CLINICAL PROTOCOL

Ferric Citrate for the Prevention of Renal Failure in Adults with Advanced Chronic Kidney Disease (FRONTIER)

Compound:	Ferric Citrate (KRX-0502)
Protocol Number:	USRC-2021-002
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Investigator-Sponsor:	US Renal Care, Inc. 5851 Legacy Circle, Suite 900 Plano, TX 75024 United States of America

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Investigator Agreement

I confirm that I have read and that I understand this protocol, the current Investigator Brochure, and other product information provided by the Investigator-Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and to make a reasonable effort to complete the study within the timelines. I further agree to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guidance for Industry, Good Clinical Practice E6 (R2).
- Good Clinical Practice (GCP) including the archiving of essential documents
- The Institutional Review Board (IRB) requirements
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I will make a copy of the protocol and any amendments available to all study personnel under my supervision for the conduct of the study. I will discuss the materials with them to ensure that they are fully informed and understand this study and are able to comply.

_____ _____

Principal Investigator Name (printed) Signature

_____

Date

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

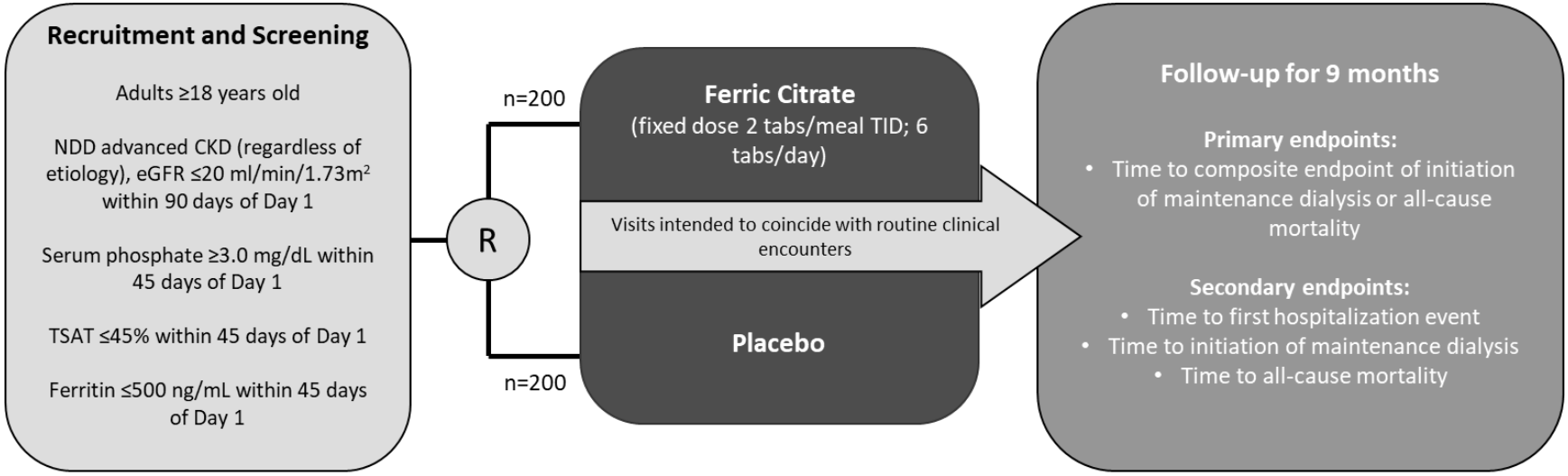
Protocol Synopsis	
Protocol Title	Ferric Citrate for the Prevention of Renal Failure in Adults with Advanced Chronic Kidney Disease (FRONTIER)
Protocol Number	USRC-2021-002
Investigational Product	Auryxia (Ferric Citrate-KRX-0502)
Reference Therapy, as applicable	Matching Placebo
Study Population	The study population will consist of adult subjects ≥18 years old with a diagnosis of non-dialysis dependent (NDD) advanced chronic kidney disease (CKD)
Number of Study Sites	Multicenter, up to 25 sites in the United States (US)
Planned Number of Subjects	Up to 400 subjects will be randomized 1:1 to receive either ferric citrate or matching placebo
Primary Objective/Endpoint	To determine the effect of ferric citrate on the time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality compared to placebo in adult patients with advanced CKD.
Secondary Objectives/Endpoints	• Time to first hospitalization event reported as a serious adverse event (SAE) (excluding disease-related hospitalization [e.g., dialysis access placement, dialysis initiation, kidney transplant] and elective procedures) • Component of Primary – Time to Initiation of Maintenance Dialysis • Component of Primary – Time to All-Cause Mortality
Methodology (study design)	Multicenter, randomized, double-blind, placebo-controlled clinical trial to determine the effect of ferric citrate on the time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality in patients with NDD, advanced CKD. Subjects will be randomized in 1:1 ratio to receive either ferric citrate or matching placebo. All subjects will initiate dosing at 2 tablets per meal or snacks, up to 3 times per day (maximum of 6 tablets/day). The dose of ferric citrate/placebo will only be adjusted based on safety/tolerability. Given the double-blind design of this trial, investigators will be instructed to not prescribe commercial Auryxia to either study arm. The study will be considered completed when all randomized subjects have completed their final study visit (Month 9 or EOT) and 30-day safety follow-up visit. Study visits during the treatment period are to be conducted as part of routine scheduled clinical encounters. Standard of care local laboratory results will be collected, including the monitoring of phosphorus and iron indices (TSAT and ferritin) at quarterly intervals. A pregnancy test in women of child-bearing potential will be required.
Study Duration	Each subject will be followed for a treatment period of approximately 9 months plus an additional 30-day safety follow-up period.
Key Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Adult patients ≥18 years old. 2. Diagnosis of NDD advanced CKD, regardless of etiology. Advanced CKD is defined as at least one local laboratory determined estimated glomerular filtration rate (eGFR) ≤20

	ml/min/1.73m^2 (calculated per any commonly used method or equation for estimating eGFR) within 90 days of Day 1. 3. Most recent transferrin saturation (TSAT) ≤45% within 45 days of Day 1. 4. Most recent serum phosphate is ≥3.0 mg/dL within 45 days of Day 1. 5. Most recent ferritin ≤500 ng/mL within 45 days of Day 1. 6. Women of child-bearing potential must have a negative serum or urine pregnancy test within 30 days prior to Day1 procedures. Can be performed on Day 1 if prior to any Day 1 procedures. Results must be available prior to the 1st dose of study drug. 7. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure. **Exclusion Criteria** 1. Patients who, in the opinion of the Investigator, have acute kidney injury rather than CKD. 2. Patients with planned/imminent maintenance dialysis, or that are anticipated to begin maintenance dialysis within 8 weeks from Screening, in the opinion of the Investigator. 3. A known allergy or intolerance to ferric citrate or any of its constituents. 4. Hypersensitivity reaction to previous oral iron therapy. 5. History of hemochromatosis or iron overload syndrome (e.g., hereditary sideroblastic anemia, thalassemia, polycythemia vera). 6. Active malignancy requiring current treatment except for non-melanoma skin cancer regardless of treatment. 7. Active drug or alcohol dependence or abuse (excluding tobacco use or use of medical or recreational marijuana) within the 12 months prior to Screening or evidence of such abuse, in the opinion of the Investigator. 8. Limited life expectancy (<6 months) in the opinion of the Investigator. 9. Females who are known to be pregnant or are breast-feeding during Screening or are planning to become pregnant and breastfeeding during the study period. 10. Evidence of a clinically active infection requiring antibiotics at Randomization. 11. Unable to comply with study requirements or in the opinion of the Investigator, not clinically stable to participate in the study. 12. Use of an investigational medication or participation in an investigational study within 30 days prior to Day 1. 13. Patients with a scheduled date for living donor kidney transplant
Safety Monitoring	All Serious Adverse Events (SAEs) will be collected. Adverse Events of Special Interest (AESI) (iron overload and hypophosphatemia) will also be collected.

Statistical considerations a. General analysis plan b. Rationale for number of subjects	The primary endpoint is the time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality. The primary endpoint will be analyzed by Cox-proportional hazards regression model. Hazards ratios and corresponding 95% confidence intervals will be presented. The sample size for this study is driven by the primary endpoint, initiation of maintenance dialysis or all-cause mortality and is based on the observed data from the pilot study using nearly identical inclusion and exclusion criteria. The observed rate of the primary composite endpoint in the pilot study (all-cause mortality, maintenance dialysis or kidney transplant) for patients in the standard of care arm was 0.94 events per person-year of follow up. The observed hazard ratio was 0.42 (58% relative risk reduction, p=0.002) for the primary composite endpoint when comparing ferric citrate treated patients versus usual care. Assuming 1 year recruitment and 0.75 years of follow up (9 months) for each individual and a hazard ratio of 0.60 (40% relative risk reduction), a sample size of 400 patients (200 per arm) provides 90% power with a 2-sided alpha p <0.05. Assuming a hazard ratio of 0.50 (50% relative risk reduction), a sample size of 225 patients provides 90% power with a 2-sided alpha p<0.05.

1.2 Schema

Figure 1. Study Schema



CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; NDD=non-dialysis dependent; R=randomization; tabs=tablets; TID=three times per day; TSAT=transferrin saturation

1.3 Schedule of Activities

Table 1. Schedule of Activities

Study Period			Treatment Period[b, c]				Follow-up[d]
Study Month/ Day	Screening[a]	Randomization	D1/ Baseline	Month 3 (D90)	Month 6 (D180)	Month 9 (D270) EOT	Month 10 (EOS) (Day 300)
Visit	1		2	3	4	5	6
Visit Window (days)	-45	-8	0	±30	±30	±30	±7
Visit Type	In-Person		In-person	In-person or virtual	In-person or virtual	In-person	virtual
General and Clinical Assessments							
Informed Consent	X						
Review inclusion/exclusion	X						
Demographics	X						
Medical History[k]	X						
Randomization		X					
Vital Signs[e]	X		X		X	X	
Height and Weight[f]			X		X	X	
Laboratory Assessments as Available per Standard of Care							
Pregnancy test[g]	X						
Serum Chemistry	X[a]			X	X	X[i]	
CBC	X[a]			X	X	X[i]	
eGFR	X[a]			X	X	X[i]	
Other laboratory assessments[h]	X[a]			X	X	X[i]	
Serum Phosphorus	X[a]			X	X	X[i]	
Iron indices	X[a]			X	X	X[i]	
Safety Assessments							
Concomitant medication review[j]	X		X	X	X	X	
PRBC transfusions and/or dialysis access procedures	X	←==========	==========	==========	==========	==========	==========→
Adverse Events of Special Interest[n]			←==========	==========	==========	==========	==========→
SAE Assessment[l]			←==========	==========	==========	==========	==========→
Endpoint Assessment[o]				X	X	X	X
Study intervention							
Study drug prescription/provide study drug[m]		X	X[p]	X	X		
Study drug accountability[q]					X	X	

Study Period			Treatment Period[b, c]				Follow-up[d]
Study Month/ Day	Screening[a]	Randomization	D1/ Baseline	Month 3 (D90)	Month 6 (D180)	Month 9 (D270) EOT	Month 10 (EOS) (Day 300)
Visit	1		2	3	4	5	6
Visit Window (days)	-45	-8	0	±30	±30	±30	±7
Visit Type	In-Person		In-person	In-person or virtual	In-person or virtual	In-person	virtual

CBC: complete blood count; D: Day; eGFR: estimated glomerular filtration rate; EOT: end of treatment; ET: early termination; PRBC: packed red blood cell; PTH: parathyroid hormone; SAE: serious adverse event; SOC: standard of care; TSAT: transferrin saturation.

