatemia in the Injectafer USPI.

A few months after this label update, the European Medicines Agency ("EMA") reviewed the risk of hypophosphatemic osteomalacia for all IV iron products available in the European Union, excluding iron dextran. This assessment concluded that hypophosphatemic osteomalacia is not a class effect and that a causal relationship between Injectafer and hypophosphataemic osteomalacia is at least a reasonable possibility.[44] Thus, the EMA recommended updating the labeling for any products containing ferric carboxymaltose, including Injectafer, to reflect this risk. Following the EMA's decision, the United Kingdom Medicines and Healthcare products Regulatory Agency ("MHRA") issued a drug safety update stating, among other things, that "[Injectafer] is known to be commonly associated with hypophosphatemia . . . cases have been reported of symptomatic hypophosphataemia leading to

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[40] *Id.*

[41] *Id.* at 245; *see also* Benedikt Schaefer et al., *Hypophosphataemia after treatment of iron deficiency with intravenous ferric carboxymaltose or iron isomaltoside—a systematic review and meta-analysis*, 87 BRITISH J. CLINICAL PHARMACOLOGY 2256, 2256 (2021). [hereinafter "Schaefer et al. British J. Clin. Pharmacology 2021"] (attached as Exhibit K).

[42] FDA, *Supplemental Approval NDA 203565/S-009* (Feb. 19, 2020), *available at:* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/203565Orig1s009ltr.pdf.

[43] *See id.*; *see also* Injectafer Full Prescribing Information (Feb. 2020), *available at:* https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203565s009lbl.pdf.

[44] *Annex I: Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s), available at* https://www.ema.europa.eu/en/documents/psusa/iron-parenteral-preparations-except-iron-dextran-cmdh-scientific-conclusions-grounds-variation/00010236/202001_en.pdf (attached as Exhibit L).

infrequent reports of hypophosphataemic osteomalacia and fractures in patients with existing risk factors and following prolonged exposure to high doses – some cases required clinical intervention, including surgery . . . advise patients to seek medical advice if they experience symptoms indicative of hypophosphataemia, including new musculoskeletal symptoms or worsening of tiredness – be aware these symptoms may be confused with those of iron deficiency anaemia . . . if hypophosphataemia persists, re-evaluate treatment with ferric carboxymaltose."[45] This update also identified vitamin D deficiency, calcium and phosphate malabsorption, secondary hyperparathyroidism, inflammatory bowel disease, and osteoporosis as pre-existing risk factors for hypophosphatemia. The update recommends monitoring serum phosphate in these patients as well as those requiring multiple administrations of Injectafer at higher doses and those on long-term treatment with Injectafer.[46]

These regulatory developments are strongly corroborated by findings in randomized clinical trials. The FIRM (A Phase III, Randomized, Multicenter, Double-Blind, Safety Study of Ferumoxytol Compared to Ferric Carboxymaltose for the Treatment of Iron Deficiency Anemia) trial, a randomized, multicenter, double-blinded, controlled, noninferiority trial, compared the safety and efficacy of a single FDA-approved course of IV ferumoxytol versus Injectafer for the treatment of iron deficiency anemia.[47] A secondary prespecified analysis of this trial evaluated the incidence of, and clinical risk factors for, hypophosphatemia.[48] 1,997 patients were enrolled between February 2016 and January 2017 and randomized 1:1 to 510 mg of ferumoxytol or 750 mg of Injectafer, administered intravenously over 15 minutes at baseline and 1 week later. This trial found that "the incidence of severe hypophosphatemia (<2.0 mg/dl) and extreme hypophosphatemia (<1.3 mg/dl) was significantly higher in the [Injectafer] group versus the ferumoxytol group (<2.0 mg/dl, 50.8% vs. 0.9%; <1.3 mg/dl, 10.0% vs. 0.0%; $P < 0.001$)."[49] In addition, "[c]ompared with none of the ferumoxytol-treated patients, 29.1% of [Injectafer]–treated patients remained hypophosphatemic at the end of the 5-week study period ($P < 0.001$), including 4.7% with extreme hypophosphatemia <1.3 mg/dl."[50] In addition, a multivariable model found that treatment with Injectafer was the strongest risk factor for incident hypophosphatemia (odds ratio 250.6, 95% CI 115.4–544.5).[51]

Another set of studies, known as the PHOSPHARE (A Randomized, Open-label, Comparative Trial Comparing the Incidence of Hypophosphatemia in Relation to Treatment With Iron Isomaltoside/Ferric Derisomaltose and Ferric Carboxymaltose in Subjects With Iron Deficiency Anaemia) trials, consisted of two identically designed, open-label, randomized

