PROTOCOL NUMBER:	FeCitrate
TITLE:	Transition to Ferric Citrate among Hemodialysis and Peritoneal Dialysis Patients:
STUDY PHASE:	Phase IV
IND OR IDE#:	N/A
PRINCIPAL INVESTIGATOR:	Victoria A. Kumar, M.D. or Hui Xue, M.D. Nephrology LAMC 4700 Sunset Bl Los Angeles, CA 90027
CONTACT INFORMATION:	NCT03079869
FUNDED BY:	Keryx Medical Affairs One Marina Park Drive, Tenth Floor Boston, MA 02210
STUDY SITES:	LAMC
AMENDMENTS/REVISIONS:	Protocol Version 1.4, dated 26-Jun-2018

KPSC IRB Approved: 05-Jul-2018

TABLE OF CONTENTS

KPSC IRB Approved: 05-Jul-2018

KPSC IRB Approved: 05-Jul-2018

DESCRIPTION OF PROTOCOL AMENDMENT

Original Protocol Version 1.1. 20MAY2016
Amendment Version 1.2 Dated 16JUL2017

Amendment 1.3 Dated 28OCT2017

Number of global amendment		1.1
Date of CTP revision		20MAY2016
Protocol Number		FeCitrate
Title of protocol		Transition to Ferric Citrate among Hemodialysis and Peritoneal Dialysis Patients: A Phase 4 "Real World" Experience Study from Kaiser Permanente Southern California)
To be implemented only after approval of the IRB	X	
Section to be changed		Principal Investigator
Description of Change		Dr. Hui Xue added
Section to be changed		Title Page
Description of Change		Amendment/Revision Section added 1.2.
Section To be changed		Table of Contents
Description of change		Table of Contents added protocol amendment summary to page 5 and updated table of contents pages
Section to be changed		Section 3: Study Design
Description of change		Added the following sentence to bullet point 3: "If study staff is unable to meet with patient during routine visit or if the patient requests more time to consider participation, peritoneal dialysis patients may be asked to return to clinic for an additional visit to sign the informed consent. This will only apply to peritoneal dialysis patients."
Section to be changed		Section 9.4 Study Calendar

Description of change		Footnote 4 added "If study staff is unable to meet with patient during routine visit or if the patient requests more time to consider participation, peritoneal dialysis patients may be asked to return to clinic for an additional visit to sign the informed consent. This will only apply to peritoneal dialysis patients."

DESCRIPTION OF PROTOCOL AMENDMENT

Number of global amendment		1.2
Date of CTP revision		16JUL2017
Protocol Number		FeCitrate
Title of protocol		Transition to Ferric Citrate among Hemodialysis and Peritoneal Dialysis Patients: A Phase 4 "Real World" Experience Study from Kaiser Permanente Southern California)
Section to be changed		Title Page
Description of Change		Amendment/Revision Section changed to 1.3
Section To be changed		Table of Contents
Description of change		Updated table of contents pages
Section to be changed		Section 4.7 Concomitant Medication/Treatments
Description of Change		Removed "and cinacalcet (Sensipar)"
Section to be changed		Section 5.1.1. removed "3 to 19 pills per day"
Description of Change		Revised "3 to 19 pills per day" to 3+ pills"
Section to be changed		Throughout the protocol
Description of Change		Minor grammatical, formatting, or spelling change were made.

KPSC IRB Approved: 05-Jul-2018

DESCRIPTION OF PROTOCOL AMENDMENT

Number of global amendment		1.3
Date of CTP revision		28OCT2017
Protocol Number		FeCitrate
Title of protocol		Transition to Ferric Citrate among Hemodialysis and Peritoneal Dialysis Patients: A Phase 4 "Real World" Experience Study from Kaiser Permanente Southern California)
Section to be changed		Title Page
Description of Change		Amendment/Revision Section changed to 1.4
Section To be changed		Table of Contents
Description of change		Updated table of contents pages
Section to be changed		Description of Protocol Amendment version 1.1
Description of Change		Number of global amendment and date of CTP Version
Section to be changed		List of Abbreviations
Description of Change		Minor format change
Section to be changed		Section 3.0 Study Design
Description of Change		Added the following sentence to bullet point #3. "If at any time during the study, a peritoneal, dialysis patient changes to hemodialysis, the patient can continue study at the principal investigator's discretion. If at any time during the study, a hemodialysis patient changes dialysis to peritoneal, the patient can continue on study at the principal investigator's discretion. In such event, patient's group assignment for analysis will be determined at the discretion of the Principal Investigator. Patients will be allowed to continue in the trial given that they can continue to meet all study participation requirements."
Section to be changed		Section 7.2 Criteria for Removal from Treatment

KPSC IRB Approved: 05-Jul-2018

Description of Change		Added the following: "7.2.6 At the discretion of the principal investigator, a patient may be removed from the study if they initiate dialysis care at a non-outside/Non-Kaiser Permanente facility."
Section to be changed		Throughout the protocol
Description of Change		Minor grammatical, formatting, or spelling change were made.

