KRX-0502 (FERRIC CITRATE)

STUDY KRX-0502-402

A PHASE 4 STUDY OF KRX-0502 (FERRIC CITRATE) DOSE REGIMENS IN SUBJECTS WITH NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE AND IRON DEFICIENCY ANEMIA: THE COMPASS TRIAL

IND Number: 120,629

Protocol History

Original (version 0.1)	03 April 2017
Administrative Letter #1	25 May 2017
Amendment 1	13 December 2017

Sponsor:

Keryx Biopharmaceuticals, Inc.

12th Floor, One Marina Park Drive

Boston, MA 02210 USA

NCT Number: NCT03236246
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Rationale for Amendment 1:

This protocol amendment includes changes to eligibility criteria and screening processes that will facilitate subject enrollment. These changes address barriers to enrollment that have been identified during study start-up and study conduct, as evidenced by a screen failure rate that, to date, has been higher than anticipated. The adjustments to the inclusion laboratory thresholds for eligibility (specifically, estimated glomerular filtration rate [eGFR], hemoglobin [Hgb], and serum ferritin), and the allowance to include subjects who require low-dose oral steroid use, are clinically appropriate for the target population, and do not add any safety concerns for the enrolled subjects.

This amendment also incorporates the change addressed in Administrative Letter #1, replacing the incorrect FACIT Scale questionnaire with the correct FACIT Fatigue Scale questionnaire in the appendix, and reflects the FDA approval (on 06 November 2017) for the use of ferric citrate as "an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis".

Purposes for Amendment 1:

The purposes of this amendment are to:

- Change the lower limit of eGFR for eligibility from >20 to ≥20 mL/min (Inclusion #3).
- Change the Hgb range for eligibility, from ≥9 and ≤11.0 g/dL, to ≥8.5 and ≤11.5 g/dL (Inclusion # 4).
- Revise the Hgb level for allowing ESA therapy, or for withdrawing the subject from the study if all ESA rescue therapy requirements are not met, from <8.5 to <8.0 g/dL.
- Raise the serum ferritin eligibility requirement from ≤200 ng/mL to ≤500 ng/mL (Inclusion #5).
- Allow subjects on low-dose oral corticosteroids (eg, ≤5 mg/day prednisone or the relative equivalent dose of another corticosteroid) to enter the study (Exclusion #14).
- Allow re-testing for specific inclusion/exclusion criteria during a re-screening episode, if applicable, as well as during the first screening episode.
- Clarify that Medical Monitor consultation is not required when the Investigator decides to re-test or re-screen a subject. (Note, this is a clarification of initial intent, not a change to protocol procedures).
- Increase the number of clinical sites from approximately 25 to approximately 30.
- Replace the incorrect FACIT Scale questionnaire with the correct FACIT Fatigue Scale questionnaire in Appendix B.
- Incorporate a description of the FDA approval (on 06 November 2017) for the use of ferric citrate as "an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis".
- Revise the Signature Page with the current Study Biostatistician information.
- Change "Quintiles" to "IQVIA™" to reflect the integration of IMS Health and Quintiles under this new organization name.

For specific examples of changes in text and where the changes are located, see Appendix C.

PROTOCOL SIGNATURE PAGE

The undersigned have reviewed the format and content of this protocol and have approved Protocol No. KRX-0502-402 Amendment 1 for issuance.

RESPONSIBLE SPONSOR MEDICAL OFFICER

[redacted]
Clinical Development
Keryx Biopharmaceuticals, Inc.
Boston, MA

[redacted] [redacted]
Signature Date

STATISTICIAN

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Biostatistics
IQVIA™
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Signature Date

COORDINATING INVESTIGATOR

[redacted]
Renal Associates PA
San Antonio, TX

Signature Date

PROTOCOL SIGNATURE PAGE

The undersigned have reviewed the format and content of this protocol and have approved Protocol No. KRX-0502-402 Amendment 1 for issuance.

RESPONSIBLE SPONSOR MEDICAL OFFICER

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[redacted]
Renal Associates PA
San Antonio, TX

[redacted]
Signature [redacted] Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for KRX-0502. I have read the Study 402 protocol Amendment 1, and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I understand the protocol and will work according to it, the principles of Good Clinical Practice (GCP) (current International Council for Harmonisation [ICH] guidelines), and the Declaration of Helsinki (1964), including all amendments up to and including the Brazil revision (2013).

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

STUDY CONTACT INFORMATION

Medical Monitor (24-hour coverage)

[redacted]
[redacted]
Immunology & Internal Medicine,
Medical Strategy & Science
Therapeutic Science & Strategy Unit

IQVIA™
10188 Telesis Court, Suite 400
San Diego, CA 92121

Contact directly on mobile phone, for urgent issues:
Mobile: [redacted]
Email: [redacted]

The below numbers can be used for 24 hour Urgent Medical Contact if the medical monitor or designated coverage cannot be reached:
Tel. + 1 973 659 6677
Tel. + 1 570 819 8565 (alternative number)

2. SYNOPSIS

Name of Sponsor/Company:
Keryx Biopharmaceuticals, Inc.

Name of Investigational Product:
KRX-0502 (ferric citrate)

Name of Active Ingredient:
Ferric citrate

Title of Study:
A Phase 4 study of KRX-0502 (ferric citrate) dose regimens in subjects with non-dialysis dependent chronic kidney disease and iron deficiency anemia: the COMPASS Trial

Study center(s): Multicenter; approximately 30 sites in the United States

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: 3rd Quarter 2017 Estimated date last subject completed: 2nd Quarter 2019	4

Objectives:
The objectives of this study are to assess the long-term efficacy and safety of different dose regimens of KRX-0502 in the treatment of iron deficiency anemia (IDA) in adult subjects with non-dialysis dependent chronic kidney disease (CKD).

Methodology:
This is a 48-week, Phase 4, randomized, open-label, multicenter clinical study comprised of 2 periods: a 24-week Dose Titration Period, followed by a 24-week Dose Maintenance Period. The study will consist of 12 scheduled clinic visits over a period of 48 weeks and additional visits as needed.