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[45] MHRA, Drug Safety Update, *Ferric carboxymaltose (Ferinject▼): risk of symptomatic hypophosphataemia leading to osteomalacia and fractures* (Nov. 16, 2020) [hereinafter "MHRA Drug Safety Update"], *available at:* https://www.gov.uk/drug-safety-update/ferric-carboxymaltose-ferinject-risk-of-symptomatic-hypophosphataemia-leading-to-osteomalacia-and-fractures (attached as Exhibit M).
[46] *Id.*
[47] Myles Wolf et al., *Randomized trial of intravenous iron-induced hypophosphatemia*, JCI INSIGHT, Dec. 2018, at 1. [hereinafter "Wolf et al. 2018"] (attached as Exhibit N).
[48] The nomenclature and thresholds for the severity of hypophosphatemia differ across the studies discussed in this section. This emphasizes that there remains inconsistent classification and grading of hypophosphatemia in clinical trials and settings.
[49] Wolf et al. 2018 at 1.
[50] *Id.*
[51] *Id.*

clinical trials conducted at 30 sites across the United States between October 2017 and June 2018 ("Trial A") and October 2017 and May 2018 ("Trial B") to compare the incidence, severity and mechanisms of hypophosphatemia, and effects on biochemical biomarkers of mineral and bone homeostasis of treatment with iron isomaltoside/ferric derisomaltose or Injectafer in patients with iron deficiency anemia. A total of 245 patients were enrolled (Trial A: n=123; Trial B: n=122) and randomized 1:1 to iron isomaltoside/ferric derisomaltose or Injectafer. The primary endpoint was the incidence of hypophosphatemia, defined as serum phosphate level less than 2.0 mg/dL, at any time from baseline to day 35. The incidence of hypophosphatemia at any time from baseline to day 35 was significantly lower among patients treated with iron isomaltoside/ferric derisomaltose than with Injectafer (Trial A: 7.9% vs 75.0% [adjusted rate difference, –67.0% {95% CI, –77.4% to –51.5%}], P < .001; Trial B: 8.1% vs 73.7% [adjusted rate difference, –65.8% {95% CI, –76.6% to –49.8%}], P < .001). In fact, by day 7 of both trials, the prevalence of hypophosphatemia was significantly lower in patients treated with iron isomaltoside/ferric derisomaltose than Injectafer (pooled analysis: 3.3% vs 33.6 %), despite the Injectafer group having received only 750 mg of iron by that time vs 1000 mg in the iron derisomaltose group.[52] Moreover, "[s]evere hypophosphatemia (serum phosphate ≤1.0 mg/dL) was not observed in iron isomaltoside[/ferric derisomaltose]–treated patients, but developed in 11.3% of [Injectafer]–treated patients in the pooled analysis (P < .001)."[53]

A secondary analysis of the PHOSPHARE trials found that Injectafer was the only consistent risk factor for hypophosphatemia (< 2.0 mg/dl; odds ratio versus iron isomaltoside/ferric derisomaltose: 38.37; 95% CI: 16.62, 88.56; P < 0.001).[54] It also found that "[p]atients who developed severe or persistent hypophosphatemia after [Injectafer] treatment manifested more severe derangements in bone and mineral metabolism. Changes in bone biomarkers continued beyond resolution of hypophosphatemia, suggesting ongoing effects on bone that may help explain the association of [Injectafer] with osteomalacia and fractures."[55] Ultimately, the authors found that lower serum phosphate and active vitamin D on day 7 to be independent predictors of persistent hypophosphatemia at day 35 and, therefore, recommended that all patients who receive Injectafer have their serum phosphate tested at baseline and day 7 to determine whether to administer the second 750 mg dose of Injectafer in an FDA-approved treatment course.[56]

In addition to these randomized trials, a number of systematic literature reviews have found a strong association between the use of Injectafer and hypophosphatemia. In particular, at least two reviews found that the highest hypophosphatemia rates were consistently seen with

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[52] Myles Wolf et al., *Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials*, 323 JAMA 432, 435 (2020). [hereinafter "Wolf et al. 2020"] (attached as Exhibit O).
[53] *Id.* at 437.
[54] Benedikt Schaefer et al., *Risk Factors for and Effects of Persistent and Severe Hypophosphatemia following Ferric Carboxymaltose*, J. CLINICAL ENDOCRINOLOGY AND METABOLISM, Nov. 2021, at 2. [hereinafter "Schaefer et al. J. Clinical Endocrinology and Metabolism 2021"] (attached as Exhibit P).
[55] *Id.*
[56] *Id.* at 6.