A: Laboratory Assessments used for screening eligibility must be within 45 days prior to Day 1 with the exception of eGFR which must be within 90 days of Day 1. The screening visit may be conducted as part of a routine scheduled clinical encounter.
B: Study visits are scheduled to occur every 90 days +/-30 days during the treatment period and are anticipated to be conducted as part of a routine scheduled clinical encounter.
C: Virtual visits may be conducted via telephone or electronic format (i.e., zoom call) and will be documented in source documents.
D: Subjects will conclude the study with a follow-up virtual visit 30 days after their last dose of study drug to assess for SAEs and vital status.
E: Vital signs will include systolic blood pressure, diastolic blood pressure, and resting heart rate. These may be captured using data from the subject's clinical encounter. If SOC vital signs are collected prior to signing of informed consent at the screening visit, those vital signs may be captured and do not need to be repeated.
F: Both height and weight will be collected at the Day 1 visit. Height may be self-reported. Weight only will be collected during the treatment period and may be captured using data from the clinical encounter.
G: Serum or urine pregnancy test (women of childbearing potential) must be done at any point within 30 days of Day 1. Can be performed on Day 1 if prior to any Day 1 procedures. Results must be available prior to the 1st dose of study drug.
H: Other laboratory assessments include urine chemistry, hepatic panel, magnesium, cystatin-C and PTH if available (section 9.4, Table 2).
I. The most recent laboratory assessments prior to EOT will be utilized
J. Routine concomitant medications will be assessed at each in-person visit (Screening, Day 1, Month 9). Concomitant medications of interest will be assessed at Screening at then at each subsequent study visit (see Section 9.5.1).
K. Targeted medical history (refer to section 9.2.1)
L. Collection begins at initiation of study drug treatment (1st dose of study drug) and continues through the follow-up visit. Refer to Section 9.5.2.
M. Prescription for study drug must be sent to USRC Rx Pharmacy for processing at time of randomization to ensure on-time delivery prior to Day 1. Refill prescriptions or changes to prescription will be sent to the pharmacy as needed. Dispensing will be a minimum of 3 months supply.
N. Collection begins at initiation of study drug treatment (1st dose of study drug) and continues through the follow-up visit. Refer to Section 9.5.2.
O. Endpoint assessment includes initiation of dialysis, vital status (alive or decreased), transplant, and hospitalization. Any subject who either receives a kidney transplant or initiates maintenance dialysis, and has not withdrawn consent from study participation, will have a vital status check performed at 30-days following the relevant event.
P. If there are delays related to shipment from the USRC Rx pharmacy, study drug will be provided to subjects within 12 days of the Day 1 visit.
Q. Study drug accountability is performed at in-person visits only.

2.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
BL	Baseline
CKD	chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
DD	dialysis-dependent
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ESA	erythropoiesis-stimulating agent
ET	early termination
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IDA	iron deficiency anemia
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KFRE	Kidney Failure Risk Equation
MedDRA	Medical Dictionary for Regulatory Activities
NDD	non-dialysis-dependent
RBC	Red Blood Cell

Abbreviation or Term	Definition
PP	per protocol
QC	quality control
SAE	serious adverse event
SoA	Schedule of Activities
SOC	standard of care
TEAE	treatment-emergent adverse event
TSAT	transferrin saturation
US	United States
USRDS	United States Renal Data System

3.0 INTRODUCTION

This is a multicenter, randomized, double-blind, placebo-controlled clinical trial to determine the effect of ferric citrate on time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality compared to placebo in adult patients with advanced chronic kidney disease (CKD). This study is funded by Akebia Therapeutics, Inc.

3.1 Study Rationale

Ferric citrate is an iron-based phosphate binder and has been extensively studied for the treatment of hyperphosphatemia in subjects with dialysis-dependent chronic kidney disease (DD-CKD) and for the treatment of iron deficiency anemia (IDA) in subjects with non-dialysis-dependent chronic kidney disease (NDD-CKD). Epidemiological evidence suggests that patients with CKD are at greater risk of adverse outcomes due to higher incidence of anemia in this population. The severity of anemia is directly related to the occurrence of cardiovascular events in this patient population. A pilot randomized trial of ferric citrate compared to standard of care in 200 subjects with advanced CKD showed that subjects treated with ferric citrate demonstrated significant changes in laboratory values associated with improvements in anemia and iron. Additionally, this pilot study demonstrated a clinically significant reduction in the risk of the composite endpoint of death, dialysis, or transplantation in patients randomized to ferric citrate. [Block 2019]. It has been recommended by a KDIGO Conference Report that there is a priority need to study the effects of iron repletion in those without overt anemia. This study is being conducted in a population of patients chosen purposefully to reflect the broad characteristics of individuals with advanced CKD and is not restricted only to those with iron deficiency nor hyperphosphatemia.

This study is being conducted to determine if ferric citrate will delay the progression of advanced CKD to kidney failure requiring maintenance dialysis or death, compared to placebo in adult patients with advanced CKD.

3.2 Background

3.2.1 Iron Deficiency Anemia

CKD affects up to 14.9% of adults in the United States (US) [USRDS 2020] and markedly increases the risk of premature cardiovascular events [McCullough 2021, Foley 2005]. Anemia is a common complication of CKD, and is associated with mortality and cardiovascular events, even after accounting for CKD stage and other cardiovascular risk factors, including albuminuria, diabetes mellitus, smoking, and hypercholesterolemia [Kovesdy 2006]. International clinical practice guidelines for anemia in CKD by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 anemia work group recommend evaluation for and resolution of correctable causes of anemia in subjects with CKD and anemia [KDIGO 2012]. While the anemia of CKD is multifactorial in origin, 60% to 73% of persons with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 are iron-deficient [Fishbane 2009]. Therefore, in persons with CKD and anemia (hemoglobin [Hb] <13 g/dL for men; <12 g/dL for women), the

guidelines suggest a trial of iron to increase the Hb if transferrin saturation (TSAT) is ≤30% and serum ferritin is ≤500 ng/mL.

The goals of iron therapy are to avoid iron storage depletion, to prevent impairment of erythropoiesis due to iron deficiency, and to help achieve and maintain target Hb levels. When prescribing iron therapy, the guidelines recommend to "balance the potential benefits of avoiding or minimizing blood transfusions, erythropoiesis-stimulating agent (ESA) therapy, and anemia-related symptoms against the risks of harm in individual subjects (e.g., anaphylactoid and other acute reactions, unknown long-term risks)" [Van Wyck 2000, KDIGO 2012].

For CKD patients on dialysis, iron is usually given intravenously, but oral iron is preferred in patients with NDD-CKD for its convenience and low cost. However, the tolerability and efficacy of currently available oral iron formulations is often limited by gastrointestinal (GI) side effects, poor adherence to therapy, and poor absorption [Drüeke 2012; Cancelo-Hidalgo 2013; Macdougall 2016]. IV iron use remains low in persons with NDD-CKD [Wetmore 2015]. Anaphylactoid and other acute reactions are infrequent but potentially life-threatening complications of IV iron treatment [Wang 2015]. These risks have resulted in black box warnings, or Warnings and Precautions. IV iron administration requires additional safety measures for administration, resulting in higher personnel costs and more time required for these therapies. The long-term safety of IV iron administration has also not been established, and there are concerns that patients may be exposed to increased oxidative stress and greater vulnerability to infections [Macdougall 2016]. Further, IV iron administration can be burdensome for patients, requiring visits to clinics or infusion centers.

ESAs are another treatment modality for anemia of CKD that are widely used in DD-CKD patients but safety concerns due to excess cardiovascular risk for ESAs resulted in black box warnings in 2007.

3.2.2 Hyperphosphatemia

In healthy individuals, phosphate is primarily eliminated by the kidneys, which effectively regulate phosphate balance and blood phosphate concentration. With decreasing kidney function, and other changes associated with CKD, there is a marked decrease in phosphorus excretion in the urine, leading to hyperphosphatemia. Hyperphosphatemia contributes to bone disease, vascular calcification, cardiovascular events, and mortality [Martin and Gonzalez 2011].

Restriction of dietary phosphate is usually not sufficient to control hyperphosphatemia in patients with DD-CKD; therefore, these patients are treated with orally administered phosphate binders which effectively bind dietary phosphate and facilitate fecal elimination rather than intestinal absorption. However, different phosphate binders differ in their safety profile, and all pose a high pill burden [Salusky 2006]. Specific safety or cost concerns with existing phosphate binders resulted in a persistent high level of unmet need for patients with hyperphosphatemia, which resulted in the development of ferric citrate as a phosphate binder in patients with DD-CKD.

Ferric citrate reduces intestinal phosphate absorption by precipitating phosphate in the intestine. The ferric iron from ferric citrate reacts with the phosphorus in the GI tract and precipitates as ferric phosphate or ferrous phosphate. The latter are insoluble and are excreted in the stool. Citrate is absorbed, potentially alleviating the metabolic acidosis that occurs in patients with

renal failure. Ferric citrate is approved for the control of serum phosphorus levels in adult patients with CKD on dialysis.