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
ESA	Erythropoiesis Stimulating Agent
CRO	Contract Research Organization
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience

PROTOCOL SUMMARY

Title	Transition to Ferric Citrate among Hemodialysis and Peritoneal Dialysis Patients: A Phase 4 "Real World" Experience Study from Kaiser Permanente Southern California
Short Title	FeCitrate
Protocol Number	KP FeCitrate
Study Phase	4
Study Site(s)	Los Angeles Kaiser Sunset Medical Center
Number of Subjects	55
Study Arms	1
Indication	Hyperphosphatemia in end stage renal disease
Primary Purpose	To evaluate the efficacy of ferric citrate for control of serum phosphorus levels and maintenance of adequate iron stores among dialysis-dependent patients before and after conversion from traditional phosphate binders in a "real world" environment
Overview of Study Design	prospective non-randomized cohort study of 6-9 months duration (active study period 6 months).
Investigational Product Administration	One to two tablets of Ferric Citrate phosphorus binder administered by mouth before every meal to prevent dietary phosphorus absorption.
Eligibility Criteria	Inclusion criteria: • On 3 + per day of calcium acetate, sevelamer, lanthanum, aluminum, or calcium carbonate • Mean serum phosphorus 4.0-<8.0 mg/dl for the past 6 months • No allergy to iron • Mean corrected calcium >8.0mg/dl for past 6 months • Mean PTH < 1000 pg/ml for past 6 months

	• Mean ferritin < 1500 ng/ml and mean iron sat < 50% for past 6 months • Patients with diabetes will be included Exclusion criteria • History of gastrointestinal bleeding within past 6 months • History of hospitalization for gastroparesis, bowel obstruction, or abdominal surgery within past 6 months • Active malignancy • Renal transplant • History of autoimmune disease, hemoglobinopathy, hemochromatosis, or sickle cell disease
Study Endpoint	Mean serum phosphorus levels and rate of successful phosphorus control (<5.5mg/dl) 6 months before and after treatment with ferric citrate
Statistical Methods	Not powered to detect statistical significance

1 INTRODUCTION

1.1 Background

High serum phosphorus levels are associated with a greater risk of mortality among patients with chronic kidney disease (CKD) and non-chronic kidney disease populations(1-5). Elevated phosphorus levels are also associated with increased cardiovascular complications among dialysis patients. As renal function declines, dietary intake and adherence to phosphate binders becomes more and more important for phosphorus control and prevention of CKD-associated mineral bone disease (CKD-MB).

Reduction of serum phosphorus levels by phosphate binding agents is associated with a lower risk of both cardiovascular and all-cause mortality in patients with end stage renal disease (ESRD)(6), but side effects of phosphate binders, high pill burden, and long term safety concerns remain an issue. Calcium based binders are associated with vascular calcifications(7, 8), which led to national guidelines that limit total elemental calcium intake in ESRD patients. Aluminum hydroxide and lanthanum carbonate are potential alternatives to calcium based binders and sevelamer carbonate/hydrochloride, but pose the risk for long term buildup in the body and potential untoward consequences since they are metals. (9, 10)

While much effort is placed on dietary counseling regarding low phosphorus diets, proper use of phosphate binders and vitamin D analogs, a high prevalence of CKD-MB associated complications still exists among patients, especially dialysis dependent patients. Valvular heart disease, isolated systolic hypertension, calcific uremic ateriolopathy (calciphylaxis), peripheral vascular disease, and hip fractures are all more common in CKD patients, leading to greater morbidity and mortality(11, 12). The pathophysiology of vascular disease in CKD patients is complex. It occurs as a consequence of reduced renal function, increases in calcium and phosphorus balance, precipitation of calcium and phosphorus and the uremic milieu. Previous observations using electron beam computed tomography have demonstrated an association between higher calcification and cardiovascular disease.(12, 13)

Circulatory function is further compromised by declining hemoglobin levels and anemia in the CKD population. The insufficient erythropoiesis that occurs as renal function declines likely compounds the vascular pathology that occurs in the setting of CKD-MB. In addition, elevated serum phosphorus levels and associated hyperparathyroidism lead to bone marrow suppression, compounding the anemia. Erythropoiesis stimulating agents (ESA's) are a routine part of management of patients with CKD/ESRD, but are not without adverse effects, including an increased risk of cardiovascular events, mortality, and malignancy. Current recommendations regarding use of ESA's in ESRD patients are to use the minimum dose required to prevent blood transfusion. Maintenance of adequate iron stores ensures adequate erythropoiesis and avoids excessive use of ESA's.

Control of serum phosphorus levels can be a challenge for patients with ESRD and depends largely on patient adherence to diet and phosphate binder use. Many patients have difficulty tolerating binders, possibly due to pill size and high pill burden(14, 15). It is not unusual for ESRD patients to consume upwards of 10 pills per day in an effort to control serum phosphorus levels. Simpler medication regimens for phosphorus control would likely result in improved compliance and better outcomes for patients with ESRD.

1.2 Study Medication

Ferric citrate is an iron-based phosphate binder approved by the FDA for control of serum phosphorus levels in patients with chronic kidney disease on dialysis. It has been shown to increase serum iron parameters, including ferritin, iron and TSAT. In dialysis patients treated with ferric citrate in a 52-week study in which IV iron could also be administered, mean (SD) ferritin levels rose from 593 (293) ng/mL to 895 (482) ng/mL, mean (SD) TSAT levels rose from 31% (11) to 39% (17) and mean (SD) iron levels rose from 73 (29) mcg/dL to 88 (42) mcg/dL. In contrast, in patients treated with active control, these parameters remained relatively constant.

1.3 Preclinical Data

Ferric citrate has already been FDA approved.

1.4 Clinical Data to Date

Ferric citrate coordination complex (ferric citrate) is an intestinal phosphate binder that has been shown previously to replete iron stores, increase hemoglobin levels, and reduce serum phosphate levels in patients with ESRD undergoing hemodialysis.