Approximately 200 eligible subjects with non-dialysis dependent CKD and IDA will be randomized in the study into 1 of 2 active treatment groups:

- Group 1: KRX-0502 1 tablet thrice daily (TID; total of 3 tablets/day) with meals
- Group 2: KRX-0502 2 tablets twice daily (BID; total of 4 tablets/day) with the largest 2 daily meals

At Week 12, those subjects with a hemoglobin (Hgb) increase of ≥0.5 g/dL from Baseline and an Hgb ≥10 g/dL will maintain the same dose, otherwise their dose will be increased as follows:

- Group 1: KRX-0502 2 tablets TID (total of 6 tablets/day) with meals
- Group 2: KRX-0502 3 tablets BID (total of 6 tablets/day) with the largest 2 daily meals

Number of subjects (planned):
Two hundred (200) subjects are planned to be randomized

Diagnosis and main criteria for inclusion:
Inclusion criteria
Subjects meeting all of the following inclusion criteria will be randomized in this study:

1. Age ≥18 years

2. Men and women. Women of childbearing potential must have a negative serum pregnancy test at Screening
3. Estimated glomerular filtration rate ≥20 mL/min and <60 mL/min at Screening
4. Hgb ≥8.5 g/dL and ≤11.5 g/dL at Screening
5. Serum ferritin ≤500 ng/mL and transferrin saturation (TSAT) ≤25% at Screening
6. Serum intact parathyroid hormone ≤600 pg/mL at Screening
7. Must consume a minimum of 2 meals per day
8. Willing and able to give written informed consent
9. Female subjects who are not surgically sterile (by bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or postmenopausal (no menstrual period within 1 year of Screening) must agree to use adequate contraception throughout the study and for at least 4 weeks following their final study visit. Adequate contraception is defined as:
    - Total abstinence from sexual intercourse starting at least 1 complete menstrual cycle prior to Screening visit, or
    - Having a vasectomized partner, or
    - Use of hormonal contraceptives (oral, parenteral, or transdermal) for at least 3 months prior to study drug administration or intrauterine contraception/device, or
    - Use of a double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap *together with* spermicidal foam/gel/film/suppository) starting at Screening

    There is no restriction for female partners of male subjects.

<u>Exclusion criteria</u>

Subjects will be excluded if they meet any of the following criteria:

1. Serum phosphate <3.0 mg/dL at Screening
2. Liver transaminases (alanine aminotransferase or aspartate aminotransferase) >3× upper limit of normal at Screening
3. Intravenous (IV) iron administered within 4 weeks prior to Screening or during the Screening Period
4. Erythropoiesis-stimulating agents (ESA) administered within 4 weeks prior to Screening or during the Screening Period
5. Blood transfusion within 4 weeks prior to Screening or during the Screening Period
6. Treatment with any investigational drug within 4 weeks prior to Screening or during the Screening Period
7. Cause of anemia other than iron deficiency anemia of CKD

8. Symptomatic gastrointestinal bleeding within 12 weeks prior to Screening or during the Screening Period
9. Symptomatic inflammatory bowel disease within 12 weeks prior to Screening or during the Screening Period
10. Dialysis within 12 weeks prior to Screening or during the Screening Period, or initiation of dialysis planned within 6 months following Screening
11. Kidney transplant recipient or kidney transplant scheduled within 6 months following Screening
12. Planned surgery or hospitalization (anticipated to last >72 hours) in the 6 months following Screening other than dialysis access-related surgery
13. Requires treatment with myelosuppressive therapy and/or immunosuppressive therapy at Screening or during the Screening Period
14. Requires treatment with oral corticosteroids at Screening or during the Screening Period (use of low-dose oral corticosteroids, eg, ≤5 mg/day prednisone or the relative equivalent dose of another corticosteroid, is not an exclusion); IV corticosteroids administered within 2 weeks prior to Screening or during the Screening Period.
15. Active infection requiring treatment with antibiotics at Screening or during the Screening Period
16. Malignancy except for subjects that have been disease-free for at least 2 years after curative therapy or non-melanoma skin cancer regardless of treatment
17. History of hemochromatosis
18. Subjects who are pregnant or breast feeding
19. Active drug or alcohol dependence or abuse (excluding tobacco use or medicinal or recreational marijuana use where legal unless there is evidence of abuse) within the 12 months prior to Screening or evidence of such abuse (in the opinion of the Investigator)
20. Subjects with known allergic reaction to previous oral iron therapy
21. Prior treatment with KRX-0502
22. Any other medical condition that, in the opinion of the Investigator, renders the subject unable or unlikely to complete the study or that would interfere with optimal participation in the study or produce significant risk to the subject

Investigational product, dosage and mode of administration:

KRX-0502 will be supplied as tablets containing 1 g ferric citrate (210 mg of ferric iron).

Subjects should take KRX-0502 orally with meals or snacks or within 1 hour after their meals or snacks.

Visits need to occur in the morning, non-fasted and subjects instructed to hold KRX-0502 until blood is drawn.

Laboratory values will be checked at each scheduled visit in a Central Laboratory, and the study drug dose may be adjusted in response to these results. When laboratory retesting is necessary, it will be done as an unscheduled visit, unless it coincides with a scheduled visit.

Scheduled Dose Adjustment During the Dose Titration Period (Week 12):

The starting dose of KRX-0502 during the 24-week Dose Titration Period will be determined at Randomization:

- Group 1: KRX-0502 1 tablet TID with meals
- Group 2: KRX-0502 2 tablets BID with the largest 2 daily meals

There will be only one scheduled dose titration step at Week 12. At Week 12, subjects with an Hgb increase of ≥0.5 g/dL from Baseline and an Hgb ≥10.0 g/dL will maintain the same dose; otherwise, their dose will be increased to:

- Group 1: KRX-0502 2 tablets TID with meals
- Group 2: KRX-0502 3 tablets BID with the largest 2 daily meals

The maximum dose before Week 12 is the dose determined at randomization, ie, 3 or 4 g/day depending on randomized group. The maximum dose after Week 12 is the dose determined in Week 12, ie, 3, 4, or 6 g/day depending on randomized group and dose titration at Week 12. Only subjects who complete the 24-week Dose Titration Period will be eligible to enter the Dose Maintenance Period. During the Dose Maintenance Period, subjects will continue on the dose determined during the Dose Titration Period. The maximum dose is the dose determined in Week 12.

Unscheduled Dose Titration at Any Time During the Study:

Unscheduled dose adjustments may be necessary at any point during the study. The guidance below aims to assist the Investigator with decision making about dose modification in the presence of laboratory abnormalities or AEs. Investigators are responsible for evaluating the appropriateness of applying these guidelines to any particular clinical situation for an individual subject. Dose interruption refers to holding of the drug, usually for a short term with the intent to resume dosing when possible. To discuss dosing decisions, including extended dose interruption, Investigators should contact the Medical Monitor.