Injectafer when compared to other IV iron replacement products.[57] One of these reviews further noted that Injectafer-induced hypophosphatemia "does not resolve for at least 3 months in a large proportion of affected patients."[58] In fact, a subsequent comprehensive case review found that Injectafer-induced hypophosphatemia cases occurred after a single dose in 25 out of 77 individual case reports detailing Injectafer-induced hypophosphatemia.[59]

Additionally, a single-center retrospective study examined the incidence and clinical consequences of hypophosphatemia after IV administration of Injectafer in hospitalized patients with iron deficiency anemia in the U.K. This study found the incidence of moderate/severe hypophosphatemia (defined as serum phosphate < 0.65 mmol/L) post-Injectafer to be 33.7% and the incidence of severe hypophosphatemia (defined as serum phosphate ≤ 0.32 mmol/L) within this group to be 8.8%. Moreover, 29.8% of cases with moderate/severe hypophosphatemia required IV phosphate intervention with an average of 4.4 infusions per case.[60] This study ultimately concluded that "[m]oderate/severe hypophosphataemia is a frequent adverse drug reaction with [Injectafer]. In our study, [Injectafer]-induced moderate/severe hypophosphataemia was also persistent, often required treatment, and was associated with longer hospital stay."[61]

e) *Study Integrity in Eastern Europe*

As noted above, a significant portion of sites and patients involved in the FAIR-HF and CONFIRM-HF trials were from Eastern Europe, a region with publicized clinical trial integrity issues. One of the most notable examples is the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial.[62] The TOPCAT trial enrolled 3,445 patients from the United States, Canada, Brazil, Argentina, Russia, and Georgia between August 10, 2006 and January 31, 2012 with a mean follow up of 3.3 years. The primary outcome for this trial was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure in patients that received spironolactone or placebo. Post hoc analyses showed "a marked regional variation in event rates, with patients in the placebo group who were enrolled in Russia or Georgia having a much lower likelihood of a primary-outcome event than those enrolled in the Americas."[63]

This significant regional difference in event rates, as well as clinical profiles and responses to spironolactone, raised concerns as to study conduct at the Russian and Georgian sites.[64] Concentrations of canrenone (an active metabolite of spironolactone) were measured in

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[57] Glaspy et al. 2020 at 245 (attached as Exhibit J); Schaefer et al. British J. Clin. Pharmacology 2021 at 1 (attached as Exhibit K).
[58] Schaefer et al. British J. Clin. Pharmacology 2021 at 1.
[59] Schaefer et al. Bone 2022 at 1.
[60] Konstantinos C. Fragkos et al., *Hypophosphataemia after intravenous iron therapy with ferric carboxymaltose—Real world experience from a tertiary centre in the UK*, GASTROHEP, 2020, at 3 (attached as Exhibit Q).
[61] *Id.* at 1.
[62] Bertram Pitt et al., *Spironolactone for Heart Failure with Preserved Ejection Fraction*, 370 NEW ENG. J. MED. 1383, 1383 (2014) (attached as Exhibit R).
[63] *Id.* at 1391.
[64] Simon de Denus et al., Correspondence, *Spironolactone Metabolites in TOPCAT — New Insights into Regional Variation*, 376 NEW ENG. J. MED. 1690, 1690 (2017) (attached as Exhibit S).

patients in the TOPCAT trial from the United States and Russia to further investigate these disparities. This analysis found that, in "the participants who reported taking the assigned doses of spironolactone, a significant correlation between the doses of spironolactone that the participants reported taking and canrenone concentrations was found among the participants from the United States and Canada, but not among the participants from Russia."[65] Such findings showed "significant regional discrepancies in the reported use and the actual use of spironolactone, as assessed by measurement of metabolite concentrations. Taken together with other reported regional differences in the TOPCAT trial, the results of the current study arouse concerns regarding study conduct at some sites in Russia and, by implication, Georgia, where event rates and responses to spironolactone were also of concern . . . . Our findings suggest that the trial results obtained in Russia do not reflect the true therapeutic response to spironolactone."[66] In fact, at the time, the then-current FDA Commissioner Dr. Robert Califf said that the finding "is disturbing and it's good to get it published. I'll just say that globalization of trials is much needed since 96% of people don't live in the U.S., but 'offshoring' for financial reasons is bad because it raises the risk of malfeasance."[67]

2. <u>FDA should deny any Injectafer sNDAs for labeling changes based on the FAIR–HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless intended to add or strengthen a contraindication, warning, precaution, or adverse reaction.</u>