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

A thorough summary of the risks of ferric citrate is provided in the Investigator Brochure. (Edition 14, 10 March 2020). The main source of information on the safety of ferric citrate in humans comes from two main datasets. One dataset, the risks Pooled Safety Set – Hyperphosphatemia, is based on the integrated data from four completed studies (Studies 304, 305, PBB00101, and 201). These studies involved subjects with DD-CKD treated for hyperphosphatemia with ferric citrate for up to 1 year at dosages of up to 12 g/day. In these four studies, a total of 557 subjects received ferric citrate, 149 subjects received active control and 111 subjects received placebo.

The second dataset, the Pooled Safety Set – IDA, is based on the integrated data from 3 studies (Studies 306, 204, and 207). These studies involved 405 unique subjects (excluding 9 subjects treated in Study 204 and Study 306) with NDD-CKD IDA. In these 3 studies, 301 received ferric citrate (including 81 subjects treated with placebo in the Randomized Period and ferric citrate in the Extension Period of Study 306 and excluding 2 subjects treated with ferric citrate in Study 204 and Study 306) and 188 received placebo (excluding 1 subject treated with placebo in Study 204 and Study 306).

In the hyperphosphatemia pooled safety set, the incidence of subjects who experienced at least one treatment-emergent adverse event (TEAE) was lower in the all ferric citrate group (77.5%) compared with subjects on active control (89.3%). The most common TEAEs in subjects receiving ferric citrate were diarrhea (20.8%), discolored feces (19.4%), and nausea (11.1%). The most common TEAEs in subjects receiving active control were vomiting (14.8%), nausea (14.1%), diarrhea (14.1%), dyspnea (13.4%), vascular access complication (11.4%), hypotension (10.7%), and cough (10.1%).

In the IDA pooled safety set in the randomized periods, the incidence of subjects who experienced at least 1 TEAE was higher among subjects who received ferric citrate (75.3%) than among subjects who received placebo (61.7%). The most common TEAEs in subjects receiving ferric citrate were discolored feces (21.6%), diarrhea (20.5%), constipation (18.4%), nausea (9.5%), hyperkalemia (5.3%), and abdominal pain (4.7%). The most common TEAEs in subjects receiving placebo were diarrhea (12.2%), constipation (10.1%), and nausea (4.3%).

Iron accumulation is a potential risk of long-term treatment with ferric citrate or other iron-containing medicinal products. Continued excessive iron uptake can lead to iron deposition in body tissues and ultimately to organ damage. To prevent excessive iron accumulation, laboratory iron measures will be monitored regularly, and the ferric citrate, oral or IV iron dose will be adjusted in response to sustained elevations of TSAT.

3.3.2 Known Potential Benefits

The ability of ferric citrate to lower serum phosphorus in adult patients with CKD on dialysis was demonstrated in Study KRX-0502-304. In that pivotal study, the efficacy of ferric citrate for controlling serum phosphorus levels was similar to that of calcium acetate and/or sevelamer carbonate, and better than that of placebo.

Study KRX-0502-204 was a 12-week, double-blind, placebo-controlled study.
Study KRX-0502-306 was a 24-week study consisting of a 16-week, randomized, double-blind, placebo-controlled, efficacy period followed by an 8-week, open-label, safety extension period in which all subjects remaining in the study, including those in the placebo group, received ferric citrate. Both studies showed reduction in serum phosphorus levels with ferric citrate treatment compared with placebo. In addition, the efficacy of ferric citrate for the treatment of IDA was demonstrated in 2 controlled studies in adult subjects with CKD not on dialysis.

Ferric citrate's potential benefits are supported by its approval for use in the US for the control of serum phosphorus levels in adult patients with CKD on dialysis, and for the treatment of IDA in adult patients with CKD not on dialysis.

3.3.3 Overall Benefit: Risk Conclusion

No significant change in the safety profile of ferric citrate has been identified in post-marketing surveillance. A recent study demonstrated that treatment with ferric citrate significantly improves anemia in subjects with advanced CKD without the routine use of supplemental iron or ESAs. The results of the study suggest that treatment with ferric citrate can improve clinical outcomes for these subjects, is safe, and potentially beneficial [Block 2019]. The risk-benefit profile of ferric citrate in the treatment of adult patients with CKD remains favorable in the commercial setting.

4.0 OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

4.1.1 Primary Objective

To determine the effect of ferric citrate on the time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality compared to placebo in adult patients with advanced CKD.

4.1.2 Secondary Objective

To evaluate the impact of ferric citrate on time to all-cause hospitalization and individual components of the primary endpoint.

4.2 Study Endpoints

4.2.1 Primary Endpoint

Time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality

4.2.2 Secondary Endpoints

Secondary endpoints include:

1. Time to first hospitalization event reported as a serious adverse event (SAE) (excluding disease-related hospitalization [e.g., dialysis access placement, dialysis initiation, kidney transplant] and elective procedures)
2. Component of Primary – Time to Initiation of Maintenance Dialysis
3. Component of Primary – Time to All-Cause Mortality

4.2.3 Exploratory Endpoints

Exploratory endpoints include:

1. Annualized hospital days prior to initiating maintenance dialysis
2. Receipt of kidney transplant prior to initiating maintenance dialysis
3. Cumulative utilization of rescue therapy for anemia including (individually, [ESA, intravenous iron, RBC transfusion]) prior to initiating maintenance dialysis
4. Time to a composite of death, dialysis, or kidney transplant

5.0 STUDY DESIGN

5.1 Overall Design

This is an investigator-initiated multicenter, randomized, double-blind, placebo-controlled, pragmatic clinical trial in patients with advanced CKD to determine the effect of ferric citrate versus matching placebo on the time to a composite endpoint of maintenance dialysis or all-cause mortality.

Subjects who meet all inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio (stratified by site and eGFR) to receive either ferric citrate or matching placebo. All subjects will receive a fixed dose of 2 tablets orally taken with meals or snacks up to 3 times per day. The maximum daily dose is 6 tablets/day. Subjects will remain on study drug for up to 9 months followed by an additional 30-day safety follow-up period. Study drug will be stopped for subjects who initiate maintenance dialysis or receive a kidney transplant. Subjects who undergo maintenance dialysis or receive a kidney transplant will be removed from study with no follow-up visit, however, these subjects will have a vital status check (to ascertain mortality) performed at 30-days following the relevant event.

The study periods are:

- Screening Period: Up to 45 days prior to Day 1. Standard of Care (SOC) laboratory collection permitted up to 45 days (up to 90 days for eGFR) prior to Day 1.
- Treatment Period: Up to 9 months
- Safety follow-up Period: 30 days after EOT

Each randomized subject will complete 5 study visits (2 in-person and 3 phone/virtual or in-person). In-person study visits should attempt to coincide with routine standard of care office visits and relevant clinical data from such standard of care visits (including assessments for possible endpoint events or adverse events) will be collected and entered into the electronic case report form (eCRF). Standard of care (SOC) laboratory assessments as ordered by the primary nephrologist will be utilized. Iron status and serum phosphate collection and monitoring will be required as part of the SOC laboratory assessments. Laboratory assessments captured in the eCRF other than a screening pregnancy test for women of child-bearing potential and non-SOC iron and serum phosphorus labs, will utilize local laboratory results.

Study drug is not intended to be used as a treatment for either serum phosphorus or iron repletion. Management of serum phosphorus and iron sufficiency will be directed at the discretion of the treating physician and/or Investigator independent of study drug with the exception of protocol required safety adjustments of study drug. The prescribed dose of study drug will be adjusted only in the event of a safety or tolerability concern (as described in Section 7.1.2.1). Investigators will be instructed not to prescribe commercial ferric citrate (Auryxia) to any study participant; however, all other phosphate lowering therapy or iron repletion therapy may be prescribed at the discretion of the PI according to local standard of care.

Subjects may or may not be prescribed phosphate-lowering or iron-repletion therapy prior to Day 1; however, if a subject is receiving commercial ferric citrate (Auryxia), it must be stopped at or prior to Day 1.

5.1.1 Replacement of Participants

Subjects who sign the informed consent form (ICF) and are randomized but do not receive the study intervention may be replaced at the discretion of the Investigator or Investigator-Sponsor. Subjects who sign the ICF and are randomized, receive any dose of the study intervention, and then subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

5.2 Scientific Rationale for Study Design

A pilot randomized trial of ferric citrate in patients with advanced CKD demonstrated that, as compared to standard of care therapy, patients randomized to ferric citrate showed a significant reduction in progression to maintenance dialysis (p=0.001) as well as a significantly lower incidence of the composite endpoint of death, dialysis, or transplant (p=0.002). In addition, compared with usual care, ferric citrate treated subjects had significantly fewer annualized hospitalization admissions and fewer days in the hospital. [Block, 2019, Figure 4].

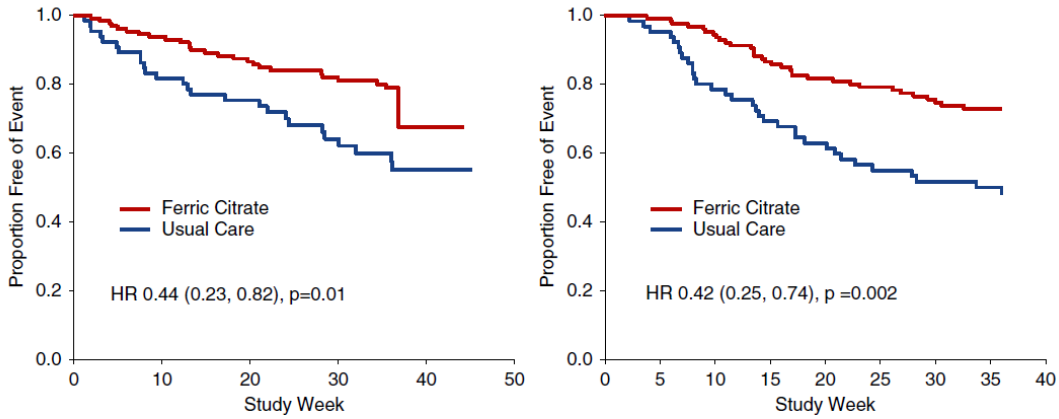


Figure 4. Kaplan–Meier survival function curve for time to first hospitalization (A) and time to the composite end point of death, dialysis, or transplant in all patients (B).