Low serum phosphorus level:

- If serum phosphorus is <2.0 mg/dL, interrupt dosing.
  - Two weeks after interrupting the dose, repeat the laboratory tests:
    - If serum phosphorus is ≥2.5 mg/dL, resume dosing at the dose prior to the dose interruption.
    - If serum phosphorus is ≥2.0 to <2.5 mg/dL, resume dosing at a reduced dose compared to the dose prior to the dose interruption.
    - If serum phosphorus is <2.0 mg/dL, continue to dose interruption.
- If serum phosphorus is ≥2.0 to <2.5 mg/dL, reduce the KRX-0502 dose by 1 to 3 tablets/day without complete dose interruption.
  - Two weeks after reducing the dose, repeat the laboratory tests:
    - If serum phosphorus is ≥2.5 mg/dL, increase the dose to the dose prior to the dose reduction.
    - If serum phosphorus is ≥2.0 to <2.5 mg/dL, reduce the dose again.
    - If serum phosphorus is <2.0 mg/dL, interrupt dosing.

- Decisions about resuming or increasing dosing and at which dose should take into consideration the absolute levels and trends of the serum phosphorus in the context of the prior dose changes as well as Hgb and TSAT.
- After resolution of a low serum phosphorus, an attempt should be made to increase the dose to the highest dose tolerated prior to the dose interruption or reduction, if supported by the Investigator's clinical judgement.

Elevated TSAT:

- If TSAT is ≥50%, repeat laboratory tests with care to assure that the blood draw is performed before dosing with KRX-0502.
  - If the TSAT is ≥70%, interrupt dosing.
  - If the TSAT is ≥50 and <70%, the response should consider the Hgb level.
    - If Hgb is ≥12 g/dL, interrupt dosing.
    - If Hgb is <12 g/dL, reduce the dose.
      - If the TSAT is <50%, continue current dose and repeat laboratory tests at the next scheduled visit.
- After a dose reduction, repeat laboratory tests at the next scheduled visit.
- Two weeks after interrupting dosing, repeat laboratory tests.
  - If the TSAT is ≥70%, continue dose interruption and check laboratory tests after 2 weeks.
  - If TSAT is <70%, consult the Medical Monitor.
- Decisions about resuming and increasing dosing and at which dose should take into consideration the absolute levels and trends of the TSAT and Hgb in the context of the prior dose changes, as well as serum phosphorus levels.
- After resolution of an elevated TSAT, an attempt should be made to increase the dose to the highest dose tolerated prior to the dose interruption or reduction, if supported by the Investigator's clinical judgement.

Elevated ferritin:

An elevated ferritin level alone (ie, ferritin >1000 ng/mL) does not require dose interruption or dose reduction because it is a poor indicator of iron stores in patients with CKD. However, an elevated ferritin level should prompt clinical evaluation for inflammation or infection and, in review together with the Hgb and TSAT, may lead an Investigator to the decision to interrupt or reduce dosing.

Other laboratory abnormality or AE:

Another laboratory abnormality or AE may require a dose interruption or reduction. Upon resolution of the laboratory abnormality or AE, the dose should subsequently be resumed and/or increased to the highest dose tolerated prior to dose interruption or reduction, if supported by the Investigator's clinical judgement.

Prohibited Therapies

The use of IV iron, blood transfusions, phosphate binders other than KRX-0502, oral iron therapy other than KRX-0502 as treatment for iron deficiency (multivitamins containing iron are permitted), commercial ferric citrate, aluminum-containing therapies, or investigational drugs other than KRX-0502 will not be permitted at any time during the study (beginning with the Screening visit).

The use of ESA is also not permitted during the study, except if used in the specifically defined scenario of ESA rescue therapy (see Section 9.2.2)

If a subject receives a dose of IV iron or a blood transfusion, the subject will immediately discontinue KRX-0502, complete the Early Termination visit assessments, and exit the study. Any subject who is to receive or has received any prohibited medications other than IV iron or a blood transfusion should be discussed with the Medical Monitor as soon as possible to determine the most appropriate course of action (see Section 9.2.1 and Section 9.2.2).

Duration of treatment:

24-week Dose Titration Period followed by a 24-week Dose Maintenance Period (48 weeks total)

Reference therapy, dosage and mode of administration:

Not applicable

Criteria for evaluation:

Efficacy:

Primary endpoint:

The primary efficacy endpoint is the change in Hgb from Baseline at Week 24.

Secondary endpoints:

Secondary endpoints are as follows:

1. Change in Hgb from Baseline at Week 48
2. Change in TSAT from Baseline at Weeks 24 and 48
3. Change in ferritin from Baseline at Weeks 24 and 48
4. Change in serum phosphate from Baseline at Weeks 24 and 48
5. Change in scores for Work Productivity and Activity Impairment (WPAI) questionnaire from Baseline at Weeks 24 and 48
6. Change in score of Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale from Baseline at Weeks 24 and 48
7. Number of hospitalizations and duration (days)

Safety:

Safety evaluations will be based on the following:

- Incidence, seriousness, intensity, duration, and type of AEs
- Clinically significant changes in the subject's vital signs and laboratory test results

Statistical methods:

Efficacy:

The change in Hgb from Baseline is the primary endpoint of interest. Ninety-five percent confidence intervals (CI) will be constructed for change from Baseline at Week 24 and change from Baseline at Week 48 based on the entire sample and by randomized dose groups. No imputation will be performed for these analyses.

Additionally, a Mixed Model Repeated Measures model will be fitted to the change from Baseline Hgb incorporating all visits at which Hgb is measured for each subject. Baseline Hgb and randomized dose group will be applied as fixed effects, as will time (in weeks) and time-by-dose group interaction. An unstructured within-subject covariance structure will be assumed.

TSAT, ferritin, and serum phosphorus will be analyzed in a manner similar to the primary endpoint stated above. Changes for the WPAI questionnaire, the FACIT Fatigue Scale, and frequency and duration of hospitalizations will be analyzed descriptively.

Efficacy analyses will be repeated, substituting the dosing sequence groups for the randomized dose groups if appropriate, based on the distribution in the 4 dosing sequence groups (3-3, 3-6, 4-4, and 4-6 tablets/day). The dosing sequence groups will be determined based on actual doses received by each subject.

Safety:

All safety analyses will be conducted based on the Safety Analysis Set.

Safety data will include AEs, vital signs, and clinical laboratory measurements. Observed data will be listed by subject and summarized using descriptive statistics overall and by dose group based on the Safety Analysis Set.