1.5 Hypothesis

We seek to determine the efficacy and potential pleotropic effects of the new FDA approved phosphorus binder, ferric citrate, in patients with ESRD, including both hemodialysis and peritoneal dialysis patients. This study is expected to expand upon results obtained in previous published studies, providing “real world” experience with ferric citrate.

2 OBJECTIVES AND PURPOSE

SPECIFIC AIMS

1) To determine efficacy and tolerability of ferric citrate in dialysis-dependent patients treated for hyperphosphatemia

2) To compare dose efficacy of ferric citrate to calcium acetate and sevelamer carbonate for control of serum phosphorus levels
3) To determine changes in iron saturation and ferritin after conversion to ferric citrate
4) To determine iron requirements after conversion to ferric citrate
5) To determine changes in hemoglobin after conversion to ferric citrate
6) To determine ESA doses and requirements after conversion to ferric citrate

3 STUDY DESIGN

- Type: non-randomized, single arm, phase IV, cohort pilot study
- Study population: end stage renal disease patients who are on chronic hemodialysis or peritoneal dialysis with elevated serum phosphorus.
- 55 chronic dialysis patients (28 hemodialysis and 27 peritoneal dialysis) who are currently using oral phosphorus binders will be enrolled. Potential participants will be screened from both the chronic hemodialysis unit and the home dialysis unit at the LAMC site. Potential study patients will be approached by study investigators during any routine visit. If the patient consents to participation, the study coordinator will see patients during the same visit. If study staff is unable to meet with patient during routine visit or if the patient requests more time to consider participation, peritoneal dialysis patients may be asked to return to clinic for an additional visit to sign the informed consent. This will only apply to peritoneal dialysis patients. If the patient chooses not to enter the study, the reason will be noted by the study coordinator. At the appropriate time in the study, the study coordinator will dispense the study medication, Ferric Citrate, and provide instructions per study protocol. The study coordinator will meet with the participant every month during either a hemodialysis visit (for hemodialysis patients) or a monthly clinic visit (for peritoneal dialysis patients) with his/her provider, and laboratory values/data and study questionnaire will be updated each month. If at any time during the study, a peritoneal, dialysis patient changes to hemodialysis, the patient can continue study at the principal investigator's discretion. If at any time during the study, a hemodialysis patient changes dialysis to peritoneal, the patient can continue on study at the principal investigator's discretion. In such event, patient's group assignment for analysis will be determined at the discretion of the Principal Investigator. Patients will be allowed to continue in the trial given that they can continue to meet all study participation requirements. The six month period prior to enrollment will be used to evaluate the

participants' baseline laboratory values and medication use, including phosphorus binder use. Laboratory values and medication use will also be evaluated and recorded monthly during the six months of active study. The duration of the study will be six months on ferric citrate. At the end of the study, the participant can be provided with a prescription of ferric citrate by his/her nephrologist if the participant wishes to continue with ferric citrate, or he/she can go back to the phosphorus binder used before enrolling in this study.

3.1 Treatment Arms

This is a single arm study in which all participants will be changed to the study medication for a total of six months.

3.2 Study Duration

Patients who satisfy inclusion criteria will be enrolled in the study during an initial period of up to 3 months. After initial enrollment and consent, patients will continue for a total of 6 months on the study drug.

4 STUDY PRODUCT INFORMATION

4.1 Description

Ferric Citrate is known chemically as iron (+3), *x* (1, 2, 3-propanetricarboxylic acid, 2- hydroxy-), *y* (H_2O) x=0.70 – 0.87, y = 1.9 – 3.3.

Ferric citrate's trade name is Auryxia. Auryxia 210 mg ferric iron tablets, equivalent to 1g ferric citrate, are film-coated, peach-colored, and oval-shaped tablets embossed with "KX52". The inactive ingredients are pregelatinized starch and calcium stearate. In addition, the film-coating contains the following inactive ingredients; hypromellose, titanium dioxide, triacetin, and FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake, FD&C Red #40/Allura Red AC Aluminum Lake, and FD&C Blue #2/Indigo Carmine Aluminum Lake.

Mechanism of Action

Ferric iron binds dietary phosphate in the GI tract and precipitates as ferric phosphate. Ferric phosphate is insoluble and is excreted out of the body in the stool. By binding phosphate in the GI tract and decreasing absorption, ferric citrate lowers the phosphate concentration in the serum.

4.2 Acquisition and Accountability

Ferric Citrate will be supplied by the manufacture, Keryx Biopharmaceuticals, Inc., in 200 tablet foil sealed bottles to the study site. This study is to be conducted at a single site, at LAMC, and the medication will be stored in a secure, locked location within LAMC campus pharmacy that is accessible only to the study investigators and staff. Medication will be

delivered every 2 months based on need. Participants will be able to keep any unused investigational product already dispensed at the termination of the study. Any medication that is unused or returned by participating patients will be properly disposed of with the aide of the study pharmacist per LAMC pharmacy's waste medication disposal protocol.

4.3 Formulation, Packaging, and Labeling

Auryxia, 210 mg ferric iron tablets equivalent to 1 g of ferric citrate are supplied as 200 tablets in 400-cc high-density polyethylene bottles.

4.4 Storage and Stability

Store at 20 to 25°C (68 to 77°F): excursions permitted to 15° to 30°C (59°F to 86°F) Protect from moisture.

4.5 Dosage, Preparation and Administration

Study medication will be dispensed in multiple of 200 tablet bottles on a monthly basis, based on a given participant's phosphorus binder requirement. Following the physician's monthly dialysis rounding, patient will be seen by the study coordinator on the same day, and the following month's supply of ferric citrate will be dispensed. In center hemodialysis patients will be asked to bring their study drug with them to the dialysis center, where they will undergo a weekly pill count. Peritoneal dialysis patients will have weekly telephone follow up by the study coordinator regarding medication compliance, and will have an in person monthly pill counting during their monthly dialysis follow up visit.