There are a number of fundamental flaws with the FAIR-HF and CONFIRM-HF trials that should preclude FDA from approving any sNDA for Injectafer, except those intended to add or strengthen a contraindication, warning, precaution, or adverse reaction. First, the primary endpoints used in FAIR-HF and CONFIRM-HF are insufficient to support approval of an expanded indication. These trials used quality-of-life-related and functional endpoints instead of objective clinically meaningful cardiovascular outcomes, such as reduction in hospitalization for heart failure and cardiovascular death, and are modest in size and duration. FDA should require clinical data submitted in support of a label extension in this patient population to utilize objective, clinically meaningful endpoints that are evaluated for a sufficient duration of time in studies that are sufficiently powered by an adequate patient population.

The primary endpoints were evaluated at Week 24 in both studies, and they do not provide any long-term safety or efficacy data beyond 24 weeks in FAIR-HF and 52 weeks in CONFIRM-HF. Long-term data are essential in a fragile population, such as patients with heart failure with reduced ejection fraction, especially in the absence of data regarding objective, clinically meaningful endpoints. This is further exacerbated by the low number of patients studied in each of these trials, which collectively amounted to 800 patients. As such, it is questionable that FAIR-HF and CONFIRM-HF are sufficient to provide meaningful data and analyses regarding efficacy in this patient population or permit fair and responsible conclusions

[65] *Id.* at 1692.
[66] *Id.*
[67] Larry Husten, *CardioBrief: Series Questions Raised About Validity Of International Trials*, MEDPAGETODAY (April 26, 2017), https://www.medpagetoday.com/cardiology/cardiobrief/64810 (attached as Exhibit T).

that Injectafer will have its purported effect in this patient population. Thus, such data and analyses fall short of constituting substantial evidence necessary for sNDA approval.

Even if quality-of-life-related and functional endpoints were appropriate, which we are not conceding, peak VO_2 is the gold standard endpoint for evaluation of exercise improvement and should have been used instead. For example, while 6MWT is a surrogate, cardiopulmonary exercise testing with an assessment of peak VO_2 permits assessment of the organ system limiting gas exchange. In addition, in contrast to 6MWT, peak VO_2 has been shown to be immune to a training or familiarization effect with repeated measures in heart failure.[68] In fact, the CONFIRM-HF manuscript even acknowledges that peak VO_2 provides more objective information.[69] With respect to FAIR-HF, PGA is a crude 7 step score, where the patient is asked about if his/her medical condition since starting in the trial. When cardiac specific scores have been developed (*e.g.*, Kansas City Cardiomyopathy Questionnaire), it would have been preferable to use that as part of the primary endpoint. NYHA is a 4 step score. Furthermore, both endpoints are open for bias if the complex double-blinding procedure has not been performed entirely according to protocol.

Second, the safety results in FAIR-HF and CONFIRM-HF do not provide sufficient information for FDA to evaluate the risk-benefit profile of Injectafer for any label extensions. As already noted, FAIR-HF and CONFIRM-HF have limited total exposure times and lack long-term data due to their modest duration (24 weeks and 52 weeks, respectively) and enrollment sizes. Moreover, neither FAIR-HF nor CONFIRM-HF assess the risk of hypophosphatemia, which is a common and potentially severe issue associated with Injectafer. Additionally, one of the initial pivotal trials for Injectafer excluded "[a]ny other laboratory abnormality, medical condition, or psychiatric disorders which in the opinion of the investigator would put the subject's disease management at risk or may result in the subject being unable to comply with study requirements."[70] This exclusion criterion would encompass patients with pre-existing risk factors for hypophosphatemia (*e.g.*, vitamin D deficiency, secondary hyperparathyroidism), thereby lessening the opportunity to study and evaluate the impact of hypophosphatemia and related side effects in such at-risk patients.[71] Moreover, Injectafer induces hypophosphatemia via an increased secretion of the phosphaturic hormone, fibroblast growth factor 23 ("FGF23").[72] Meta-analysis has suggested that individuals with increased plasma FGF23 levels might suffer a

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[68] Rajeev Malhotra et al., *Cardiopulmonary Exercise Testing in Heart Failure*, 4 J. AM. COLL. CARDIOLOGY: HEART FAILURE 607, 613 (2016) (attached as Exhibit U).

[69] Ponikowski et al. at 666. ("Cardiopulmonary exercise testing with the assessment of peak oxygen consumption is another method applied to evaluate functional capacity in [heart failure], which can provide even more objective information on exercise tolerance than 6MWT.") (attached as Exhibit H).