AEs will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA). AEs that begin after the first administration of study medication or pre-existing conditions that worsen after the first dose of study medication are considered treatment-emergent adverse events (TEAEs). The number and percentage of subjects reporting TEAEs will be summarized overall and for each randomized dose group by MedDRA system organ class and preferred term, then by severity, and by relationship to study treatment. Drug-related AEs will be considered those that are related to study drug based on the Investigator's assessment. The number and percentage of subjects reporting serious AEs and the number and percentage of subjects reporting AEs leading to treatment discontinuation will also be summarized overall and for each dose group by MedDRA system organ class and preferred term.

Vital signs and other clinical and laboratory parameters will be measured at baseline and post-baseline visits. Abnormalities observed in these parameters will be summarized using shift tables for all subjects and by randomized dose group.

Selected safety analyses (including AE analyses) will be repeated substituting the dosing sequence groups for the randomized dose groups, if appropriate, based on the distribution of the dosing sequence groups.

Sample Size:

As this is an open-label Phase 4 study designed to estimate within group changes from Baseline and describe time trends of iron parameters in sub-groups of subjects, it is appropriate to conduct a precision-based sample size estimation as opposed to a power-based calculation. The primary endpoint of interest is change in Hgb from Baseline at Week 24, for which the standard deviation is estimated as 0.9 g/dL based on the Week 16 data in a prior Phase 3 study in a similar population (Study 306).

Assuming a population standard deviation of 0.9 g/dL, with a sample size of 140 subjects, the 95% CI for mean change in Hgb from Baseline at Week 24 can be estimated, allowing for a CI half-width of 0.149 g/dL.

It is assumed that 30% of the subjects in this study will drop out or be otherwise excluded from the Per Protocol population. Hence, 200 subjects will be randomized to ensure that there will be a sufficient number of subjects at the end of the study for the longitudinal analyses. Based on prior clinical trial experience, it is estimated that half of the subjects will stay on their starting dose, and the other half will increase their dose after 12 weeks of treatment. Hence, it is expected that the 4 dosing sequence groups that will arise will have approximately equal numbers of subjects (ie, 35 subjects are expected in each of the four dosing sequence groups (3-3, 3-6, 4-4, and 4-6 tablets/day).

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AM	Ante meridiem (before midday)
AST	Aspartate aminotransferase
BID	Twice daily
BUN	Blood urea nitrogen
CBC	Complete blood count
CCP	Complete chemistry profile
CI	Confidence interval
CKD	Chronic kidney disease
CRO	Contract Research Organization
DAR	Drug Accountability Record
DD-CKD	Dialysis-dependent chronic kidney disease
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
ESA	Erythropoiesis-stimulating agents
ET	Early Termination
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF23	Fibroblast growth factor 23
GCP	Good Clinical Practice
GI	Gastrointestinal
HCT	Hematocrit
Hgb	Hemoglobin
ICH	International Council for Harmonisation
IDA	Iron deficiency anemia
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
iPTH	Intact parathyroid hormone
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web and Voice Response System
KDIGO	Kidney Disease: Improving Global Outcomes
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed Model Repeated Measures
NDD-CKD	Non-dialysis dependent chronic kidney disease
PI	Principal Investigator
PP	Per Protocol
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
sNDA	Supplemental new drug application
TEAE	Treatment-emergent adverse event
TIBC	Total iron-binding capacity
TID	3 times daily
TSAT	Transferrin saturation
UIBC	Unsaturated iron-binding capacity
US	United States
WBC	White blood cell
WBC differential	White blood cell types
WPAI	Work Productivity and Activity Impairment

5. INTRODUCTION

5.1. Background

Chronic kidney disease (CKD) affects up to 14.8% of adults in the United States (US) [USRDS 2016] and markedly increases the risk of premature cardiovascular events [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 [Hgb] <13g/dL for men; <12 g/dL for women), the guidelines suggest a trial of iron to increase the Hgb 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 Hgb levels. When prescribing iron therapy, the guidelines recommend to "balance the potential benefits of avoiding or minimizing blood transfusions, erythropoiesis-stimulating agents (ESA) therapy, and anemia-related symptoms against the risks of harm in individual subjects (eg, anaphylactoid and other acute reactions, unknown long-term risks)."

For CKD patients on dialysis iron is usually given intravenously, but oral iron is preferred in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) for its convenience and low cost. However, the tolerability and efficacy of currently available oral iron formulations is often limited by gastrointestinal side effects, poor adherence to therapy, and poor absorption [Drüeke 2012; Cancelo-Hidalgo 2013; Macdougall 2016]. Intravenous (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 in-office 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.

ESA are another treatment modality for anemia of CKD that is widely used in dialysis-dependent chronic kidney disease (DD-CKD) patients but safety concerns due to excess cardiovascular risk for ESA resulted in black box warnings in 2007. Fewer than 1 in 5 patients with NDD-CKD currently receive ESA therapy prior to initiating dialysis [Regidor 2011; Miskulin 2013].

As a result, many patients with NDD-CKD and anemia today are not optimally treated. For instance, the 2016 Annual Report from the United States Renal Data System finds that the average Hgb for patients initiating dialysis is only 9.6 g/dL [USRDS 2016].

5.2. KRX-0502 (Ferric Citrate) Known Potential Benefits and Risks

Ferric citrate was developed as a phosphate binder because it reacts with the phosphate in the gastrointestinal (GI) tract when administered with food, precipitating phosphate as ferric phosphate. The latter is insoluble and excreted in the stool, reducing the amount of phosphate that is absorbed from the GI tract and lowering serum phosphorus levels. In 2014, KRX-0502 (ferric citrate) was approved in the US for the control of serum phosphorus levels in patients with CKD on dialysis. Additionally, ferric citrate is authorized under different tradenames in Europe, Japan, and Taiwan in subjects with DD-CKD, and in Europe for the control of serum phosphorus in patients with NDD and DD-CKD.

Not all of the elemental iron from ferric citrate precipitates with phosphate, and some is absorbed in the GI tract, thereby providing iron available for erythropoiesis. Indeed, the pivotal trial of KRX-0502 that gained its FDA approval as a phosphate binder in dialysis patients (Study 304) [Lewis 2015] showed that KRX-0502 increases iron stores and reduces IV iron and erythropoietin-stimulating agent use while maintaining Hgb. The observation of this well-tolerated iron delivery in dialysis patients prompted the investigation of KRX-0502 as a treatment for IDA in NDD-CKD patients.

KRX-0502 has now shown efficacy in Phase 2 and Phase 3 trials of IDA in NDD-CKD in the absence of concomitant ESA and IV iron. The 2 adequate and well-controlled studies in the development program for IDA in NDD-CKD are described below.