4.6 Toxicity and Safety Information

Patients with iron overload syndromes (e.g., hemochromatosis) are contraindicated to take Ferric Citrate, as the iron absorption may lead to excessive elevation in iron stores. Iron levels in blood will be monitored closely on a monthly basis. Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age, therefore no children are included in this study. Patients with inflammatory bowel disease or active, symptomatic gastrointestinal bleeding were excluded from clinical trials, therefore these populations are excluded from this current study.

In clinical trials, adverse events reported in more than 5% of patients treated with Ferric Citrate, at a rate similar to the control group. Side effects reported included diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%4) as per the package insert. Gastrointestinal adverse reactions were the most common reason for discontinuing Ferric Citrate. The study medication is also associated with discolored feces.

4.7 Concomitant Medications/ Treatments

Other non-study oral phosphorus binders are excluded from concomitant medications/treatments for the study due to potential impact on serum phosphorus and calcium levels. All other concurrent treatments are allowed.

5 SELECTION AND WITHDRAWAL OF PATIENTS

5.1 Inclusion Criteria

5.1.1 Currently using 3 + pills per day of calcium acetate, sevelamer, lanthanum, or calcium carbonate
5.1.2 Mean serum phosphorus 4.0-<8.0 mg/dl for 6 months prior to enrollment
5.1.3 No allergy to iron
5.1.4 Mean corrected serum calcium > 8.0 mg/dl for 6 months prior to enrollment
5.1.5 Mean PTH < 1000 pg/ml for 6 months prior to enrollment
5.1.6 Mean ferritin < 1500 ng/ml and mean iron sat < 50% for 6 months prior to enrollment

5.2 Exclusion Criteria

5.2.1 History of gastrointestinal bleeding within past 6 months
5.2.2 History of hospitalization for gastroparesis, bowel obstruction, or abdominal surgery within past 6 months
5.2.3 Acute kidney injury equal to or less than 3 months before the initial screening date
5.2.4 Active malignancy
5.2.5 Functioning renal transplant
5.2.6 Patients with iron overload syndrome (e.g., Hemochromatosis)
5.2.7 History autoimmune disease, hemoglobinopathy, hemochromatosis, sickle cell disease
5.2.8 Active or past history of calciphylaxis

5.3 Withdrawal Criteria

Participants are eligible to withdraw voluntarily at any time, and will be terminated from the study based on any serious adverse event, loss to follow-up, kidney transplantation, pregnancy and/or withdrawal as determined by the study investigator.

6 STRATIFICATION/ RANDOMIZATION SCHEME

No stratification or randomization scheme is needed in this single arm study.

KPSC IRB Approved: 05-Jul-2018

7 STUDY PRODUCT ADMINISTRATION AND TOXICITY MANAGEMENT PLAN

7.1 Administration

Ferric Citrate will be administered orally with water within 30 minutes of a meal. Study drug dosing conversion will be based on type of phosphate binder that the patient is taking at the initiation of the study. Given the binding capacity of the different binders (appendix table), we will make the conversion as below

i. For calcium carbonate, calcium acetate, sevelamer carbonate
    1. 1 tablet with meals will convert to 1 tablet of ferric citrate with meals
    2. 2 tablets or higher will convert to 2 tablets of ferric citrate with meals and will be titrated up based on week 2, week 4, and subsequent routine monthly labs

ii. For Lanthanum
    1. 1 or more tablets with meals will convert to 2 tablets will convert to 2 tablets of ferric citrate with meals and will be titrated up based on week 2, week 4, and subsequent routine monthly labs

All subsequent phosphate binder dose adjustments will be based on decisions made by the nephrologists based on routine clinical laboratory results and patients subjective tolerability to binders. Laboratory monitoring of baseline labs (Calcium, phosphorus, iron levels, ferritin, hemoglobin, hematocrit) will be every 2 weeks for the first 2 months, and ferric citrate dose may be titrated every 2 weeks until stable phosphorus control is obtained.

7.1b Management of IV iron during study phase

If patient is receiving IV iron at the time active study starts (ie, start of ferric citrate administration), IV iron will be discontinued if the patient's ferritin level is > 200 ng/ml and iron saturation is > 20%. Otherwise IV iron may be continued until patient's serum ferritin level is > 200 ng/ml and iron

saturation is > 20% with concomitant use of the study drug. IV iron will not be used if the iron saturation is greater than 50%, even if a patient's serum ferritin level falls below 200 ng/ml.

If during the active study period a patient's serum ferritin level falls below 200 ng/ml and/or iron saturation level falls below 20%, IV iron may be restarted, at the discretion of the study investigator(s).

7.2 Criteria for Removal from Treatment

7.2. 1 After six months of study drug use, the study drug will no longer be provided by Keryx free of charge. Patients may continue with Ferric Citrate as their oral phosphorus binder of choice, if desired (at their own expense).

7.2.2 Patients will discontinue treatment in the event of iron overload or any serious adverse side effect deemed attributable or possibly attributable to the study drug.

7.2.3 Patient will be removed if he/she misses the medication continuously for more than 2 weeks.

7.2.4 A patient will be removed from treatment if he/she receives a renal transplant.

7.2.5 Patient will be removed from the study if consent is withdrawn or patient is lost to follow up.

7.2.6 At the discretion of the principal investigator, a patient may be removed from study if they initiate dialysis care at an outside/Non-Kaiser Permanente facility.