[70] NIH, CLINICALTRIALS.GOV, *Efficacy and Safety of Intravenous Ferric Carboxymaltose (FCM) in Patients With Iron Deficiency Anemia (IDA)*, https://clinicaltrials.gov/ct2/show/NCT00982007 (last accessed Jan. 12, 2022) (attached as Exhibit V).

[71] Additionally, the other initial pivotal trial in patients with chronic kidney disease likely masked the effects and occurrence of hypophosphatemia because decreased renal function in this patient population generally tends to increase serum phosphate levels. *See* NIH, CLINICALTRIALS.GOV, *Evaluation of Efficacy and Safety of Ferric Carboxymaltose (FCM) in Patients With Iron Deficiency Anemia and Impaired Renal Function (REPAIR-IDA)*. https://clinicaltrials.gov/ct2/show/NCT00981045 (last accessed Jan. 12, 2022) (attached as Exhibit W); *see also* Schaefer et al. Br J Clin Pharmacol 2021 (attached as exhibit K).

[72] Schaefer et al. Bone 2022 (attached as exhibit A).

higher risk of all-cause mortality and cardiovascular mortality.[73] To rule out any potential adverse cardiovascular outcomes, including cardiovascular mortality, related to Injectafer-induced elevation of FGF23, appropriately powered studies are warranted to complement existing evidence from smaller trials with moderate exposure time.

The absence of such assessments and long-term safety data in these studies is particularly troubling because they did not utilize objective, clinically meaningful endpoints, had small sample sizes and short follow up times, and in the case of FAIR-HF used a subtherapeutic dosing regimen that does not reflect current U.S. clinical practice. Specifically, FAIR-HF utilized a dosing regimen of 200 mg of Injectafer weekly and then every four weeks during the correction phase, which is significantly lower than the FDA-approved regiment of 1,000 to 1,500 mg per course. In fact, FAIR-HF notes that *"[t]he results of our study are applicable only to this dosing regimen.*" Therefore, FAIR-HF could not be used to support the safety profile of higher single doses, or any other dosing regimen.

Ultimately, these limitations make it difficult to evaluate what objective benefit Injectafer can provide in this patient population in relation to its risks. As a result, these studies present uncertainties in FDA's risk-benefit analysis as to both efficacy and particularly safety; FDA should not tolerate these uncertainties given the availability of other IV iron replacement products on the market, particularly considering that such products have less risk of hypophosphatemia. Because hypophosphatemia presents a serious safety risk associated with Injectafer, studies in support of new or expanded indications should clearly demonstrate "*direct and meaningful benefit on the most important clinical outcomes*."[74] As discussed, these studies clearly fall short of this threshold. Therefore, FDA should not rely on these trials to reach a determination that Injectafer presents a favorable risk-benefit profile in this patient population. Furthermore, as discussed below, the current USPI does not sufficiently warn against hypophosphatemia and related side effects, which should be investigated before expanding the indications for Injectafer.

Third, the FAIR-HF and CONFIRM-HF trials reflect outdated clinical practice. The last patient in FAIR-HF was enrolled in December 2008, and the last patient in CONFIRM-HF was enrolled in February 2011; therefore, there is no use of contemporary pharmacotherapy such as sacubitril/valsartan, which was approved in the U.S. and Europe in 2015 and endorsed in U.S. and European guidelines in 2016. In the 2016 ACC/AHA/HFSA guideline update, sacubitril/valsartan received a class I recommendation recommended for patients with chronic heart failure to reduce morbidity and mortality.[75] Sacubitril-valsartan (also referred to as ARNI) is today one of the cornerstone therapies in guideline-directed medical therapy for management

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[73] Zhexue Qin et al., *Fibroblast growth factor 23 as a predictor of cardiovascular and all-cause mortality in prospective studies*, ATHEROSCLEROSIS, June 2017 at 1 (attached as Exhibit X).
[74] Benefit-Risk Guidance at 4 (emphasis added).
[75] Clyde W. Yancy et al., *2016 ACC/AHA/HFSA Focused Update on New pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure*, 68 J. AM. COLL. CARDIOLOGY 1476, 1480 (2016) (attached as Exhibit Y).

of heart failure with reduced ejection fraction.[76] Therefore, consistent with FDA's consideration of the treatment landscape in evaluating a product's risk-benefit profile, FAIR-HF and CONFIRM-HF should not be used for a label extension for a population where clinical practice has experienced significant improvements since the trials were conducted.

