American Regent Announces Results From Phase 3 HEART-FID Trial with INJECTAFER®

Shirley, N.Y. (August 26, 2023) – American Regent, Inc., a Daiichi Sankyo Group company, today announced results from the phase 3 HEART-FID trial of INJECTAFER® (ferric carboxymaltose injection) for the treatment of iron deficiency in adult heart failure patients with reduced ejection fraction (HFrEF). While there was a numerical improvement in the hierarchical composite endpoint, the trial did not meet statistical significance on the primary endpoint, which was a hierarchical composite of death and heart failure hospitalization at 12 months and change from baseline to 6 months in the 6-minute walk test distance.[1] The HEART-FID trial was designed as a single pivotal study instead of two based upon a special protocol assessment with the U.S. Food and Drug Administration (FDA). As a result, the study included a significance level for the final analysis of 0.0099 for the primary endpoint preserving the overall significance at 0.01.[1] The safety profile of ferric carboxymaltose injection was consistent with previous reports with no new safety concerns identified.[1]

Data from the HEART-FID study (NCT03037931) were presented today in a late-breaking research Hot Line session at the European Society of Cardiology Congress 2023. The results were simultaneously published in the *New England Journal of Medicine*.[1]

Results from the HEART-FID study showed that for adult heart failure patients with stable chronic HFrEF who received intravenous ferric carboxymaltose, there were numerically fewer deaths and hospitalizations for heart failure through 12 months and a modest benefit in the six-minute walking distance (6-MWD) at 6 months compared to placebo.[1] At 12 months, death occurred for 131 patients (8.6%) in the ferric carboxymaltose group and 158 patients (10.3%) in the placebo group; there were 297 and 332 total hospitalizations for heart failure, respectively; and the mean change in 6-minute walk distance at 6 months was 8±60 meters and 4±59 meters, respectively.[1] The p-value for the primary composite endpoint was p=0.019. Although there was a numerical improvement in the hierarchical composite endpoint, the study did not meet the pre-specified significance level of 0.0099.[1]

“This trial addresses important clinical questions of diagnosing and treating iron deficiency in patients with heart failure at a specified dose regimen of ferric carboxymaltose to reduce rates of death and hospitalization as well as improve function,” said Robert Mentz, MD, Associate Professor in the Department of Medicine at Duke University School of Medicine, and Member of the Duke Clinical

Research Institute and Clinical Lead for the trial. "While the results from the HEART-FID study did not meet statistical significance at the pre-specified level, the totality of evidence with ferric carboxymaltose from prior studies assessing symptomatic and functional status endpoints – combined with recent clinical outcomes studies – show overall safety and potential benefits."

"These findings are important as we work to further our understanding of the efficacy of IV iron treatment with ferric carboxymaltose for iron deficiency in subsets of patients with heart failure, a progressive and chronic disease," [2] said Ravi Tayi, MD, MPH, Chief Medical Officer, American Regent, Inc. "INJECTAFER is indicated for iron deficient patients with symptomatic heart failure categorized as New York Heart Association class II/III, to improve exercise capacity, based on the CONFIRM-HF trial.[3] INJECTAFER is the most extensively studied intravenous iron and we are confident in its proven benefit and safe use for adult and pediatric patients with iron deficiency anemia, and for certain adult patients with heart failure who have iron deficiency." [3,4]

ABOUT HEART-FID

HEART-FID is the first randomized clinical trial powered to evaluate the effects of intravenous ferric carboxymaltose on a hierarchical composite endpoint of death and HF hospitalization at 12 months and change from baseline to 6 months in the 6-minute walk test distance, in adult patients with iron deficiency and symptomatic HFrEF. The multicenter, randomized, double-blind, placebo-controlled trial enrolled 3,065 patients at 281 centers in 14 countries. Eligible patients were 18 years old and older, in stable chronic heart failure with New York Heart Association functional class II to IV symptoms, ejection fraction ≤40%, iron deficiency (ferritin <100 ng/mL or ferritin 100–300 ng/mL with a transferrin saturation <20%), and documented heart failure hospitalization or elevated N-terminal pro-brain natriuretic peptide. The primary endpoint of the study was a hierarchical composite of death and heart failure hospitalization at 12 months and change from baseline to 6 months in the 6-minute walk test distance. Patients in the ferric carboxymaltose arm were treated with two doses intravenously of 15mg/kg, to a maximum individual dose of 750mg seven days apart and a maximum combined dose of 1500mg, repeated every 6 months as indicated by the results of iron indices. Patients in the placebo arm received two doses of normal saline 15ml seven days apart repeated every 6 months.