5.3 Justification for Dose

The prescribed dose of study drug will be a fixed dose of 2 tablets orally taken with meals or snacks up to 3 times per day. The maximum daily dose is 6 tablets/day. This is the dose of ferric citrate that was utilized in the pilot randomized trial demonstrating clinical benefit on time to dialysis as described in Section 5.2, and has an established safety profile as it is the approved starting dose for the treatment of iron-deficiency anemia in patients with chronic kidney disease [Auryxia USPI 2021].

5.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

The end of the study will be considered complete after all randomized subjects have completed their final study visit (Month 9 or EOT) and 30-day safety follow-up visit.

Any subject who either receives a kidney transplant or initiates maintenance dialysis, and has not withdrawn consent from study participation, will have a vital status check performed at 30-days following the relevant event. The vital status check will ascertain the subject's mortality (alive vs. deceased).

5.5 Number of Study Sites

Up to 25 investigative sites in the US.

6.0 STUDY POPULATION

6.1 Inclusion Criteria

1. Adult patients ≥18 years old.

2. Diagnosis of NDD advanced CKD, regardless of etiology. Advanced CKD is defined as at least one local laboratory determined estimated glomerular filtration rate (eGFR) ≤20 ml/min/1.73m^2 (calculated per any commonly used method or equation for estimating eGFR) within 90 days of Day 1.
3. Most recent transferrin saturation (TSAT) ≤45% within 45 days of Day 1.
4. Most recent serum phosphate is ≥3.0 mg/dL within 45 days of Day 1.
5. Most recent ferritin ≤500 ng/mL within 45 days of Day 1.
6. Women of child-bearing potential must have a negative serum or urine pregnancy test within 30 days prior to Day 1 procedures. Can be performed on Day 1 if prior to any Day 1 procedures. Results must be available prior to the 1st dose of study drug.
7. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.

6.2 Exclusion Criteria

1. Patients who, in the opinion of the Investigator, have acute kidney injury rather than CKD.
2. Patients with planned/imminent maintenance dialysis, or that are anticipated to begin maintenance dialysis within 8 weeks from Screening, in the opinion of the Investigator.
3. A known allergy or intolerance to ferric citrate or any of its constituents.
4. Hypersensitivity reaction to previous oral iron therapy.
5. History of hemochromatosis or iron overload syndrome (e.g., hereditary sideroblastic anemia, thalassemia, polycythemia vera).
6. Active malignancy requiring current treatment except for non-melanoma skin cancer regardless of treatment.
7. Active drug or alcohol dependence or abuse (excluding tobacco use or use of medical or recreational marijuana) within the 12 months prior to Screening or evidence of such abuse, in the opinion of the Investigator.
8. Limited life expectancy (<6 months) in the opinion of the Investigator.
9. Females who are known to be pregnant or are breast-feeding during Screening or are planning to become pregnant and breastfeeding during the study period.
10. Evidence of a clinically active infection requiring antibiotics at Randomization.
11. Unable to comply with study requirements or in the opinion of the Investigator, not clinically stable to participate in the study.
12. Use of an investigational medication or participation in an investigational study within 30 days prior to Day 1.
13. Patients with a scheduled date for receipt of living donor kidney transplant.

6.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing

requirements. Minimal information includes informed consent, demography, eligibility criteria and screen failure details, including screening laboratory results.

Subjects who fail to qualify for the study may be considered for rescreening at the discretion of the Investigator, if it is considered that the subject's status has changed, and the subject may now qualify for the study. A new informed consent is required to be signed prior to every rescreening. Rescreened subjects will be assigned a new screening number.

Any subject who is randomized to study intervention but does not receive study drug will be considered an early termination.

7.0 STUDY INTERVENTION

7.1 Study Intervention(s) Administration

7.1.1 Study Intervention Description

Ferric citrate will be supplied as tablets for oral administration containing 1 g ferric citrate (210 mg of ferric iron).

Placebo will be supplied as tablets, matching in color and size to ferric citrate.

Subjects should take the assigned study drug orally with meals or snacks or within 1 hour before or after their meals or snacks.

Missed doses should not be taken if greater than 1 hour from meals.

7.1.2 Dosing and Administration

Study drug is not intended to be used as a treatment for either serum phosphorus or iron repletion. Management of serum phosphorus and iron sufficiency will be directed at the discretion of the treating physician and/or Investigator independent of study drug with the only restriction being that subjects cannot be prescribed commercial Auryxia (ferric citrate).

Subjects will be randomized in a 1:1 ratio to receive either ferric citrate or placebo. All subjects will be instructed to take study drug at a fixed dose of 2 tablets per meal or snacks, up to three times per day. The maximum dose is 6 tablets/day. No additional tablets (beyond a total of 6/day) should be taken. Tablets should not be crushed or chewed.

Every effort will be made to provide study drug to subjects at the Day 1 visit. If there are delays related to shipment from the USRC Rx pharmacy, study drug will be provided to subjects within 12 days of the Day 1 visit. Dosing will begin upon receipt of study drug with the next meal/snack. This would not be considered a protocol deviation.

7.1.2.1 Dose Adjustment

No titration of study drug will be performed other than for issues of tolerability or safety.

It is expected that the Investigator will monitor serum phosphorus and iron indices per generally recognized standard of care for individuals with advanced CKD. The monitoring of iron indices

and serum phosphate is required at least every 3 months and failure to monitor these parameters will be considered a protocol deviation.

Required dose adjustments for low serum phosphorus are as follows:

- If serum phosphorus is <3.0 mg/dL captured by a single value, the study drug, and any other prescribed phosphate lowering therapy, should be temporarily held until such time as serum phosphorus is ≥3.0 mg/dL at which time study drug may be resumed at a dose that is approximately equivalent to 50% of the previous total daily dose. The reduction in dose relative to meals or snacks is at the discretion of the investigator as long as it represents a total dose reduction of 50%. Repeat assessment of serum phosphorus will be at the discretion of the Investigator. This assessment must occur at the next scheduled visit (which may be up to three months), or it may also be performed earlier. Other prescribed phosphate lowering therapy may be resumed per investigator discretion when serum phosphorus is ≥3.0 mg/dL.

Required dose adjustments for high TSAT are as follows:

- If TSAT is >45% and ≤50%, captured by a single laboratory value, the study drug should be reduced by 1 tablet per meal or snack (reduce the dose by the equivalent of 50%). Any other prescribed oral or IV iron therapy should be stopped.

  If TSAT is >50%, captured by a single laboratory value, the study drug, and any other prescribed oral or IV iron therapy, should be temporarily held until such time as TSAT is ≤50% (captured by a single laboratory value) at which time study drug may be resumed at a dose that is equivalent to 50% of the previous total daily dose. The reduction in dose relative to meals or snacks is at the discretion of the investigator as long as it represents a total dose reduction of 50%. Repeat assessment of iron indices will be at the discretion of the Investigator. This assessment must occur at the next scheduled visit (which may be up to three months), or it may also be performed earlier.

  If after a 50% reduction in total daily dose of study drug, the TSAT is >50%, the study drug should be temporarily held. Subsequent study visits including the Follow Up visit (Visit 6) should continue to be conducted as per the SoA (regardless of study drug administration). When TSAT is ≤50%, study drug may be resumed. Other prescribed oral or IV iron therapy may be resumed per investigator discretion when TSAT is ≤45%.

Required dose adjustments for high ferritin are as follows:

- If serum ferritin is >500 ng/mL, captured by a single laboratory value, the study drug, and any other prescribed oral or IV iron therapy, should be temporarily held until such time as ferritin is ≤500 ng/mL (captured by a single laboratory value) at which time study drug may be resumed at a dose that is equivalent to 50% of the current total daily dose. The reduction in dose relative to meals or snacks is at the discretion of the investigator as long as it represents a total dose reduction of 50%. Repeat assessment of iron indices will be at the discretion of the Investigator. This assessment must occur at the next scheduled visit (which may be up to three months), or it may also be performed earlier.

- If after a 50% reduction in total daily dose of study drug, the serum ferritin is >500 ng/mL, the study drug should be temporarily held. Subsequent study visits including the Follow Up visit (Visit 6) should continue to occur per the SoA (regardless of study drug administration). When serum ferritin is ≤500 ng/mL, study drug may be resumed. Other prescribed oral or IV iron therapy may be resumed per investigator discretion when ferritin is ≤500 ng/mL.

Both TSAT and ferritin laboratory values must be within ranges defined above prior to resumption of study drug.

Study drug may be titrated downward at any time during the treatment period at the discretion of the Investigator for adverse reactions determined to be related to study drug.

There is no minimum allowable dose of study drug, and the Investigator has discretion to resume dosing up to 6 tablets/day based on subject acceptance when possible (and when TSAT, ferritin, and phosphorus values are within protocol-defined ranges).

All dose adjustments should be captured in the subject specific source documentation and the eCRF.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 Acquisition and Accountability

Akebia Therapeutics will supply study drug to a centralized pharmacy known as USRC Clinical Pharmacy, LLC (USRC Rx), under temperature-controlled conditions. The central pharmacy will maintain the study level accountability and distribution records and will store the study drug under controlled temperature conditions. Investigator-Sponsor or its official designee will supply study drug from USRC Rx to the clinical sites. Please refer to the pharmacy manual for further information.

The Investigator or site designee will be responsible for maintaining accurate study drug patient level accountability, storage, destruction and/or return records for study drug that is received from the central pharmacy. All study drug that is received from the central pharmacy must be kept under controlled temperature in a secure, locked location in which access is limited until dispensed to the individual subject.

All unused and/or partially used study drug will be returned by the study subject for destruction at the investigational site in accordance with its policies and procedures. Records of disposal will be documented and maintained. No unused study drug may be disposed of until fully accounted for by the Investigator-Sponsor or designee. Empty containers may be disposed of in accordance with local procedures after fully accounted for by Investigator-Sponsor or designee.

The use of study drug for any reason other than as directed by the protocol is not permitted.

Refer to Section 7.4 for additional details on assessment of treatment compliance.

7.2.2 Formulation, Appearance, Packaging and Labeling

Blinded study drug, (ferric citrate 1g tablets or matching placebo) will be supplied to USRC Rx in high-density polyethylene bottles. Each bottle will contain 200 tablets.

The unassigned study drug supply will be stored at the USRC Rx in its original packaging. Upon subject randomization and notification to USRC Rx, study drug may be dispensed to meet a 3-9 month supply need (per site discretion) and re-supplied as required in advance of in-person or telephone study visits.

Labeling from the manufacturer will be in accordance with current GMP requirements. The USRC Rx will generate an additional label specific to this research protocol which will not obscure the manufacturers label.