Fourth, the prevalence of sites and patients from Eastern Europe together with endpoints susceptible to bias raise questions as to the integrity and reliability of the data from the FAIR-HF and CONFIRM-HF trials. As noted, 79% percent of the sites in FAIR-HF were located in Eastern Europe (27 were in Russia, 16 in Ukraine, 7 in Poland, 5 in the Czech Republic, and 4 in Romania) and 86% of all patients in CONFIRM-HF were recruited in Eastern Europe (161 [53% of all patients] from Russia, 50 from Poland, and 50 from Ukraine). This region, in particular Russia, was found to have shown significant discrepancies in the reported use and the actual use of spironolactone that, when taken together with other reported regional differences in the TOPCAT trial, raised concerns regarding study conduct. Notably, 8 out of the 36 Russian TOPCAT sites were sites in either FAIR-HF or CONFIRM-HF and overlap in ongoing study conduct exists between TOPCAT and FAIR-HF and CONFIRM-HF.

As noted, the endpoints in FAIR-HF and CONFIRM-HF are susceptible to bias if patients or study personnel have not been appropriately blinded. For IV iron, the double-blinding process is cumbersome and typically involves unblinded staff at sites due to the characteristic color of the iron, which requires significant efforts on sites to ensure appropriate blinding of patients and study personnel. Considering the finding on regional variation from TOPCAT and contemporaneous study conduct, the high number of Russian and East European sites and patients in FAIR-HF and CONFIRM-HF is a concern. Although it cannot *per se* be concluded that these patients have not been managed according to protocol, it does cast doubt on the quality of the trial conduct. If the trials had been larger, it would have been prudent to perform an analysis to explore if results from Russia and Eastern European sites differed from the overall findings.

The above deficiencies with FAIR-HF and CONFIRM-HF are significant and cannot be remedied by supportive data from AFFIRM-AHF. First, AFFIRM-AHF failed to meet its primary endpoint. Second, among the secondary endpoint, there was not even a numerical signal of reduction of cardiovascular death. The apparent lack of benefit on cardiovascular mortality may be because AFFIRM-AHF was underpowered to explore this endpoint because IV iron does not affect cardiovascular mortality in this population, or because the potential benefit of IV iron on cardiovascular mortality is counter-balanced by other properties caused by the Injectafer formulation – *e.g.*, the increase in FGF23. Third, AFFIRM-AHF suffered from similar issues as FAIR-HF and CONFIRM-HF in that there was modest total exposure time due to the limited duration of the trial of 52 weeks combined with limited sample size. As discussed above, this is not sufficient to establish long-term safety and effectiveness data, particularly in this vulnerable patient population. Fourth, AFFIRM-AHF studied Injectafer in a different patient population than FAIR-HF and CONFIRM-HF. Specifically, AFFIRM-AHF involved patients hospitalized for acute heart failure with concomitant iron deficiency and an LVEF ≤ 50%; whereas, patients

[76] Thomas M. Maddox et al., *2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction*. 77 J. AM. COLL. CARDIOLOGY 772, 772 (2021) (attached as Exhibit Z).

in FAIR-HF and CONFIRM-HF were ambulatory with LVEF ≤ 40% or 45%. These different patient populations, therefore, preclude drawing comparisons and supportive use of these studies. Fifth, AFFIRM-AHF does not sufficiently assess the risk of hypophosphatemia in patients receiving Injectafer, which should be mandated for any label extension, as discussed below. Seemingly recognizing some of these issues, American Regent is conducting an ongoing study to evaluate the incidence of death and incidence of hospitalization for heart failure in patients with stable heart failure with reduced left ventricular ejection fraction and iron deficiency.[77] Thus, in addition to the reasons discussed above, it would be premature to consider a label extension based on FAIR-HF, CONFIRM-HF, and AFFIRM-AHF given their various limitations, particularly where potentially more reliable data are being produced. As such, AFFIRM-AHF does little to rectify or resolve any uncertainties regarding the risk-benefit profile in this patient population and should not be used to support approval based on FAIR-HF and CONFIRM-HF.

For these reasons, we respectfully request that FDA deny any Injectafer sNDAs for labeling changes based on the FAIR–HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless intended to add or strengthen a contraindication, warning, precaution, or adverse reaction.