Study 306 [Fishbane 2017] was a pivotal Phase 3 study specifically designed to measure the effect of KRX-0502 on IDA in adults with Stage 3 to 5 NDD-CKD. Eligible patients had been intolerant to or had an inadequate response to other oral irons. The objectives of Study 306 were to compare the efficacy and safety of KRX-0502 to placebo as a treatment for IDA in a 16-week, randomized, double-blind period, followed by an 8-week, open-label period. The starting dose of KRX-0502 was 3 g/day and titrated up to a maximum of 12 g/day based on Hgb response. During the randomized period, the dose was uptitrated by 3 tabs/day every 4 weeks if the Hgb increase from baseline was ≤1 g/dL. The study drug was given with food, and IV iron and ESA were prohibited. The primary endpoint was the proportion of subjects who achieved an increase in Hgb of ≥1.0 g/dL at any point from Baseline through Week 16. During the Randomized Period, the average KRX-0502 dose was 5 tabs/day. The average dose over successive 4 weekly intervals during the randomized period was approximately 3.0, 4.8, 6.9, and 7.9 tabs/day.

Study 204 [Block 2014] was a prior well-controlled Phase 2 study designed to measure the effect of KRX-0502 on serum phosphorus and IDA in adults with NDD-CKD. The objectives of Study 204 were to compare the efficacy and safety of KRX-0502 to placebo as a treatment for IDA and hyperphosphatemia in a 12-week, randomized, double-blind study. The starting dose of KRX-0502 was 3 g/day and titrated up to a maximum of 12 g/day based on serum phosphorus levels. The study drug was given with food, and IV iron and ESA were prohibited. The co-primary endpoints were the changes from Baseline at Week 12 in TSAT and serum phosphorus levels. The average KRX-0502 dose was 5.1 tabs/day.

In Study 306, the difference in the proportions of subjects with a ≥1 g/dL increase in Hgb between the KRX-0502 and placebo groups was 33% (52.1% responders in KRX-0502 vs 19.1% in Placebo, $p<0.001$). The difference in response rates between KRX-0502 and placebo did not

vary across subgroups by age, sex, race, CKD stage, or baseline Hgb. The analysis of time to first Hgb increase of ≥1.0 g/dL from Baseline to Week 16 in Study 306 shows a continuous increase in responses over the entire duration of the randomized period and this explains the greater increase in Hgb observed in this study compared to Study 204 which had a 4-week shorter treatment duration. In Study 204, the difference in the proportions of subjects with a ≥1 g/dL increase in Hgb between the KRX-0502 and placebo groups was 24% (41.7% responders in KRX-0502 vs 17.4% in Placebo, p=0.002).

In both studies (Study 204 and Study 306), KRX-0502 treatment resulted in clinically meaningful increases in Hgb, with concurrent increases in TSAT and ferritin levels, which were statistically significantly different than placebo treatment, where the levels did not increase. In Study 306, the treatment group difference for the LS mean change from Baseline at Week 16 was 0.84 g/dL for Hgb, 18.4% for TSAT, and 170.3 ng/mL for ferritin (all p<0.001). Statistically significant treatment differences were seen after 1 to 2 weeks of treatment.

KRX-0502 also lowered phosphate levels in both studies. This was a desired effect in Study 204, where subjects were hyperphosphatemic at baseline. In Study 306, where mean baseline phosphate was still in the normal range (4.2 mg/dL), the phosphate reduction was modest and phosphate levels rarely went below the lower limit of the normal range (2.5 to 4.5 mg/dL)

The IDA development program further includes a supportive study (Study 207), which was a small, uncontrolled, pilot study in which the study drug was given without food and at a lower dose than in the 2 adequate and well-controlled studies (Studies 306 and 204). Study 207 was a Phase 2, single-arm, open-label study for the treatment of IDA in subjects with Stage 3 to 5 NDD-CKD. Subjects were treated for 8 weeks and the primary efficacy endpoint was the change in Hgb from Baseline at Week 8. The starting dose of KRX-0502 was 1 g/day, which could be increased to 2 g/day or reduced to 1 g/2 days, depending on the Hgb response by Week 4. The study drug was given without food, and IV iron and ESA were not permitted. The average KRX-0502 dose was 1.2 tabs/day.

The Hgb change from Baseline at Week 8 demonstrated a non-statistically significant trend (0.3 mg/dL, p=0.06). Increases in TSAT and ferritin were statistically significant with the mean change from Baseline at Week 8 in TSAT of 4.4% (p=0.0142) and the mean change from Baseline at Week 8 in ferritin of 38.7 ng/mL (p=0.0003). The changes in Hgb, TSAT, and ferritin observed in Study 207 were smaller than those observed in the adequate- and well-controlled studies but were consistent, considering the shorter treatment duration and lower dose.

The safety of KRX-0502 has been well characterized. To date, there have been over 1900 subjects exposed to KRX-0502 in clinical studies in the 2 development programs for hyperphosphatemia in predominantly DD-CKD and for IDA in NDD-CKD. Four clinical studies (1 study in NDD-CKD and 3 in DD-CKD) included treatment for up to 1 year. KRX-0502 was generally well tolerated and showed a similar safety profile in patients with DD-CKD and NDD-CKD. The most frequently reported adverse events (AEs) were in the gastrointestinal system (diarrhea, nausea, constipation, vomiting, and discolored feces) and were generally mild to moderate in severity.

As of 06 November 2017, KRX-0502 (ferric citrate) is approved in the US as "an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis."

6. STUDY OBJECTIVES AND PURPOSE

The objectives of this study are to assess the long-term efficacy and safety of different dose regimens of KRX-0502 in the treatment of IDA in adult subjects with NDD-CKD.

6.1. Study Endpoints

6.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change in Hgb from Baseline at Week 24.

6.1.2. Secondary Efficacy Endpoint

The secondary endpoints of this study are as follows:

1. Change in Hgb from Baseline at Week 48
2. Change in TSAT from Baseline at Weeks 24 and 48
3. Change in ferritin from Baseline at Weeks 24 and 48
4. Change in serum phosphate from Baseline at Weeks 24 and 48
5. Change in scores for Work Productivity and Activity Impairment (WPAI) questionnaire from Baseline at Weeks 24 and 48 (see Appendix A)
6. Change in score of Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale from Baseline at Weeks 24 and 48 (see Appendix B)
7. Number of hospitalizations and duration (days)

6.1.3. Safety Endpoints

Safety evaluations will be based on the following:

- Incidence, seriousness, intensity, duration, and type of AEs
- Clinically significant changes in the subject's vital signs and laboratory test results.