7.3 Comorbidities

Participants' comorbid conditions will be managed by their physicians per usual protocol.

8 ASSESSMENT OF EFFICACY AND SAFETY

8.1 Toxicity Monitoring

Laboratory monitoring will occur on a bi-monthly basis for the first two months, then on a monthly basis and as needed. Laboratories monitored will include

calcium, phosphorus, iron levels, ferritin, and complete blood count. In addition, participants will be screened by the study coordinator either in person or via the phone every week to two weeks on adverse side effect monitoring.

8.2 Modification of Study Product Administration based on Toxicity

Any changes in ferric citrate dosing will be at the discretion of the study investigators and will occur no more frequent than every 2 weeks. If a patient's absolute iron saturation level increases to greater than 50%, the study medication dose will be reduced by half and iron saturation and ferritin levels will be repeated in two weeks. If the iron saturation level is not improved or phosphorus control is not achievable, then the participant will be removed from the study. If a patient's ferritin level increases to >2000 ng/ml, patient's chart will be reviewed by two study investigator to assess the reason for the ferritin increase, and whether the participant should remain in the study.

8.3 Adverse Events Reporting

All Adverse event reporting will follow KPSC clinical trials reporting guideline per KPSC CT SOP 401, *Clinical Trial Regulatory Management*.

Reportable Event or Incident	Timeframe to report to IRB
Unanticipated death of a research subject that is determined by the PI to be at least possibly related to the study	Within one business day following discovery and at time of continuing review
Reportable Event or Incident Timeframe to report to IRB Internal Unanticipated Serious Adverse Events that meet the three reporting criteria	Within 10 business days following discovery and at time of continuing review
External Unanticipated Serious Adverse Events that meet the reporting criteria	Within 10 business days following discovery and at time of continuing review
External Unanticipated Serious Adverse Events that do NOT meet the reporting criteria (e.g., IND Safety Reports)	At the time of continuing review
Unanticipated Adverse Device Effect	Within 10 business days following discovery and at time of continuing review

Breach	Report to KPSC Privacy Officer and IRB immediately following discovery
Protocol Violations	Within 10 business days following discovery and at time of continuing review
Protocol Deviations	Within 10 business days following discovery and at time of continuing review
New Safety Information (e.g., updated investigators' brochure containing new safety information of which the IRB is not yet aware) that meets the reporting criteria.	Within 10 business days following discovery and at time of continuing review
Emergent modifications to the IRB-approved protocol to protect the safety, rights, or welfare of one or more research participants when there is not time to obtain IRB approval	Within five business days of beginning implementation
Incarceration of research a participant	Within two business days following discovery
Inspection by external regulatory agency,3 e.g., FDA, OHRP, DOT, non-US	Within two business days following discovery

8.3.1 Definitions

Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

All adverse events, including those that are reported by the patient spontaneously, those the study investigator observes, and those that the study investigator elicits in response to open-ended questions. Recorded adverse events will be assessed by the study investigator indicating the causal relationship of the event with the study drug and whether it meets the criteria for a Serious Adverse Event.

Some reported adverse drug reactions include diarrhea, constipation, abdominal discomfort, abdominal distension, duodenal ulcer, and nausea.

Serious Adverse Event noted in prior publications included death, duodenal ulcer, congestive heart failure, dialysis access shunt stenosis, and infections.

8.3.2 Serious Adverse Event Reporting

SERIOUS ADVERSE EVENT (SAE) is an adverse event or suspected adverse reaction if, in the view the study investigator, it meets one or more of the following criteria:

- Results in death
- Is a life-threatening adverse event (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

8.3.3 Investigator Reporting: Notifying FDA

Any SAE, including death from any cause, which occurs during the study and is deemed related or possibly related to the study drug, will be reported to the FDA and to Med Watch by the study investigator within 24 hours of detection of the SAE.

Withdrawal from the trial and all therapeutic measures taken will be at the discretion of the Principal Investigator (PI). All SAEs (related or of possible relationship to the study drug) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the subject to be stable.

Any subject experiencing one or more SAEs will receive treatment and follow-up evaluations by the Investigator or will be referred to another appropriate physician for treatment and follow-up. SAEs will be monitored from the time of consent and for up to 14 days after the subject has discontinued study drug.

All adverse events, whether serious or non-serious will be followed until resolution (or stabilization, if applicable) or until the adverse event is determined by the Investigator to be no longer clinically significant.

Reporting of SAE's to Ferric Citrate Drug Manufacturer/Supplier:

Serious Adverse Events (SAE) which occur in patients receiving ferric citrate, from the time of randomization through and including 14 days after the last administration of the study drug, must be reported to Keryx Biopharmaceuticals within 24 hours of becoming aware of the SAE. The Investigator Sponsor will submit an SAE form to Keryx (available 24 hours/day, 7 days/week) to the following:

Email: PV_Keryx@quintiles.com

Fax: 1-866-599-1342

8.3.4 Investigator Reporting: Notifying KPSC IRB

The study investigator will also notify the KPSC Institutional Review Board (IRB) of any SAE within 10 business days per the KPSC IRB SOP 502, Principal Investigator Reportable Event and Incident Requirements.

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

Adverse events are collected on a weekly basis for the in center hemodialysis patients, and on a bi-monthly basis from the home dialysis patients, and again 30days after the termination of the study.