3. <u>FDA should strengthen Injectafer warnings and precautions and its dosage and administration in relation to severe and symptomatic hypophosphatemia and its consequences.</u>

The current warnings and precautions in the USPI for Injectafer are insufficient to safeguard patient safety. The USPI limits the requirement to monitor serum phosphate to patients receiving a "repeat course of treatment," where the recommended "treatment course" consists of two separate infusions at least 7 days apart.[78] Data shows, however, that Injectafer-induced hypophosphatemia can already occur after the first dose is administered within the treatment course. Specifically, the PHOSPHARE trials found that 33.6% of Injectafer-treated subjects had hypophosphatemia at day 7 prior to receiving a second dose.[79] Additionally, a comprehensive literature case review found that Injectafer-induced hypophosphatemia cases occurred after a single dose in 25 out of 77 individual case reports of Injectafer-induced hypophosphatemia.[80] Based on a secondary analysis of the PHOSPHARE trials finding that lower serum phosphate and active vitamin D on day 7 are independent predictors of persistent hypophosphatemia, the authors recommended that monitoring of serum phosphate occur at baseline and day 7 to determine whether a second Injectafer dose should be given.[81] As such, the

[77] NIH, CLINICALTRIALS.GOV, *Randomized Placebo-controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency (HEART-FID)*, https://clinicaltrials.gov/ct2/show/NCT03037931 (last accessed Jan. 12, 2022) (attached as Exhibit AA).
[78] We acknowledge that the USPI provides for an "alternative dose" of a maximum 1,000 mg single-dose treatment course.
[79] Wolf et al. 2020 at 436-437 (attached as Exhibit O).
[80] Schaefer et al. Bone 2022 at 4.
[81] Schaefer et al. J Clin. Endocrinology and Metabolism 2021 at 9 (attached as exhibit P).

lack of these specific monitoring recommendations presents a potentially significant patient health risk.[82]

The USPI is also deficient in that it fails to outline all types of patients who may be at risk for symptomatic hypophosphatemia. Specifically, the USPI fails to include patients with osteoporosis and inflammatory bowel disease, which were cited in the MHRA drug safety update. In addition, the USPI fails to mention the risk of fractures as also highlighted in the MHRA drug safety update, which stated that "[Injectafer] is known to be commonly associated with hypophosphatemia . . . cases have been reported of symptomatic hypophosphataemia leading to infrequent reports of hypophosphataemic osteomalacia and fractures in patients with existing risk factors and following prolonged exposure to high doses – some cases required clinical intervention, including surgery."[83] A comprehensive literature case review supports MHRA's concerns as it identified osteomalacia with fractures in 34 of 77 individual case reports of Injectafer-induced hypophosphatemia.[84]

All in all, there has been a significant body of data published after the February 2020 Injectafer USPI update that presents new safety information regarding the risk of hypophosphatemia in patients receiving Injectafer. Hypophosphatemia symptoms, particularly myopathy, osteomalacia and fractures, can arise, and have arisen, to the level of a "serious risk" in that they can place a patient at immediate risk of inpatient hospitalization or prolongation of hospitalization and/or a substantial disruption of the ability to conduct normal life functions. Thus, FDA has sufficient ground to warrant further safety labeling-related changes for Injectafer, particularly given the current lack of data fully assessing hypophosphatemia in Injectafer, including in pivotal clinical trials, and the availability of other IV iron replacement products on the market that do not present these same risks based on currently available data. Therefore, we respectfully request that FDA require the USPI to be updated to address these gaps, including as follows:[85]

(i) **Highlights of Prescribing Information - Warnings and Precautions**

Symptomatic Hypophosphatemia: Monitor serum phosphate levels in all patients at baseline and on day 7, and only administer the second dose of Injectafer if the patient has a normal serum phosphate level ~~risk for low serum phosphate who require a repeat course of treatment~~. Do not administer Injectafer to patients with one or more existing risk factors for hypophosphatemia. (5.2)

[82] Including this type of monitoring requirement in the USPI would not be burdensome. The diagnosis of iron deficiency anemia in clinical practice is based on blood tests and, therefore, requiring baseline phosphate measurement would present low cost and effort, particularly when employed as a means to improve patient safety by potentially mitigating hypophosphatemia and its complications.
[83] MHRA Drug Safety Update (attached as Exhibit M).
[84] Schaefer et al. Bone 2022 at 3 (attached as Exhibit A).
[85] The text below shows the proposed edits to the label. Proposed additions are shown in blue and proposed deletions are show in red strikethrough. Green text is used for a sentence that is being proposed to be moved.

(ii) **2.3 Repeat Treatment Monitoring Safety Assessment**

Injectafer treatment may be repeated if IDA reoccurs. Monitor serum phosphate levels in all patients at baseline and on day 7, and only administer the second dose of Injectafer if the patient has a normal serum phosphate level ~~at risk for low serum phosphate who require a repeat course of treatment~~. Do not administer Injectafer to patients with one or more existing risk factors for hypophosphatemia *[see Warnings and Precautions (5.2)]*.