6.2. Study Rationale

Previous clinical studies in both the NDD-CKD and DD-CKD populations have demonstrated the ability of KRX-0502 to increase Hgb, TSAT, and ferritin, as well as to reduce serum phosphate and fibroblast growth factor 23 (FGF23). In Study 306, this was achieved with repeated prompt uptitration of KRX-0502 to optimize the rapidity of the response and spare patients who had been intolerant to or had an inadequate response to other oral irons any repeated exposure to those agents or treatment initiation with IV iron or ESA.

The current study has been designed to estimate the effect of different dosing regimens of KRX-0502 as chronic therapy for IDA in NDD-CKD. KRX-0502 will be started at 1 of 2 treatment regimens (1 tablet 3 times daily [TID] or 2 tablets twice daily [BID]) utilizing a slower titration and lower maximal dose relative to the 2 prior adequate and well-controlled studies (Study 306 and Study 204). Patients will be observed for a longer duration on treatment than in these prior studies to describe longer-term trends of Hgb and iron parameters in the different groups. Less

frequent visits will more closely align with the office visit frequency in routine clinical care. Thus, the study will serve to directly inform the real-world management of patients with NDD-CKD and IDA treated with KRX-0502.

This Phase 4 study was named the COMPASS trial. The name was chosen to denote that this trial is designed to provide additional direction for the use of KRX-0502 in the anticipated “real world” setting. The name is not an acronym.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 48-week, Phase 4, randomized, open-label, multicenter clinical study, comprised of 2 periods: a 24-week Dose Titration Period followed by a 24-week Dose Maintenance Period (Figure 1). The study will consist of approximately 12 scheduled clinic visits over a period of 48 weeks with additional visits as needed. There will be a Screening period of up to 21 days. Two Hundred (200) eligible subjects with non-dialysis dependent CKD and IDA will be randomized in the study into 1 of 2 active treatment groups:

- **Group 1:** KRX-0502 1 tablet TID (total of 3 tablets/day) with meals
- **Group 2:** KRX-0502 2 tablets BID (total of 4 tablets/day) with the largest 2 daily meals

Study drug dose adjustment will occur at Week 12 and will be based upon the Hgb increase relative to Baseline and an Hgb threshold. Those subjects with an Hgb increase of ≥0.5 g/dL from Baseline and an Hgb ≥10 g/dL will maintain the same dose as determined at Randomization; subjects with an Hgb increase <0.5 g/dL from Baseline (at Randomization) or an Hgb <10 g/dL will have their dose of KRX-0502 increased to the following:

- **Group 1:** KRX-0502 2 tablets TID (total of 6 tablets/day) with meals
- **Group 2:** KRX-0502 3 tablets BID (total of 6 tablets/day) with the largest 2 daily meals

Detailed guidance on dosing and dose adjustments is provided in Section 7.5.

A complete blood count (CBC; including white blood cell [WBC], white blood cell types [WBC differential], red blood cell [RBC] count, hematocrit (HCT), Hgb, RBC indices and platelet [thrombocyte] count) will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); and all subsequent visits.

A complete chemistry profile (CCP; including sodium, potassium, phosphorus, calcium [adjusted for albumin], chloride, carbon dioxide/bicarbonate, glucose, blood urea nitrogen [BUN], creatinine, eGFR, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, total protein, and albumin) will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); and all subsequent visits.

Iron studies (TSAT, ferritin, unsaturated iron-binding capacity [UIBC], total iron-binding capacity [TIBC] and serum iron) will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); and all subsequent visits.

FGF23 (intact and C-terminal) testing will be performed at Visit 2 (Randomization), Visit 9 (Week 24), Visit 12 (Week 48), and the Early Termination (ET) visit.

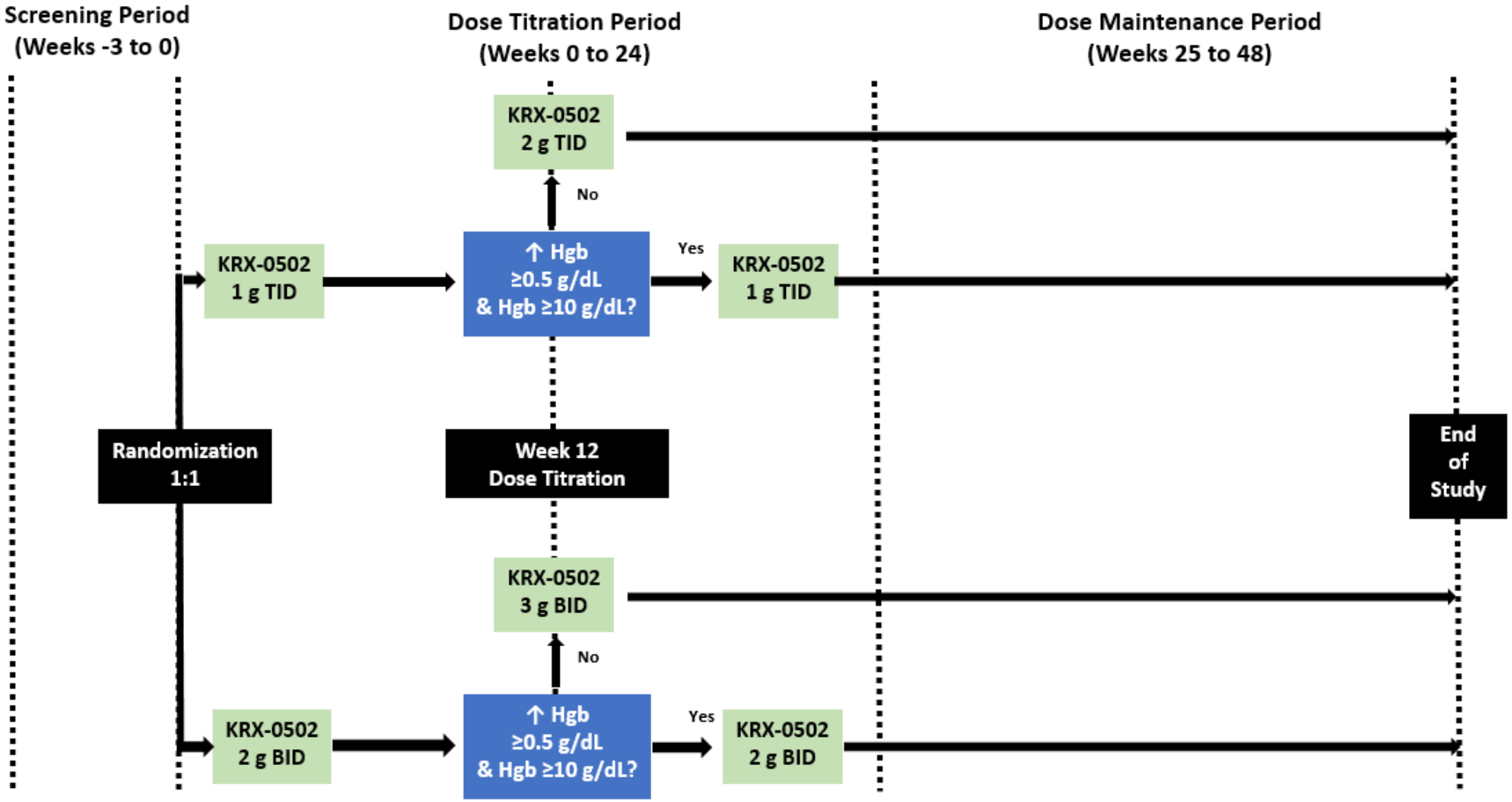
Intact parathyroid hormone (iPTH) testing will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); Visit 9 (Week 24); Visit 12 (Week 48); and the ET visit.