7.2.3 Product Storage and Stability

Please consult the Pharmacy Manual for details on storage and temperature monitoring procedures and managing temperature excursions.

7.3 Measures to Minimize Bias: Randomization and Blinding

7.3.1 Randomization

Eligible subjects will be stratified by site and by eGFR (above or equal to/below 15 ml/min/1.73m^2) randomized in a 1:1 ratio to receive either ferric citrate or matching placebo. eGFR can be calculated using any commonly used method or equation for estimating eGFR.

7.3.2 Blinding

This is a randomized, double-blind, placebo-controlled study. Treatment assignment will be done through a validated electronic system. The Investigator-Sponsor, Investigator, and study teams will not be aware of which treatment will be assigned next.

In case of an emergency, the Investigator has responsibility for determining if unblinding of a subject's treatment assignment is warranted. The Investigator must consult with the Medical Monitor prior to unblinding of a subject's treatment assignment. Subject safety must always be the first consideration in making such a determination. All unblinding requests should be generated within the EDC system. If it is not possible to access the EDC system, the study-specific unblinding request form can be used. If a subject's treatment assignment is unblinded, the Investigator-Sponsor must be notified within 24 hours after breaking the blind. Emergency unblinding procedure details will be provided in the Pharmacy manual. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Unblinding a subject's treatment assignment by the Investigator or study site personnel under any other circumstances (except as noted above) will be considered a protocol deviation.

If a subject's treatment assignment is unblinded, they will be considered an early termination. The subject will permanently discontinue study drug. The subject will be followed as per instructions in Section 8.1.2.

7.4 Study Intervention Compliance

Study personnel will instruct the subjects and caregivers on the correct number of tablets to take each day with their meals or snacks. Subjects will be instructed to return with their bottle(s) of study drug at each in-person visit so that compliance may be assessed. Unused study drug will be re-dispensed to the subject at the end of each in-person visit.

Throughout the study, subjects will be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study drug. The Investigator or designee will also maintain study drug accountability itemizing all study drug dispensed to and returned from each subject during the study. Treatment compliance will be determined from these logs and subject questioning.

Subjects who miss doses will be counseled on the importance of compliance. Subjects will not be withdrawn from the study for reasons related to study drug compliance.

7.5 Concomitant Therapy

7.5.1 Phosphate Lowering Therapy

Investigators may continue or newly prescribe non-Auryxia phosphate lowering therapy as needed throughout the study to maintain serum phosphorus according to the local community standard.

Commercial Auryxia may not be prescribed to any subject for the duration of the study. See Section 7.5.4

In the event of an adverse event of special interest (serum phosphorus <2.5 mg/dL), the Investigator must review other prescribed phosphate-lowering therapies and make adjustments accordingly. Additionally, in the event of a serum phosphorus <3.0 mg/dL, other prescribed phosphate lowering therapy may also require adjustment as per Section 7.1.2.1.

All changes in phosphate-lowering therapy will be captured in source documentation and in the eCRF.

7.5.2 Iron Supplementation

Investigators may continue or newly prescribe iron supplementation (IV, oral) as needed throughout the study to maintain ferritin and TSAT according to the local community standard with the exception of protocol required safety changes in study drug as outlined in Section 7.1.2.1.

In the event of an adverse event of special interest (iron overload), the Investigator must review other prescribed iron supplementation (IV and oral) and make adjustments accordingly. Additionally, in the event of elevated iron indices (TSAT >45% or ferritin >500 ng/mL), other prescribed oral or IV iron therapy may also require adjustment as per Section 7.1.2.1.

All changes in iron supplementation therapy will be captured in source documentation and in the eCRF.

7.5.3 Erythropoiesis-Stimulating Agents (ESAs) or Packed Red Blood Cell (PRBC) Transfusion

There are no restrictions on the use of ESA and dose adjustments may be made at the discretion of the Investigator. All changes in ESA therapy will be captured in source documentation and in the eCRF

Receipt of RBC transfusions will be captured in source documentation and in the eCRF.

- Subjects who receive repeated red blood cell transfusions during the study may need to temporarily hold study drug. For the purpose of the study, "repeated blood transfusion" will be defined as receipt of >4 units of red blood cells within any 6-month period of time. Prior to study drug hold please contact the medical monitor. If study drug is permanently discontinued, subsequent study visits including the Follow Up visit (Visit 6) should occur per the SoA.

7.5.4 Prohibited Medications/Procedures

Potentially eligible subjects may or may not be receiving phosphate-lowering or iron-repletion therapy prior to Day 1; however, if a subject is receiving commercial ferric citrate (Auryxia), it must be stopped at or prior to Day 1.

Prescription of commercial Auryxia is prohibited for all subjects at any time after Day 1/Baseline in the study. All other therapies may be administered per SOC. Receipt of commercial Auryxia for longer than 4 consecutive weeks during trial participation will be considered a protocol deviation. If the Investigator is unwilling to discontinue commercial Auryxia, study drug should be discontinued, and the subject should continue to be followed per the SoA including the Follow Up Visit (Visit 6).

Since ferric citrate will be administered to 50% of subjects, standard drug-drug interactions reported in the Auryxia package insert approved by the Food and Drug Administration (FDA) in the US shall be followed. [Auryxia USPI 2021].

7.5.5 Permitted therapy

There are no restrictions on use of any concomitant medications other than that identified in Section 7.5.4

7.5.6 Potential Drug-Drug Interactions

An interaction with ferric citrate is known to occur with doxycycline and ciprofloxacin. If prescribed, doxycycline should be taken at least 1 hour before study drug and ciprofloxacin should be taken at least 2 hours before or after study drug.

The following drugs, by drug category, did **not** show an interaction with ferric citrate:

- Antibiotics: levofloxacin.
- Anticoagulants/antiplatelets: aspirin, clopidogrel, and warfarin.
- Antidiabetics: glimepiride and sitagliptin.

- Antihyperlipidemics: atorvastatin, fluvastatin, and pravastatin.
- Antihypertensives: amlodipine, diltiazem, enalapril, losartan, metoprolol, and propranolol.
- Cardiac glycoside: digoxin.
- Vitamin D analogs: calcitriol and doxercalciferol.

Consider separation of the timing of the administration of study drug with drugs where a reduction in their bioavailability would have a clinically significant effect on safety or efficacy. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended-release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

8.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Drug

8.1.1 Temporary Interruption of Study Drug

Discontinuation from study drug is different from discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol. The Investigator is strongly encouraged to resume study drug as soon as the reason for temporary interruption is over. Reasons for temporary discontinuation of study drug include:

- Drug-related AEs per the Investigator's discretion
- Unforeseen circumstances per the Investigator's discretion
- Serum phosphorus <3.0 mg/dL
- TSAT is >50%
- Ferritin >500 ng/mL
- Repeated red blood cell transfusions (>4 units of red blood cells within any 6-month period of time). See Section 7.5.3.
- Significant elevation in liver enzymes (SGOT and/or SGPT) >3X ULN or pancreatic enzymes (amylase and/or lipase) >2X ULN or elevation in total bilirubin >2X ULN, without an identifiable alternate etiology. Study drug should not be resumed prior to discussion with Medical Monitor.

The study drug may be restarted when the reason for temporary discontinuation is resolved. If study drug is temporarily discontinued due to elevations in iron indices, both TSAT and ferritin laboratory values must be within protocol-defined ranges prior to resumption of study drug.

The data to be collected at the time of study drug discontinuation should be in accordance with the SoA.

8.1.2 Permanent Discontinuation of Study Drug

Subjects are free to withdraw from taking study drug at any time upon request. Subjects who permanently discontinue study drug will be asked to continue study participation (either by in person visits or by allowing access to medical records) in accordance with the SoA, through completion of the study. The endpoint assessment will be considered the End of Study date.

If a subject declines to continue study visits and withdraws consent to be followed, the subject is an early termination, and NO endpoint assessment will be performed. The subject's early termination date will be considered the End of Study date.

An Investigator **may** discontinue study drug or withdraw a subject from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinically significant AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Iron overload supported by liver biopsy, magnetic resonance imaging and persistent elevations in TSAT or ferritin
- If the TSAT remains >50%; Refer to Section 7.1.2.1
- If the ferritin remains >500 ng/mL; Refer to Section 7.1.2.1
- If the serum phosphorus remains <3.0 mg/dL; Refer to Section 7.1.2.1
- Investigator-Sponsor decision
- Lost to follow-up

The reason for study drug discontinuation will be recorded in source documentation and in the eCRF.

8.2 Withdrawal from Study

Subjects are free to withdraw from participation in the study at any time upon request. Reasons for withdrawal from the study includes:

- Withdrawal of consent from study participant.
- Subjects who initiate maintenance dialysis.
- Subjects who receive a kidney transplant.

Subjects who initiate maintenance dialysis or who receive a kidney transplant, but have not withdrawn consent from study participation, will have a vital status check performed at 30-days following the relevant event. Vital status (alive vs. deceased) will be ascertained using available methods (e.g., phone call, in-person interaction, medical record, dialysis facility records, public records).

Subjects who withdraw their consent will discontinue study drug and be considered an early termination. The reason for subject discontinuation or withdrawal from the study will be recorded in source documentation and in the eCRF. The early termination date will be considered the End of Study date.

8.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled in-person or phone visits and is unable to be contacted by the study site staff. The following actions must be taken if a subject fails to be available for a required study visit:

- The site will attempt to contact the subject and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (a minimum of 3 documented telephone calls, or e-mails or certified letter to subject's listed address). These contact attempts should be documented in the subject's medical record or source documentation.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- Available methods (e.g., phone call, in-person interaction, medical records, dialysis facility records, public records) will be used to attempt to ascertain dialysis status, transplant status, and vital status for all subjects deemed lost to follow-up. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 General Study Periods

9.1.1 Screening, Enrollment, and/or Randomization

Written informed consent must be obtained prior to the subject entering the study and before protocol-directed procedures are performed. Study visits are intended to coincide with the standard of care (SOC) nephrology visit. Initial informed consent discussion, in most cases, will occur at a SOC visit.

- The *Screening period* will be a maximum of 45 days in duration. It is defined as the period of 45 days prior to Day 1 (Baseline). Local laboratory assessments used for eligibility must be within 45 days prior to Day 1, with the exception of eGFR which must be within 90 days of Day 1

If found eligible (and informed consent has been obtained), the subject will be randomized. Dosing will begin on Day 1.