(iii) **5.2 Symptomatic Hypophosphatemia**

Symptomatic hypophosphatemia, including osteomalacia and fractures, requiring clinical intervention has been reported in patients at risk of low serum phosphate in the postmarketing setting. These cases have occurred mostly after repeated exposure to Injectafer in patients with no reported history of renal impairment. Lower serum phosphate and active vitamin D on day 7 after a single treatment has been identified as independent predictors of hypophosphatemia lasting at least 5 weeks. In most cases, hypophosphatemia resolved within three months.

Do not administer Injectafer to patients with one or more existing risk factors for hypophosphatemia. Possible risk factors for hypophosphatemia include a history of inflammatory bowel disease and gastrointestinal disorders associated with malabsorption of fat-soluble vitamins or phosphate, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, osteoporosis, vitamin D deficiency, and/or malnutrition. ~~In most cases, hypophosphatemia resolved within three months.~~

Monitor serum phosphate levels in all patients at baseline and on day 7, and only administer the second dose of Injectafer if the patient has a normal serum phosphate level ~~at risk for low serum phosphate who require a repeat course of treatment~~ *[see Dosage and Administration (2.3)]*.

In addition to these specific labeling changes, we respectfully request that FDA ensure appropriate steps are taken to ensure awareness of these warnings and precautions among treating physicians and their patients by either adding a boxed warning to the USPI for hypophosphatemia reflecting the above language and/or issuing a "Dear Doctor" letter.[86]

[86] FDA to Cooley Godward Kronish LLP – Response to Citizen Petition, FDA-2007-P-0345-0005 at 14 (Dec. 11, 2008) (concluding that the benefit of increasing awareness among healthcare professionals of serious injury justified a boxed warning under 21 C.F.R. § 201.57(c)).

4. Require for any potential future expansion or additional indication for Injectafer to be based on well-controlled clinical studies that specifically assess the risks of severe and symptomatic hypophosphatemia and its consequences for such intended use.

As discussed above, hypophosphatemia is a common and potentially severe adverse reaction associated with Injectafer that has not been adequately assessed in clinical trials to date and for which the current USPI for Injectafer does not provide adequate warnings. Moreover, there is currently a lack of consistent definitions and measurement of hypophosphatemia and systematic inclusion of detailed reporting of serum phosphate in trials and clinical practice such that the prevalence of hypophosphatemia in patients taking Injectafer may be underestimated. As such, the risk of hypophosphatemia presents a significant uncertainty as to the risks of Injectafer. Given the potential severity of hypophosphatemia and availability of other IV iron replacement products, FDA should not tolerate this uncertainty in its risk-benefit assessment. Therefore, FDA should not be able to determine whether the benefits of Injectafer outweigh its risks in the absence of adequate and well-controlled studies that specifically assess hypophosphatemia in the intended patient population.

5. Conclusion

The FAIR-HF and CONFIRM-HF trials exhibit several significant deficiencies, including having insufficient exposure times and lacking long-term safety and efficacy data, that should prevent FDA from reaching a favorable risk-benefit assessment as to Injectafer for use in patients with iron deficiency and heart failure with reduced ejection fraction. In addition, data from the subsequent AFFIRM-AHF trial are insufficient to support approval based on these trials as AFFIRM-AHF suffers from its own limitations, including having a modest total exposure time and studying a different patient population. Moreover, it has become more evident since the February 2020 USPI update for Injectafer that there is a strong association between Injectafer and hypophosphatemia, including its severe sequelae such as osteomalacia and fractures. The current Injectafer labeling is insufficient to address these risks as it omits the risk of fractures, certain at-risk patient populations, and new recommendations for monitoring patients for hypophosphatemia. The prevalence and risk of hypophosphatemia with Injectafer is likely underestimated, and there remains inconsistencies in how this adverse reaction is documented and assessed in both clinical trials and clinical practice.

Therefore, to help mitigate the potential for significant patient harm, we respectfully request that FDA: (i) deny any Injectafer sNDAs for any labeling changes based on the FAIR–HF and CONFIRM-HF trials, including any supportive data from AFFIRM-AHF, unless intended to add or strengthen a contraindication, warning, precaution, or adverse reaction; (ii) strengthen Injectafer warnings and precautions and its dosage and administration in relation to severe and symptomatic hypophosphatemia and its consequences; and (iii) require any potential future expanded or additional indication for Injectafer to be based on well-controlled clinical studies that specifically assess the risks of severe and symptomatic hypophosphatemia and its consequences for such intended use.

C. Environmental Impact

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

D Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Chad A. Landmon