Subjects should take KRX-0502 orally with meals or snacks or within 1 hour after their meals or snacks.

Visits need to occur in the morning, non-fasted and subjects instructed to hold KRX-0502 until blood is drawn. This is to standardize blood draws to occur at trough levels at least 10 to 12 hours after last study drug intake on the day before the visit, because iron parameters rise acutely in the hours following oral intake [Kobune 2011].

A schedule of assessments is presented in Table 2.

Figure 1: Study Periods



BID=twice daily; Hgb=hemoglobin; TID=3 times daily.
1 g =1 tablet of KRX-0502. All doses of study drug will be taken with food. Treatment groups on a BID regimen will be dosed with the 2 largest meals of the day.
Scheduled study drug titration to occur after Visit 6 in Week 12 of Dose Titration Period.

Table 2: Schedule of Assessments

	Screening/ Baseline		Dose Titration Period								Dose Maintenance Period			
	Visit 1A Screening	**Visit 1B Re -Screening[a]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**ET Visit**
	Day -21 to -1	**Day -21 to-1**	**Randomization[b] W0 (Day 1)**	**W2 ±3 d**	**W4 ±3 d**	**W8 ±5 d**	**W12 ±5 d**	**W16 ±5 d**	**W20 ±5 d**	**W24 ±5 d**	**W32 ±7 d**	**W40 ±7 d**	**W48 ±7 d**	
Informed consent[c]	X	X												
Inclusion/exclusion[d]	X	X	X											
Medical history[e]	X	X												
Demographics	X	X												
Randomization			X											
Height	X	X												
Weight	X	X	X							X			X	X
Vital signs[ef]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense/record study drug dose; review diary[h]			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (serum)	X	X												
CBC[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening/ Baseline		Dose Titration Period								Dose Maintenance Period			
	Visit 1A Screening	**Visit 1B Re -Screening[a]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**ET Visit**
	Day -21 to -1	**Day -21 to-1**	**Randomization[b] W0 (Day 1)**	**W2 ±3 d**	**W4 ±3 d**	**W8 ±5 d**	**W12 ±5 d**	**W16 ±5 d**	**W20 ±5 d**	**W24 ±5 d**	**W32 ±7 d**	**W40 ±7 d**	**W48 ±7 d**	
Iron studies[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete chemistry profile[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
iPTH	X	X	X							X			X	X
iFGF23, cFGF23			X							X			X	X
Serum for freezing			X							X			X	X
Spot urine for protein-to-creatinine ratio			X											
WPAI questionnaire			X							X			X	X
FACIT Fatigue Scale			X							X			X	X
Hospitalizations and duration			X	X	X	X	X	X	X	X	X	X	X	X
KRX-0502 dose titration[l]							X							

AE=adverse event; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; cFGF23= C-terminal fibroblast growth factor 23; EOS=End of Study; ET=Early Termination; FACIT=Functional Assessment of Chronic Illness Therapy; HCT=hematocrit; Hgb=hemoglobin; iFGF23=intact fibroblast growth factor 23; iPTH=intact parathyroid hormone; RBC=red blood cell; TIBC=total iron-binding capacity; UIBC= unsaturated iron-binding capacity; W=week; WBC= white blood cell; WBC differential=white blood cell types; WPAI=Work Productivity and Activity Impairment.

Note: All visits other than screening need to occur in the morning, non-fasted and subjects instructed to hold KRX-0502 until blood is drawn (see Section 7.1),

[a] Visit 1B (Re-screening) is optional and may be completed if subject screen fails after first screening and is eligible to be re-screened.

[b] Randomization should occur as soon as possible, but no later than 21 days from the date of Screening or Re-screening. All assessments must be performed prior to randomization

[c] No more than 7 days before Screening or Re-screening.

[d] During Screening and/or Re-screening, subjects may be re-tested for specific inclusion and exclusion criteria that were not met at the initial testing. If a re-test is conducted, it needs to occur within 10 days of Screening (Visit 1A) or Re-screening (Visit 1B) (see Section 10.1.1.1).
[e] Significant pre-existing medical conditions prior to receiving first dose of study medication.
[f] Includes seated heart rate and blood pressure after at least 5 minutes of rest.
[g] AEs will be collected starting at the time of informed consent.
[h] Diary will be dispensed at Visit 2 and collected at Visit 12 or ET visit.
[i] CBC includes WBC count, WBC differential, RBC count, HCT, Hgb, RBC indices, and platelet (thrombocyte) count.
[j] Iron studies includes TSAT, ferritin, UIBC, TIBC, and serum iron. Labs to be drawn as trough levels (see Section 7.1).
[k] Complete chemistry profile includes sodium, potassium, phosphorus, calcium, calcium (adjusted for albumin), chloride, carbon dioxide/bicarbonate, glucose, BUN, creatinine, eGFR, total protein, albumin, total bilirubin, alkaline phosphatase, AST and ALT.
[l] All subjects will be evaluated for dose increase at Week 12; subjects with an Hgb increase <0.5 g/dL from Baseline (randomization) or an Hgb <10 g/dL at Week 12 will have their dose increased as described in Section 7.5.

7.2. Number of Subjects

Approximately 600 adult subjects with NDD-CKD and IDA will be screened to yield 200 subjects eligible for randomization. Eligible subjects will be randomized in a 1:1 ratio into 1 of 2 active treatment groups. It is expected that each of these treatment groups will have 70 evaluable subjects at the end of the study (Section 15.2).