About INJECTAFER

In the U.S., INJECTAFER (ferric carboxymaltose injection) is indicated for the improvement of exercise capacity for iron deficient adult patients with symptomatic heart failure; iron deficiency anemia (IDA) in

adult and pediatric patients 1 year of age and older who have either intolerance to oral iron or an unsatisfactory response to oral iron; and adult patients with IDA who have non-dialysis dependent chronic kidney disease. For patients weighing 50 kg (110 lbs.) or more, it is given intravenously (into the vein) by a healthcare provider in two doses of 750 mg each at least seven days apart.[1] For patients weighing less than 50 kg, each of the two doses is administered as 15 mg/kg body weight separated by at least seven days. INJECTAFER dosing for iron deficiency in adult patients with heart failure and New York Heart Association class II/III is based on patient weight (154.3 lbs.) and hemoglobin level (ranges from <10 to 14-15 grams per deciliter (g/dl), starting at a single 500 mg dose up to two 1000 mg doses separated by 6 weeks). A maintenance dose of 500 mg may be administered at 12, 24 and 36 weeks for certain patients based on their serum ferritin levels and transferrin saturation value.

Injectafer is manufactured and marketed under the name of Ferinject® (Ferric Carboxymaltose) by CSL Vifor outside of North America.

U.S. Important Safety Information for INJECTAFER

INDICATIONS
Injectafer® (ferric carboxymaltose injection) is indicated for the treatment of iron deficiency anemia (IDA) in adult and pediatric patients 1 year of age and older who have either intolerance or an unsatisfactory response to oral iron, and in adult patients who have non-dialysis dependent chronic kidney disease. Injectafer is also indicated for iron deficiency in adult patients with heart failure and New York Heart Association class II/III to improve exercise capacity.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
Injectafer is contraindicated in patients with hypersensitivity to Injectafer or any of its inactive components.

WARNINGS AND PRECAUTIONS

Symptomatic Hypophosphatemia
Symptomatic hypophosphatemia with serious outcomes including osteomalacia and fractures requiring clinical intervention has been reported in patients treated with Injectafer in the post-marketing setting. These cases have occurred mostly after repeated exposure to Injectafer in patients with no reported history of renal impairment. However, symptomatic hypophosphatemia has been reported after one dose. Possible risk factors for hypophosphatemia include a history of gastrointestinal disorders associated with malabsorption of fat-soluble vitamins or phosphate, inflammatory bowel disease, concurrent or prior use of medications that affect proximal renal tubular function, hyperparathyroidism, vitamin D deficiency, and malnutrition. In most cases, hypophosphatemia resolved within three months. Correct pre-existing hypophosphatemia prior to initiating therapy with Injectafer. Monitor serum phosphate levels in patients at risk for chronic low serum phosphate. Check serum phosphate levels prior to a repeat course of treatment in patients at risk for low serum phosphate and in any patient who receives a second course of therapy within three months. Treat hypophosphatemia as medically indicated.

Hypersensitivity Reactions
Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-

threatening and fatal, have been reported in patients receiving Injectafer. Patients may present with shock, clinically significant hypotension, loss of consciousness, and/or collapse. Monitor patients for signs and symptoms of hypersensitivity during and after Injectafer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Injectafer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. In clinical trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving Injectafer. Other serious or severe adverse reactions potentially associated with hypersensitivity which included, but were not limited to, pruritus, rash, urticaria, wheezing, or hypotension were reported in 1.5% (26/1775) of these subjects.