9 STUDY SCHEDULE: CLINICAL/ LABORATORY EVALUATIONS

9.1 Study Schedule

9.1.1 Screening Visit

Screening visit will occur during the participant's routine monthly dialysis follow up visit by the participant's nephrologist. Patients who meet the inclusion criteria based on chart review by the study coordinator will be approached and

offered to discuss the study in an opt-in fashion introduced by the patient's nephrologist.

Obtain and document consent from potential patient

- Review medical history to determine preliminary eligibility based on protocol eligibility criteria
- Obtain comprehensive medical history and limited physical exam from the medical history, supplemented by information from the patient
- Assign participant a study ID
- Collect blood specimens for aluminum level

9.1.2 Recording of baseline data

A baseline assessment of patient's compliance with usual medications will be performed.

The study coordinator will then review previously obtained routine monthly laboratory values from the dialysis unit, including complete blood count, iron saturation, ferritin, phosphorus, calcium, parathyroid hormone (a total of 6 months of previous data to be reviewed). The study coordinator will then use this baseline data to help determine a patient's eligibility for participation in the active portion of the study, based on the criteria listed in section 5.1. After it is determined that patient actually qualifies for participation in the study, the following will be recorded by the study coordinator:

- Patient's average weekly IV iron and erythropoiesis stimulating agent use (6 months of retrospective data)
- 6 months of retrospective routine laboratory data (CBC, iron saturation, ferritin, calcium, phosphorus, albumin, intact parathyroid hormone levels) will be recorded for each of the previous 6 calendar months
- 6 months of retrospective data regarding medication use will be recorded for each of the previous 6 calendar months (including calcitriol or other vitamin D analogs, cinacalcet, and phosphorus binders), including frequency and dose

After baseline data is obtained, participants will be dispensed a 1 month supply of the study medication, with the starting dose of 1-2 tablets per meal, three times a day. This will mark the start of the active study drug phase.

9.1.3 Study phase monthly visit 1-5 (V1, V2, V3, V4, V5) ± 14 days

Participants will be evaluated in person by the study coordinator on a monthly visit, during the same visit when the subject is seen by his/her dialysis provider. Study records will be updated with the following:

- Limited physical exam from the dialysis provider's notes
- Updates in medical history
- Monthly routine dialysis laboratory values from the dialysis unit, including complete blood count, iron saturation, ferritin, phosphorus, calcium, parathyroid hormone
- Provide blood test tube to draw monthly aluminum level
- Update patient's IV iron and erythropoiesis stimulating agent use.
- Assess for study medication compliance via pill counting
- Dispense study medication supply for the following month
- Assess for adverse events

9.1.4 Lab draw 2 weeks and 6 weeks into the study (L0.5, L1.5) with optional visit ± 7 days

Participant will have lab draw 2 weeks into the study, and possibly again 6 weeks into the study (if deemed necessary by the study investigator), in between their routine monthly labs, to help adjust the study drug dose to control the serum phosphorus level.

- Collect blood specimens at dialysis unit for complete blood count, iron saturation, ferritin, phosphorus, calcium
- Study coordinator will review laboratory tests with study investigator to assess if study drug dose adjustment is needed.
- Optional visit by study coordinator with the patient to review study medication dosage change

9.1.5 Weekly in-center & bi-monthly home dialysis follow up ± 7 days

Participants who are in center dialysis patients will be visited by the study coordinator once a week for pill count and adverse side effect evaluation. Participants who are home dialysis patients will have bi-monthly telephone follow up by the study coordinator to assess medication compliance and adverse side effect evaluation.

9.1.4 Withdrawal/ Final Visit (V6) ± 14 days

At end of 6 months of study drug use, or patient's withdrawal from the study, study coordinator will perform the following:

- Update comprehensive medical history
- Update limited physical exam from dialysis provider's note
- Update medical history from health records
- Collect blood specimens for aluminum level test
- Adverse event assessment
- Update laboratory values from the dialysis unit, including complete blood count, iron saturation, ferritin, phosphorus, calcium, parathyroid hormone
- Update patient's average weekly IV iron and erythropoiesis stimulating agent use.
- Perform final pill count to assess medication compliance
- Collect unused investigational product from patient who withdrew from the study
- Record patient preference for oral phosphorus binder at the end of study.

Any participant who wishes to continue with the study drug as their oral phosphorus binder of choice will be provided a prescription for Ferric Citrate. Participants who wish to return to their previous phosphorus binder will be returned to their original binder.

9.1.5 30 day post study termination follow-up ± 14 days

Study coordinator will follow up with each participant 30 days after termination or study by patient withdrawal or study completion. Following assessment will be completed:

KPSC IRB Approved: 05-Jul-2018

- Adverse event assessment
- Laboratory values from patient's dialysis unit on complete blood count, iron saturation, ferritin, phosphorus, calcium

9.2 Clinical Evaluations

Laboratory testing will include: complete blood count, iron saturation, ferritin, phosphorus, calcium, parathyroid hormone, and aluminum level

Symptoms evaluation will include: any hospitalizations, infections, GI bleed, dialysis access complications, diarrhea, constipation, abdominal discomfort, abdominal distension, duodenal ulcer, nausea, and stool color changes.

9.3 Laboratory Evaluations

Routine dialysis laboratory values will be collected from the patient's dialysis unit on a monthly basis per current standard of care. At week 2 and week 6, additional complete blood count, iron saturation, and ferritin levels will be collected at the patient's dialysis unit. Six aluminum levels will be drawn for each participant over the course of the study. Aluminum level tests will be collected in a single vial (royal blue top tube, approximately 4 ml of blood) by the study coordinator and transported on ice to the LAMC laboratory.