The Screening laboratory values will be defined as the most recent local laboratory assessments obtained prior to Day 1 (within 45 days) with the exception of eGFR which must be within 90 days of Day 1.

9.1.2 Treatment Period

The treatment period of this study includes the following visits:

- Baseline/Day 1 Visit
- Treatment Period: 270 days (9 months)

Each randomized subject will complete 5 study visits during the Treatment Period (2 in-person and 3 telephone/virtual or in-person). Study visits during the treatment period are intended to be conducted as part of routine scheduled clinical encounters.

Every attempt should be made to complete all study visits within the window as outlined in the SoA. If a visit is missed, the reason for the missed visit should be documented in the source chart.

The monitoring of iron indices and serum phosphate is required at least every 3 months and failure to monitor these parameters will be considered a protocol deviation.

9.1.3 End of Treatment Visit

Subjects completing study treatment will undergo a final in-person visit at Month 9 according to the SoA (Section 1.3).

9.1.4 Month 10/End of Study (EOS)

There is a 30-day safety follow-up visit after the Month 9 visit which will be performed via a telephone call/virtual visit.

Any subject who either receives a kidney transplant or initiates maintenance dialysis, and has not withdrawn consent from study participation, will have a vital status check (alive or deceased) performed at 30-days following the relevant event.

9.2 Clinical Assessments

The following clinical assessments will be conducted during the study, according to the SoA (Section 1.3).

9.2.1 Medical History and Demographics

- Medical History and Demographics: Targeted medical history and demographic information will be collected. Targeted medical history will include an assessment of relevant medical history with particular emphasis on medical conditions that may lead to exclusion. Significant ongoing medical conditions or diseases should be documented.

Only the starting year of a condition will be required (e.g., not month or day). For conditions that may have multiple occurrences (e.g., myocardial infarction), only the year of the most recent event will be captured.

- Targeted relevant surgical history will be captured.
- The primary cause of CKD, current transplant status and current dialysis access (if applicable), will be collected.

9.2.2 Vital Sign Measurement

Heart rate, blood pressure, and weight may be collected from data available in the clinical encounter for in-person visits.

Height may be collected either from data available in the clinical record or from subject self-reported height. Height will be collected at Baseline/Day 1 only.

9.3 Efficacy Assessments

The primary endpoint is the time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality. It will be considered as confirmatory evidence of efficacy.

9.4 Laboratory and Other Assessments

Laboratory assays will be conducted by each sites' local laboratory. Given the requirement for all subjects to have advanced NDD-CKD it is anticipated that Investigators will collect the laboratory assessments described in the SoA at intervals no less frequent than quarterly. All Investigators will receive protocol specific training regarding the anticipated laboratory assessment schedule. Routine laboratory values, as required in the SoA, will be documented in the source documentation and eCRF.

Results of these laboratory assays will be reviewed by the primary treating nephrologist, Investigator, or designee as a part of routine SOC.

Investigators or their designee are required to acknowledge and review the local laboratory test results, however, they will not be required to provide independent assessment of SOC laboratory test results with regard to their 'clinical significance' or to direct intervention **(except as noted below)**. Review of the laboratory parameters should be captured in the subject source documentation.

Phosphorus and Iron Indices

Collection and evaluation of phosphorus and iron indices (TSAT and ferritin) must be performed and reviewed at an interval no less than quarterly. Failure to monitor these parameters is considered an important protocol deviation.

In all instances in which phosphorus and iron indices are collected, the Investigator must independently review these results to assess clinical significance and determine whether study drug dose changes or temporary discontinuation are required. Timely review of the laboratory assessments by the Investigator or designee is anticipated. Appropriate documentation of clinical

significance and any resulting dose adjustments will be documented in the subject source documentation and eCRF.

In the event the Investigator determines that a specific quarterly assessment of phosphorus and iron indices (TSAT and ferritin) is outside SOC, a study-specific lab kit will be provided by the sponsor and used to collect blood for assessment of TSAT, ferritin, and phosphorus by a central laboratory. Central laboratory details are provided in a laboratory information sheet.

Blood or urine will be collected for the following laboratory evaluations listed below and will be conducted during the course of the study. For details regarding the timing of these assessments refer to Section 1.3.

- Pregnancy Test: A serum or urine pregnancy test will be performed according to the SoA (Section 1.3) for females of childbearing potential. These results must be available and must be negative before the subject takes the first dose of study drug. Additional serum or urine pregnancy tests may be conducted throughout the study at the discretion of the Investigator to establish the absence of pregnancy during the study.

Table 2 Typical Quarterly Laboratory Assessments

Hematology	Iron Indices	Serum Chemistry
Complete Blood Count	Ferritin* TSAT* Total iron Total iron binding capacity	Phosphorus* Calcium Renal Panel (sodium, potassium, bicarbonate, chloride, BUN, creatinine, glucose) Hepatic Panel (albumin, AST, ALT total bilirubin, ALP, total protein) Magnesium eGFR
Additional Laboratory Tests	Urine Tests	
PTH Cystatin-C	Urine albumin or protein; creatinine ratio	

ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; PTH: parathyroid hormone; TSAT: transferrin saturation.

*Assessment required at a frequency of no less than quarterly (90 days).

9.5 Safety and Other Assessments

9.5.1 Concomitant Medication Recording

Routine concomitant medications (name, indication for use, route, start and stop dates), including prescription and over the counter medications will be collected at Screening, Day 1, and Month 9.

Concomitant medications of interest will be captured beginning at Screening and then at each subsequent study visit.

The concomitant medications of interest include:

- Erythropoietin Stimulating Agents (ESA)
- All forms of oral or IV iron excluding oral iron in multivitamins
- All phosphate-lowering therapy
- HIF-Stabilizers

For medications of interest, the name, indication, dose, route of administration, frequency and start/stop date will be collected and captured in the source documentation and in the eCRF.

Blood Transfusions will be captured and recorded in the source and eCRF.

9.5.2 Adverse Event Assessment

Auryxia (ferric citrate) is approved by the FDA for use as an oral iron replacement product in adult patients with NDD-CKD and iron deficiency at doses up to 12 tablets per day which is 100% (2 times) greater than the maximum dose allowed in this clinical study.

The safety profile of ferric citrate in the NDD-CKD population has been described by the FDA in the Auryxia USPI and by Akebia Therapeutics, Inc. in the Investigators Brochure.

As such, adverse events will only be collected in the following instances:

If they meet the definition of an SAE (see Section 9.6.1.2) or meet the requirements for reporting as an IND safety report. If there is any doubt whether the information constitutes an AE or SAE, please contact the Medical Monitor for discussion.

Adverse Events of Special Interest:

- If an event of iron overload occurs it will be captured as an adverse event of special interest. Iron overload is defined as any liver biopsy findings or MRI imaging consistent with this diagnosis in the setting of persistent TSAT >45%. In the event of an adverse event of special interest, the Investigator must review other prescribed iron supplementation (IV and oral) and make adjustments in accordance with Section 7.1.2.1.
- If a clinically significant episode of hypophosphatemia occurs it will be captured as adverse events of special interest. Clinically significant hypophosphatemia is defined as serum phosphorus <2.5 mg/dL. In the event of an adverse event of special interest, the Investigator must review other prescribed phosphate-lowering therapies and make adjustments in accordance with Section 7.1.2.1.

Subjects will be followed for protocol required SAEs and AEs of special interest until the final required protocol visit or until all drug-related toxicities and AEs have resolved (or are considered chronic/stable), whichever is later.

9.6 Adverse Events and Serious Adverse Events

9.6.1 Definitions of Adverse Events and Serious Adverse Events

9.6.1.1 Adverse Events

As defined by the Code of Federal Regulations section 312.32 an adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE may include medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with pre-existing underlying conditions that were not present prior to the AE reporting period.

AEs therefore may include the following:

- All AEs, whether suspected to be causally related to study drug or otherwise
- All AEs secondary to any medication overdose, medication error, abuse, withdrawal, sensitivity, or toxicity
- Illnesses apparently unrelated to study drug, including the worsening of a pre-existing illness
- Injury or accidents.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event.

9.6.1.2 Serious Adverse Events

Each AE is to be classified by the Investigator as serious or nonserious. An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Death
- Life-threatening (see below for definition)
- In-patient hospitalization or prolongation of existing hospitalization (see paragraph below on hospitalization)
- Persistent or significant disability/incapacity (see paragraph below on disability)
- Congenital anomaly/birth defect
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject, or may require medical or surgical intervention to prevent one of the criteria listed in this definition.

Serious may also include any other event that the Investigator and Investigator-Sponsor judges to be serious. If there is any doubt whether the information constitutes an AE or SAE, the information is to be treated as an SAE.

Life-threatening – Any event in which the subject was at risk of death at the time of the event; 'life-threatening' does not refer to an event which hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization – Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the study for a pre-existing condition that has not worsened during the AE reporting period does not constitute an SAE unless an untoward event occurs related to the procedure (e.g., elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the course of the study).

Disability – Defined as a substantial disruption in a person's ability to conduct normal life functions.

The following guidelines are to be used when reporting SAEs for this study:

Medical Diagnoses – Whenever possible, a medical diagnosis term should be used to report SAEs instead of signs and symptoms due to a common etiology, as determined by qualified medical study staff. Signs and symptoms should be reported as event terms only when the medical diagnosis remains unknown and revised to a medical diagnosis term once it has been established.

Procedures – Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, when a subject is hospitalized for an acute appendicitis that begins during the SAE reporting period, appendicitis should be reported as the SAE and the resulting appendectomy noted in the narrative.

Pre-planned therapeutic procedures or surgeries not associated with a new medical condition or worsening pre-existing condition should not be reported as SAEs.

The only procedures to be captured include the placement of dialysis access (e.g., Arteriovenous Graft or Fistula [AVG/ AVF], Peritoneal Dialysis [PD] Catheters, Central Venous Catheters [CVC]). Diagnostic procedures (e.g., x-rays, ultrasounds, echocardiograms) are not required to be captured.

Transplantation – It is anticipated that subjects may receive a kidney transplant during this study. Kidney transplant will be captured as a Study Endpoint and will not be recorded as an SAE. Adverse events resulting in prolongation of hospitalization during the index kidney transplant will be captured as an SAE. Subjects will discontinue study drug following receipt of a

kidney, other solid organ, hematopoietic stem cell or bone marrow transplant. Receipt of a kidney transplant will be considered an exception to the requirement for a 30-day safety follow up period, however any subject who receives a kidney transplant, and has not withdrawn consent from study participation, will have a vital status check performed at 30-days following the kidney transplant.