Hypertension
In clinical studies, hypertension was reported in 4% (67/1775) of subjects in clinical trials 1 and 2. Transient elevations in systolic blood pressure, sometimes occurring with facial flushing, dizziness, or nausea were observed in 6% (106/1775) of subjects in these two clinical trials. These elevations generally occurred immediately after dosing and resolved within 30 minutes. Monitor patients for signs and symptoms of hypertension following each Injectafer administration.

Laboratory Test Alterations
In the 24 hours following administration of Injectafer, laboratory assays may overestimate serum iron and transferrin bound iron by also measuring the iron in Injectafer.

ADVERSE REACTIONS

Adults
In two randomized clinical studies [Studies 1 and 2], a total of 1775 patients were exposed to Injectafer, 15 mg/kg of body weight, up to a maximum single dose of 750 mg of iron on two occasions, separated by at least 7 days, up to a cumulative dose of 1500 mg of iron. Adverse reactions reported by >2% of Injectafer-treated patients were nausea (7.2%); hypertension (4%); flushing (4%); injection site reactions (3%); erythema (3%); hypophosphatemia (2.1%); and dizziness (2.1%).

Pediatric
The safety of Injectafer in pediatric patients was evaluated in Study 3. Study 3 was a randomized, active-controlled study in which 40 patients (1 to 12 years of age: 10 patients, 12 to 17 years of age: 30 patients) received Injectafer 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; 38 patients evaluable for safety in the control arm received an age-dependent formulation of oral ferrous sulfate for 28 days. The median age of patients who received Injectafer was 14.5 years (range, 1-17); 83% were female; 88% White and 13% Black. The most common adverse reactions (≥4%) were hypophosphatemia (13%), injection site reactions (8%), rash (8%), headache (5%), and vomiting (5%).

Patients with Iron Deficiency and Heart Failure
The safety of Injectafer was evaluated in adult patients with iron deficiency and heart failure in randomized controlled trials FAIR-HF (NCT00520780), CONFIRM-HF (NCT01453608) and AFFIRM-AHF (NCT02937454) in which 1016 patients received Injectafer versus 857 received placebo. The overall safety profile of Injectafer was consistent across the studied indications.

Post-Marketing Experience
The following adverse reactions have been identified during post approval use of Injectafer. Because

these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been reported from the post-marketing spontaneous reports with Injectafer: *cardiac disorders*: tachycardia; *general disorders and administration site conditions*: chest discomfort, chills, pyrexia; *metabolism and nutrition disorders*: hypophosphatemia; *musculoskeletal and connective tissue disorders*: arthralgia, back pain, hypophosphatemic osteomalacia; *nervous system disorders*: syncope; *respiratory, thoracic and mediastinal disorders*: dyspnea; *skin and subcutaneous tissue disorders*: angioedema, erythema, pruritus, urticaria; *pregnancy*: fetal bradycardia.

CLINICAL CONSIDERATIONS IN PREGNANCY

Untreated IDA in pregnancy is associated with adverse maternal outcomes such as postpartum anemia. Adverse pregnancy outcomes associated with IDA include increased risk for preterm delivery and low birth weight.

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.

You are encouraged to report Adverse Drug Events to American Regent, Inc. at 1-800-734-9236 or to the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088**.**

Please see accompanying full Prescribing Information and Medication Guide.

About American Regent, Inc.
American Regent, Inc., a Daiichi Sankyo Group company, is an industry leading injectable manufacturer. For over 50 years, American Regent has been developing, manufacturing and supplying quality generic and branded injectables for healthcare providers. For more than 20 years, we have been a leader in IV iron therapy.

American Regent is committed to US-based manufacturing. To that end, over the last several years, we have made significant investments in expanding and modernizing our manufacturing facilities in Ohio and New York. This expansion will nearly double our capacity and allow us to better serve our customers now and in the future.

Speed counts. Flexibility matters. Reliability and quality are paramount. Because patients should never have to wait for the medications they need.

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References

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