KPSC IRB Approved: 05-Jul-2018

9.4 Study Calendar

Study Procedures	Screening	Baseline Data to be collected	Study phase monthly Visit # 1-5, V1-V5 [1]	Laboratory on week 2 and week 6 [2]	weekly in-center & bi-monthly home dialysis follow up	End of Treatment	30 post follow up
Signed Consent Form	X [4]						
Assessment of Eligibility	X	X					
Comprehensive History	X					X	
Limited Physical Exam	X		X			X	
Update Medical History		X	X			X	
Complete Blood Count	X	X	X	X		X	
Iron saturation	X	X	X	X		X	
Ferritin	X	X	X	X		X	
Phosphorus	X	X	X	X		X	
Calcium	X	X	X	X		X	
IV iron use	X	X	X			X	
Parathyroid Hormone (iPTH)	X	X	X			X	
Aluminum level[3]			X				
Mean weekly ESA agent dose	X	X	X			X	
Medication dispensed			X				
Medication compliance update			X		X	X	
Adverse Event Assessment		X	X		X	X	X

1 Each visit will correspond with monthly hemodialysis or peritoneal dialysis monthly laboratory result round

2 Blood test will be drawn during routine hemodialysis. Home dialysis patients will be asked to go to any KPSC laboratory (normal routine for these patients).

3 Aluminum level blood tube will be brought by study coordinator to be drawn at hemodialysis with the patient's regular monthly labs. Aluminum test tube will be transported on ice to the LAMC laboratory. Home dialysis patients will be referred to any KPSC laboratory for aluminum testing, when needed.

4 Screening visit: If study staff is unable to meet with patient during routine visit or if the patient requests more time to consider participation, peritoneal dialysis patients may be asked to return to clinic for an additional visit to sign the informed consent. This will only apply to peritoneal dialysis patients.

10 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Primary Endpoints

Mean serum phosphorus levels and rate of control (<5.5mg/dl) 6 months before and after treatment with ferric citrate, including PTH, calcium, iron saturation, ferritin, hemoglobin and aluminum levels

10.2 Secondary Endpoints

i. Total cumulative and average weekly dose, number of doses of iv iron administered before and after treatment with ferric citrate
ii. Total ESA dose and mean weekly dose administered 6 months before and after ferric citrate treatment
iii. Total dose of ferric citrate and average number of pills/day required to maintain phosphorus control compared to previous dose and pill burden with binder
iv. Compare serious adverse events including tolerability of ferric citrate compared to previous binder

11 SPECIAL INSTRUCTIONS

N/A

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documentation

Electronic medical records, worksheets, study questionnaires will be used, and all paper material will be kept in a locked, secure office on LAMC campus. All electronic records will be kept only on KPSC approved electronic device with encryption and password protection, stored in secure KPSC buildings.

12.2 Serious Adverse Event Monitoring Form

Serious adverse event monitoring form will be de-identified, scanned electronically, and shared with the study sponsor. Original forms will be kept at LAMC with all other sources documents.

12.3 Record Retention

All paper records will be scanned into electronic files, and paper records will be destroyed after 2 years via KPSC's secure recycling (bins are kept locked and papers shredded). All electronic data containing any personal identifying information such as name, contact telephone number, will be permanently deleted after 24 months. All de-identified study data will be maintained for future research. Data containing personal identifiers will be housed in a separate (also password protected) database from those with study/clinical information to maximize participant anonymity.

12.4 Data Management

Study data will only be accessible to IRB approved personnel. All data will be stored on KPSC issued computers and KPSC computer server with encryption and password protection.

13 STUDY OVERSIGHT

13.1 Data Safety Review Panel

In this pilot study with an FDA approved medication, a modified Data Safety Review Panel will be established with 2 study investigators and one non-study nephrologist. The Data Safety Review Panel will meet on a quarterly basis to evaluate any adverse events, including patients whose serum ferritin increased to >1500. If Data Safety Review Panel identifies new drug related adverse event, reporting will follow per previously outlined protocol. Study coordinator will help to keep records of the Data Safety Review Panel meetings.

13.2 Study Site Monitoring

Study investigators are responsible for study site monitoring and supervision of the study coordinator. Participant records will be reviewed on an intermittent basis to ensure proper and clear record keeping by the study coordinator. Study investigator will also be responsible for resolving any identified issues.

14 STATISTICAL CONSIDERATIONS

In this pilot study, the goal is to assess the feasibility of transitioning from current oral phosphorus binders to the newly FDA approved iron based oral phosphorus binder, and identify challenges encountered in the real world, not previously seen in stringent clinical trial settings.

14.1 Study Hypothesis

We hypothesize that the majority of patients on chronic dialysis, who do not have a contraindication to oral iron supplements, can be successfully transitioned to the new iron based oral phosphorus binder, Ferric Citrate.

14.2 Sample Size Considerations

N/A

14.3 Planned Interim Analyses

N/A

14.4 Final Analysis Plan

N/A

15 REGISTRATION GUIDELINE

Forms and records needed for registration: Informed Consent, Registration/Eligibility Worksheet, baseline data collection sheet. All participants will be given a Bill of Rights along with one copy of the Informed Consent to take home, as well as leaving a signed copy of the informed consent for study files and patient's medical chart.

16 BIOHAZARD CONTAINMENT

Participants are able to keep any used study medication at the end of the study, and to use the medication with his/her nephrologist's supervision. Any returned medication and left over study medication will be disposed of per LAMC pharmacy waste medication disposal protocol in an environmentally safe and responsible fashion.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Institutional Review Board

This study will fall under the jurisdiction of the KPSC Institutional Review Board (IRB). Any changes or updates to study protocol will be formally submitted to the IRB, and only IRB approved personnel will have access to study data. Adverse report will follow IRB guidelines as previously outlined under the section of Adverse Reporting.