Dialysis Initiation - It is anticipated that subjects may initiate maintenance dialysis during this study. Dialysis initiation will be captured as a Study Endpoint and will not be recorded as an SAE. Hospitalization days will be recorded in the eCRF and adverse events resulting in prolongation of hospitalization during the index dialysis initiation will be captured as additional SAEs. Subjects will discontinue study drug following initiation of dialysis. Initiation of dialysis will be considered an exception to the requirement for a 30-day safety follow up period, however any subject who initiates maintenance dialysis, and has not withdrawn consent from study participation, will have a vital status check performed at 30-days following the initiation of maintenance dialysis.

9.6.2 Classification of an Adverse Event

9.6.2.1 Severity of Event

The Investigator will assess each SAE as either mild, moderate, or severe using the following guidelines to describe the maximum severity of the SAE:

- Mild: Does not interfere with subject's usual function. Clinical or diagnostic observation only; no intervention indicted.
- Moderate: Interferes to some extent with subject's usual function. Requires minimal, local, or noninvasive medical intervention/medication.
- Severe: Interferes significantly with subject's usual function. Disabling, medically significant but not immediately life-threatening; may include hospitalization or prolongation of hospitalization indicated.

Note that a **severe** AE is not necessarily a **serious** AE. For example, a headache may be severe in intensity, but would not be classified as serious unless it met at least 1 of the criteria for serious events listed above.

9.6.2.2 Relationship to Study Intervention

The causal relationship of the AE to study drug will be assessed by both the Investigator and the Investigator-Sponsor.

The assessment of causal relationship to study drug should be evidence-based, and not based on the premise that all AEs are possibly causally related to study drug until proven otherwise.

Examples of evidence that would suggest a causal relationship between the study drug and the AE include the occurrence of an AE that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, and Stevens-Johnson syndrome) or an AE that is uncommon in the population exposed to the drug.

The causal relationship of the AE is assessed using a binary system, and AEs are classified as either ‘related’ or ‘unrelated.

- Related: There is ‘reasonable possibility’ that the study drug caused the AE. The AE follows a reasonable temporal sequence from the time of drug administration. There is supportive evidence (facts) to suggest a possible causal relationship, irrespective of the degree of certainty between the observed AE and the drug.
- Unrelated: An AE does not follow a reasonable temporal sequence from administration of the study drug and/or there is no reasonable possibility that the study drug caused the AE. This assessment includes situations where the AE is related to other factors such as the subject’s clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

Default assessments using the ‘related’ category without supportive evidence for a causal relationship to study drug is generally uninformative and do not contribute meaningfully to the development of the safety profile of the drug or to subject protection.

9.6.2.3 Expectedness

The Investigator or Investigator-Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention as described in the current Investigators Brochure.

9.6.3 Time Period and Frequency for Event Assessment and Follow-up

The Investigator is to report all SAE’s either directly observed or spontaneously reported by the study subject. In addition, each study subject will be questioned about SAEs at each visit following initiation of study drug treatment.

9.6.4 Reporting Adverse Events

Non-serious AEs (with the exception of Adverse Events of Special Interest in Section 9.5.2) will not be collected in source documents or reported in the eCRF.

All SAEs will be collected in source documents and reported in the eCRF.

All Adverse Events of Special Interest will be collected in the source documents and reported in the eCRF.

9.6.5 Reporting Period

SAE and Adverse Events of Special Interest collection will begin from initiation of study drug treatment through the 30-day follow-up visit. Subjects will be followed for protocol required SAEs and Adverse Events of Special Interest until the final required protocol visit or until all drug-related toxicities and Adverse Events of Special Interest and SAEs have resolved (or are considered chronic/stable), whichever is later.

9.6.6 Serious Adverse Event Reporting

Any SAE, regardless of causal relationship, must be reported to the Investigator-Sponsor within 24 hours after the Investigator or designee becomes aware of the SAE. Compliance with this time requirement is essential so that the Investigator-Sponsor may comply with its regulatory obligations.

The initial SAE report should be completed as fully as possible but should contain, at a minimum:

- Subject number/ID, sex, and age/date of birth;
- The date of awareness;
- The date of report;
- Name of the reporter;
- Name of the suspected medicinal product, if applicable;
- A description of the event, including event term(s), seriousness criteria, and a clinical summary of the event;
- Causality assessment.

Information about all SAEs (either initial or follow-up information) should be collected and recorded in English on the electronic SAE Report Form within the EDC system. The Investigator must provide an assessment of causality (relationship to study drug). If the event meets serious criteria and it is not possible to access the EDC system, a study-specific paper SAE Report Form should be sent to the Investigator-Sponsor via email (research@usrenalcare.com) within 24 hours of being made aware of the SAE. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

The Investigator must report follow-up information relating to an SAE to the Investigator-Sponsor by updating the electronic eCRF with the new information or by submitting a study-specific paper SAE Report Form in the event that the EDC is not available. When the EDC system becomes available, the SAE information must be entered. The subject should be observed and monitored carefully until the condition resolves or stabilizes.

All deaths are to be thoroughly investigated and reported. Autopsy reports and death certificates are to be obtained, if possible, and summarized as appropriate.

The Investigator-Sponsor and/or its designee are responsible for reporting SAEs to all applicable regulatory agencies and the central ethics committees within the required timeline.

The Investigator is responsible for submitting required safety information to their local Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as per local regulations. This information includes, but is not limited to, any safety alert letter received from the Investigator-Sponsor and any SAEs occurring at their investigative site which meet the reporting requirements of the IRB.

9.6.7 Follow-up of Unresolved Events

All reportable SAEs should be followed until they are resolved, or the Investigator assesses them as chronic or stable or the subject's participation in the trial ends (e.g., until a final report is completed for that subject).

In addition, all SAEs assessed by the Investigator as related to the study drug should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as "chronic" or "stable". Resolution of such events is to be documented on the appropriate eCRF.

9.6.8 Reporting of Pregnancy

A pregnancy in a female subject must be confirmed by a positive serum or urine test (β-human chorionic gonadotropin).

Female subjects should interrupt study drug if they think they are pregnant. The study drug should be immediately discontinued once the pregnancy of a female study subject has been confirmed. The study drug can be resumed once a negative pregnancy test is confirmed.

If any study subject becomes or is found to be pregnant while receiving study drug or within 30 days of discontinuing the study drug, the pregnancy must be recorded on the study-specific paper Pregnancy Reporting Form within 24 hours of awareness of the pregnancy.

The study-specific paper Pregnancy Reporting Form must be completed with all known information regarding the pregnancy at the time of reporting. Investigative site personnel will update the form with additional information regarding the pregnancy and the outcome of the pregnancy as it becomes available until the outcome of the pregnancy is reported.

The Investigator will follow the subject until completion of the pregnancy. Pregnancy in and of itself is not considered an AE; however, unexpected complications are considered AEs.

Additional information about pregnancy outcomes follows:

- Note that "spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as related or unrelated to the in-utero exposure to the study drug should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.

9.7 Special Situations

Certain safety events, called 'Special Situations', that occur in association with study drug may require reporting. These Special Situations include, but are not limited to, the following:

- Overdose of the medicinal product
    - Ferric citrate overdose - Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under

6 years of age. In case of accidental overdose, call a physician or poison control center immediately. Advise subjects of the risks to children and to keep ferric citrate out of the reach of children.

An overdose of iron can lead to iron toxicity. Iron toxicity can be classified as corrosive or cellular. Ingested iron can have an extremely corrosive effect on the GI mucosa, which can manifest as nausea, vomiting, abdominal pain, hematemesis, and diarrhea; patients may become hypovolemic because of significant fluid and blood loss. Cellular toxicity occurs with the absorption of excessive quantities of ingested iron. Severe overdose causes impaired oxidative phosphorylation and mitochondrial dysfunction, which can result in acidosis and cellular death. The liver is one of the organs most affected by cellular iron toxicity, but other organs such as the heart, kidneys, lungs, and the hematologic systems may also be impaired. With chronic iron overload, the deposit of iron into visceral organs can cause organ dysfunction due to siderosis [Spanierman 2010].

Acute intoxication is most commonly reported in children ingesting large quantities of ferrous sulfate or chewable vitamins with iron; thus, ferric citrate must be kept out of the reach of children unless administered under a pediatric clinical study protocol.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes, and fetal malformation.

Special situations should be collected whether they result in an SAE or not. Special situations with associated SAE should also be reported on the corresponding SAE forms, following applicable SAE process.

10.0 STATISTICAL CONSIDERATIONS

Data collected throughout the study will be summarized using descriptive statistics and listed in by-subject listings. Continuous variables will be summarized using number of subjects with data, mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated. Summaries will be provided by treatment group within appropriate analysis populations and by time point/time period, as appropriate.

10.1 Sample Size Determination

The sample size for this study is driven by the primary endpoint, initiation of maintenance dialysis or all-cause mortality and is based on the observed data from the pilot study using nearly identical inclusion and exclusion criteria. The observed rate of the primary composite endpoint in the pilot study (all-cause mortality, maintenance dialysis or kidney transplant) for patients in the standard of care arm was 0.94 events per person-year of follow up. The observed hazard ratio was 0.42 (58% relative risk reduction, p=0.002) for the primary composite endpoint when comparing ferric citrate treated patients versus usual care.

Assuming 1 year recruitment and 0.75 years of follow up (9 months) for each individual and a hazard ratio of 0.60 (40% relative risk reduction), a sample size of 400 patients (200 per arm)

provides 90% power with a 2-sided alpha p <0.05. Assuming a hazard ratio of 0.50 (50% relative risk reduction), a sample size of 225 patients provides 90% power with a 2-sided alpha p<0.05.

10.2 Populations for Analyses

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects.
- Full analysis population: defined as randomized subjects receiving one or more doses of study drug. This population will be analyzed based upon the randomized treatment.
- Safety population: defined as all subjects who received at least one dose of study drug. This population will be analyzed based upon the actual treatment received.
- Per protocol population: defined as all randomized subjects who received study drug and have no protocol deviations affecting the primary endpoint analyses. Protocol deviations leading to exclusion from the PP population will be specified prior to database lock on a blinded basis and recorded in a separate document.