17.2 Informed Consent Process

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

Written informed consent, in compliance with 21 CFR 50 will be obtained before any study-related procedures are initiated. Informed consent will be obtained from each patient or patient's legally authorized representative. Informed consent includes the principle that it is critical that the individual be informed about the potential risks and benefits of participating in this study. This information will allow individuals to make a personal risk-versus-benefit decision and understand the following general principles:

1. Participation in this program is entirely voluntary.
2. Patients may withdraw from participation in this program at any time without penalty or loss of benefits to which they are otherwise entitled.
3. Refusal to participate in this study involves no penalty.
4. The individual is free to ask any questions that will allow him/her to understand the nature of this study.

17.3 Exclusion of Women, Minorities, and Children (Special Populations)

In this small pilot study, pregnant women are excluded, as end stage renal failure and uremia is usually not compatible with pregnancy, and very few women become pregnant on dialysis. Racial and ethnic minorities are included. Children are excluded as the dialysis units are adult dialysis units without pediatric patients.

17.4 Privacy and Confidentiality

Participant privacy will be protected with the highest regards. All paper containing personal identifying information will be disposed in KPSC secure paper shred boxes, after they are scanned into the computer. A separate file containing the matching personal identifying information and the assigned study ID will be kept on a password protected secure KPSC server, and accessed only on KPSC LAMC campus through secure desktop computers.

17.5 Future Use of Stored Specimens and Other Identifiable Data

No biology specimens will be stored. All identifiable Data will be destroyed within 12 months after the completion of the study.

18 REFERENCES/ATTACHMENTS

1. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31(4):607-17.
2. Chang AR, Lazo M, Appel LJ, Gutierrez OM, Grams ME. High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. Am J Clin Nutr. 2014;99(2):320-7.
3. Naves-Diaz M, Passlick-Deetjen J, Guinsburg A, Marelli C, Fernandez-Martin JL, Rodriguez-Puyol D, et al. Calcium, phosphorus, PTH and death rates in a large sample of dialysis patients from Latin America. The CORES Study. Nephrol Dial Transplant. 2011;26(6):1938-47.
4. Sim JJ, Bhandari SK, Smith N, Chung J, Liu IL, Jacobsen SJ, et al. Phosphorus and risk of renal failure in subjects with normal renal function. Am J Med. 2013;126(4):311-8.
5. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2008;52(3):519-30.
6. Cannata-Andia JB, Fernandez-Martin JL, Locatelli F, London G, Gorriz JL, Floege J, et al. Use of phosphate-binding agents is associated with a lower risk of mortality. Kidney Int. 2013;84(5):998-1008.
7. Chertow GM, Raggi P, Chasan-Taber S, Bommer J, Holzer H, Burke SK. Determinants of progressive vascular calcification in haemodialysis patients. Nephrol Dial Transplant. 2004;19(6):1489-96.
8. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342(20):1478-83.
9. Smith AJ, Faugere MC, Abreo K, Fanti P, Julian B, Malluche HH. Aluminum-related bone disease in mild and advanced renal failure: evidence for high prevalence and morbidity and studies on etiology and diagnosis. Am J Nephrol. 1986;6(4):275-83.
10. Goodman WG. Bone disease and aluminum: pathogenic considerations. Am J Kidney Dis. 1985;6(5):330-5.
11. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007;116(1):85-97.
12. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int. 2007;71(5):438-41.
13. Haydar AA, Hujairi NM, Covic AA, Pereira D, Rubens M, Goldsmith DJ. Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography. Nephrol Dial Transplant. 2004;19(9):2307-12.
14. Arenas MD, Malek T, Gil MT, Moledous A, Alvarez-Ude F, Reig-Ferrer A. Challenge of phosphorus control in hemodialysis patients: a problem of adherence? J Nephrol. 2010;23(5):525-34.

15. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R**.** Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. Clin J Am Soc Nephrol. 2009;4(6):1089-96.
16. Dwyer JP, Sika M, Schulman G, Chang IJ, Anger M, Smith M, et al. Dose-response and efficacy of ferric citrate to treat hyperphosphatemia in hemodialysis patients: a short-term randomized trial. Am J Kidney Dis. 2013;61(5):759-66.
17. Yokoyama K, Hirakata H, Akiba T, Fukagawa M, Nakayama M, Sawada K, et al. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clin J Am Soc Nephrol. 2014;9(3):543-52.
18. Umanath K, Jalal DI, Greco BA, Umeukeje EM, Reisin E, Manley J, et al. Ferric Citrate Reduces Intravenous Iron and Erythropoiesis-Stimulating Agent Use in ESRD. J Am Soc Nephrol. 2015.
19. Rodby R, Umanath K, Niecestro R, Jackson JH, Sika M, Lewis JB, et al. Phosphorus binding with ferric citrate is associated with fewer hospitalizations and reduced hospitalization costs. Expert Rev Pharmacoecon Outcomes Res. 2014:1-6.

19 APPENDICES

Appendix I: Registration form

Appendix II: Informed Consent Form

Appendix III: Data Collection Form

Appendix IV: Serious Adverse Event Monitoring Form

20 SIGNATURE

This study will be performed in compliance with Good Clinical Practices, including the archiving of essential documents.

Name of Principal Investigator: _____

Department/Specialty: _____

Study Site/ Location Name: _____

Site Address: _____

City, State and Zip code: _____

Phone Number: _____

Signature & Date: _____