10.3 Missing Data

Discontinuation from study intervention is different from discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol unless the subject withdraws consent for participation in the study.

All data pertaining to the primary and secondary endpoints collected at any point during the study, both during study drug treatment and post-study drug treatment discontinuation, will be used for the primary analysis of the endpoints and its individual components.

Unless stated otherwise in the Statistical Analysis Plan, missing data for all other endpoints will not be imputed and the analysis will be based on observed data.

10.4 Statistical Analyses

10.4.1 General Considerations

Data summaries for categorical variables such as SAEs will use descriptive statistics including number of subjects, and proportions. Data summaries for continuous variables such as laboratory parameters will use descriptive statistics for mean, standard deviation, median, minimum, and maximum. Within-group changes from baseline for continuous parameters will be assessed.

10.4.2 Analysis of Primary Endpoint(s)

The primary endpoint is the time to composite endpoint of initiation of maintenance dialysis or all-cause mortality. It will be considered as confirmatory evidence of efficacy. The primary endpoint will be analyzed by Cox-proportional hazards regression model. HRs and

corresponding 95% confidence intervals will be presented for the primary endpoint (initiation of maintenance dialysis or all-cause mortality.

10.4.3 Analysis of Secondary Endpoint(s)

For the below secondary endpoints, Cox-proportional hazard regression model or competing risk analyses will be conducted. HRs and corresponding 95% confidence intervals will be presented.

- Time to first event hospitalization reported as a SAE (excluding disease-related hospitalization [e.g., fistula replacement, dialysis initiation, kidney transplant] and elective procedures),
- Component of Primary – time to initiation of maintenance dialysis
- Component of Primary – time to all-cause mortality

A full description of the analyses performed on secondary endpoints will be provided in the statistical analysis plan. A *pre-specified* process for identifying hospitalization events to be included in the analysis of the hospitalization secondary endpoint will be used.

10.4.4 Tertiary/Exploratory Endpoint(s)

A full description of the analyses performed on exploratory endpoints will be provided in the statistical analysis plan. Exploratory endpoints include:

- Rate of hospitalizations and rate of hospitalization days prior to initiating maintenance dialysis
- Receipt of kidney transplant prior to initiating maintenance dialysis
- Cumulative dose over time of rescue therapy for anemia including (individually, [ESA, intravenous iron, RBC transfusion]) prior to initiating maintenance dialysis

10.4.5 Safety Analyses

10.4.5.1 Analysis of Adverse Events

All analyses of safety data will use the safety population.

SAEs and Adverse Events of Special Interest will be summarized using the number and percentage for all subjects in the safety population.

All SAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) classification. Treatment-emergent SAEs will be summarized by system organ class and preferred term (PT) for each treatment group. SAEs will also be summarized by their maximum severity.

Summaries will also be provided for the following types of SAEs:

- Related SAEs (including all categories for relationship to study drug other than “Unrelated”, as determined by the Investigator)

10.4.6 Baseline Descriptive Statistics

Descriptive statistics will be generated for demographic and pretreatment variables for the randomized population defined in Section 10.2.

Medical history terms will be summarized for each treatment group based on the randomized population.

10.4.7 Planned Interim Analyses

No formal interim analysis is planned.

10.4.8 Sensitivity Analyses

Sensitivity analyses will be conducted to explore the robustness of the primary endpoint analysis. Full details of the sensitivity analyses will be described in the statistical analysis plan but may include analyses such as those related to compliance with study drug (per-protocol analysis) or excluding endpoint events occurring within 8 weeks of study start.

10.4.9 Sub-Group Analyses

Analyses of the primary, secondary, and exploratory endpoints may be performed in subgroups with more details to be included in the final SAP, including:

- eGFR within 3 months of Screening:
  - ≥15 to ≤20 ml/min/1.73 m^2
  - <15 ml/min/1.73 m^2
- 4-variable Kidney Failure Risk Equation (KFRE) score [Tangri 2011] within 3 months of Screening:
  - ≥20%
  - <20% over 2 years

11.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (2013).

In addition, the study will be conducted in accordance with the protocol, the International Council for Harmonization (ICH) E6 (R2) guideline on Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

11.2 IRB and Ethics Committees

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (e.g., recruitment advertisements, if applicable) from the IRB/IEC. All correspondence with the IRB/IEC will be retained in the Investigator File. Copies of IRB/IEC approvals will be forwarded to the Investigator-Sponsor/Investigator or its designee.

In case of a substantial protocol amendment, the Investigator-Sponsor/Investigator will obtain approval from responsible Regulatory Authorities before implementation.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator will notify the IRB/IEC and the Investigator-Sponsor in writing immediately after the implementation.

11.3 Informed Consent Process

The Investigator or designee will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related procedures being performed on the subject, the informed consent form (ICF) will be reviewed, signed, and dated by the subject or their legally acceptable representative, as well as the person who administered the informed consent, and any other signatories, according to local requirements. Informed consent may be obtained using an electronic consent process (e-consent) following all applicable ICH/GCP and IRB guidelines and regulations. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor, auditor, regulatory authorities and/or IRB/IEC and other applicable individuals upon request.

The ICFs will be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The ICFs used in this study, and any changes made during the course of the study, will be prospectively approved by both the IRB/IEC and the Investigator-Sponsor before use.

11.4 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor-Investigator with sufficient, accurate financial information, as requested, to allow the Sponsor-Investigator to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests, during the course of the study, and for 1 year after completion of the study.

11.5 Confidentiality and Data Privacy

All parties will ensure protection of subject personal data and will not include subject names on any Investigator-Sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, the Investigator-Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The Investigator/Investigator-Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Investigator-Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the Investigator-Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the Investigator-Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

11.6 Data Handling and Record Keeping

11.6.1 Data Collection and Management Responsibilities

This study will utilize an electronic data capture (EDC) system to manage data collection during this trial that is fully Code of Federal Regulations 21 part 11 compliant. An EDC system contains certain functionality including, but not limited to, a graphical user interface to help facilitate data entry, a data validation element to check user data, and a reporting function. eCRFs available through this system are required and will be completed for each randomized subject.

Any form of data from the electronic system are the sole property of the Investigator-Sponsor and will not be made available in any form to third parties, except for authorized representatives of the Investigator-Sponsor or appropriate regulatory authorities, without written permission from the Investigator-Sponsor.

The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered in the eCRF or any other data collection forms.

In most cases, the source documents are contained in the subject's chart at the hospital or the physician's office. In these cases, data collected on the eCRFs will match the data in those charts.

11.6.2 Study Records Retention

To enable evaluations and/or audits from regulatory authorities or the Investigator-Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient

information to link records (e.g., eCRFs and hospital records)), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone calls reports). The records will be retained by the Investigator according to the ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable, for any reason, to continue to retain study records for the required period (e.g., retirement and relocation), the Investigator-Sponsor will be prospectively notified. The study records will be transferred to a designee acceptable to the Investigator-Sponsor, such as another Investigator, another institution, or to the Investigator-Sponsor. The Investigator will obtain Investigator-Sponsor's written permission before disposing of any records, even if retention requirements have been met.

11.7 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Investigator-Sponsor will be informed immediately.

In addition, the Investigator will inform the Investigator-Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP, defined as a breach that will likely affect the safety or physical or mental integrity of subjects or the scientific value of the trial, that comes to the attention of the Investigator.

11.8 Study Discontinuation and Closure

The Investigator-Sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator will contact all participating subjects, within a time period specified by the Investigator-Sponsor, to inform them of the decision to discontinue the study.

11.8.1 Criteria for Premature Termination or Suspension of the Study

The following criteria may result in either temporary suspension or early termination of the study:

- New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety
- Request from regulatory agencies

The Investigator-Sponsor reserves the right to discontinue the study for other valid administrative reasons. If the study has been suspended or terminated, prompt notification will

be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

11.8.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the study site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

The Investigator will notify the Investigator-Sponsor if the trial is terminated by the Investigator or the IRB at the site. If the Investigator, IRB, or Investigator-Sponsor decides to terminate or suspend the trial conduct at a particular study site for safety, non-enrollment, non-compliance with the protocol, or other unanticipated reasons, the above parties will be promptly notified.

11.8.3 Criteria for Premature Termination or Suspension of the Study or Study Sites

In the event that the Investigator-Sponsor elects to terminate or suspend the study or the participation of an investigational study site, a study-specific procedure for early termination or suspension will be provided by the Investigator-Sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

11.9 Safety Oversight

Subject safety will be monitored through collection of SAEs.

11.10 Quality Assurance and Quality Control

The Investigator-Sponsor will verify that the clinical trial is conducted, and data are documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices [GLP], Good Manufacturing Practices [GMP]).

Each clinical site will perform ongoing internal quality management review of their study conduct, data documentation and completion. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Investigator-Sponsor, and inspection by local and regulatory authorities.

11.10.1 Clinical Monitoring

During study conduct, the Investigator-Sponsor or its agent will conduct periodic on-site or remote monitoring visits to ensure that the protocol and GCP are being followed. The Investigator-Sponsor or designee will review source documents to confirm that the data recorded on the eCRFs is accurate. The Investigator/institution will allow the Investigator-Sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject to Quality Assurance audits performed by the Investigator-Sponsor or companies working with or on behalf of the Investigator-Sponsor, and/or review by the IRB, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11.10.2 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an Investigator to deviate from the protocol.

For the purposes of this protocol, deviations requiring notification to the Investigator-Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment, including commercial Auryxia
- Does not discontinue prescribed phosphate-lowering therapy or oral/IV iron therapy in response to low phosphorus or elevated iron indices, per Section 7.1.2.1
- Does not receive quarterly monitoring of serum phosphorus and iron indices (with documented Investigator review).

When one of these deviations from the protocol is identified for an individual subject, the Investigator or designee must ensure the Investigator-Sponsor is notified. If the Investigator determines that the deviation impacts the safety of a subject, the Investigator must contact the Investigator-Sponsor immediately. The Investigator-Sponsor will follow-up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be filed in the Investigator Site Files and will be provided to the Investigator-Sponsor and maintained within the Trial Master File.

Note: Other deviations outside of the categories defined above, that are required to be reported by the IRB/IEC in accordance with local requirements, will be reported, as applicable.

12.0 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Investigator-Sponsor and the Investigator and/or the Investigator's institution. The Investigator-Sponsor will have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study

prior to submission for publication/presentation. Any information identified by the Investigator-Sponsor as confidential will be deleted prior to submission.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including: Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

13.0 REFERENCES

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