7.3. Study Sites

There will be approximately 30 sites in the US participating in this study. Each site may randomize a maximum of 25 subjects.

7.4. Treatment Assignment

Following a Screening visit, eligible subjects will be randomized in a 1:1 ratio into the 24-week Dose Titration Period. Subjects who complete the Dose Titration Period will continue treatment with KRX-0502 in the 24-week Dose Maintenance Period at the dose determined in the Dose Titration Period.

7.5. Dosing and Dose Adjustment Criteria

KRX-0502 will be supplied as tablets containing 1 g ferric citrate (210 mg of ferric iron). Subjects should take KRX-0502 orally with meals or snacks or within 1 hour after their meals or snacks. Subjects on a TID regimen should take their daily dose as equally distributed (with meals/snacks throughout the day) as possible, and subjects on a BID regimen should take their daily dose with the 2 largest daily meals. A subject who is randomized to a TID dose regimen but eats only 2 meals per day should be instructed to take the third daily dose with a snack. Subjects will be instructed to initiate dosing the day after randomization.

The frequency of dosing (eg, TID and BID) should be maintained. However, subjects may require different dose distributions in a given day due to snacks, missed meals, or a study visit. If the subject is receiving the total number of pills per day required by protocol in any distribution with meals or snacks, the distribution does not need to be approved by the Medical Monitor or Keryx. A KRX-0502 tablet should not be divided.

Visits need to occur in the morning, non-fasted and subjects instructed to hold KRX-0502 until blood is drawn. On a visit day, the morning dose should be taken after the blood draw with a meal or snack or added to the dose with the next meal or snack.

This is a fixed dose study with 1 scheduled dose titration step at Week 12. The starting dose is determined at Randomization (ie, 3 or 4 g/day depending on randomized group). The maximum dose before Week 12 is the dose determined at Randomization. The maximum dose after Week 12 is the dose determined at Week 12, ie, 3, 4, or 6 g/day depending on the randomized group and dose titration at Week 12. Only subjects who complete the 24-week Dose Titration Period will be eligible to enter the Dose Maintenance Period. During the Dose Maintenance Period, subjects will continue on the dose determined during the Dose Titration Period. The maximum dose is the dose determined at Week 12.

Unscheduled dose adjustments can be made at any time during the study for AEs or abnormal laboratories (see Section 7.5.2).

All dose changes should be based on Central Laboratory values. Laboratory results will be checked at each scheduled visit, and the dose may be adjusted in response to these results. When repeat testing of laboratory values is necessary, it will be done as an unscheduled visit, unless it coincides with a scheduled visit. Repeat laboratory testing to guide KRX-0502 dosing should include a CBC, iron studies, and CCP. The Investigator should contact the subject as soon as possible after review of the laboratory results for any scheduled or unscheduled dose adjustments.

Additional information regarding drug-drug interactions is provided in Section 14.

7.5.1. Scheduled Dose Adjustment During the Dose Titration Period

Scheduled study drug titration will occur in Week 12 and will be based upon the Hgb increase relative to Baseline and an Hgb threshold. The Baseline assessment value is the last non-missing value prior to the subject's first dose of study medication. If the Week 12 assessment is missing, the Hgb increase from Baseline will be assessed based on the first non-missing value after Week 12.

Those subjects with an Hgb increase of ≥0.5 g/dL from Baseline and an Hgb ≥10 g/dL will maintain the same dose as determined at Randomization; subjects with an Hgb increase <0.5 g/dL from Baseline or an Hgb <10 g/dL will have their dose of KRX-0502 increased as shown in Table 3.

Due to the random variability of Hgb values, if a Hgb level at Visit 6 (Week 12) appears not plausible (as defined as more than 1 g/dL difference from the most recent Hgb value obtained in the prior 6 weeks), the Investigator may choose to repeat it. In that case, the Hgb from the repeat laboratory draw will determine the dose titration.

For subjects with a scheduled dose titration, the dose change should begin the day after notification.

Table 3: Scheduled Study Drug Titration After Visit 6 (Week 12)

Study Drug Titration at Week 12	
Group 1 (starting dose: 1 tablet TID with meals)	
Hgb increase ≥0.5 g/dL from Baseline and an Hgb ≥10 g/dL	No change
Hgb increase <0.5 g/dL from Baseline or an Hgb <10 g/dL	2 tablets TID (total of 6 tablets/day) with meals
Group 2 (starting dose: 2 tablets BID with meals[a])	
Hgb increase ≥0.5 g/dL from Baseline and an Hgb ≥10 g/dL	No change
Hgb increase <0.5 g/dL from Baseline or an Hgb <10 g/dL	3 tablets BID (total of 6 tablets/day) with meals[a]

BID=twice daily; Hgb=hemoglobin; TID=3 times daily. The baseline assessment value is the last non-missing value prior to the subject's first dose of study medication.

[a] Dose to be taken with the largest 2 daily meals

7.5.2. Unscheduled Dose Adjustments

Unscheduled dose adjustments may be necessary at any point during the study. Below guidance and the dosing algorithms depicted in Figure 2, Figure 3, and Figure 4 aim to assist the Investigator with decision making about dose modification in the presence of laboratory abnormalities or AEs. They are not intended to define a standard of care, nor should they be interpreted as prescribing an exclusive course of management. Investigators are responsible for evaluating the appropriateness of applying these guidelines to any particular clinical situation for an individual subject. Dose interruption refers to holding of the drug, usually for a short term with the intent to resume dosing when possible. To discuss dosing decisions, including extended dose interruption, Investigators should contact the Medical Monitor.

- Serum phosphorus <2.5 mg/dL:
- If serum phosphorus is <2.0 mg/dL, interrupt dosing.
  - Two weeks after interrupting the dose, repeat the laboratory tests:
    - If serum phosphorus is ≥2.5 mg/dL, resume dosing at the dose prior to the dose interruption.
    - If serum phosphorus is ≥2.0 to <2.5 mg/dL, resume dosing at a reduced dose compared to the dose prior to the dose interruption.
    - If serum phosphorus is <2.0, continue dose interruption.
- If serum phosphorus is ≥2.0 to <2.5 mg/dL, reduce the KRX-0502 dose by 1 to 3 tablets/day without complete dose interruption.
  - Two weeks after reducing the dose, repeat the laboratory tests:
    - If serum phosphorus is ≥2.5 mg/dL, increase the dose to the dose prior to the dose reduction.

  - If serum phosphorus is ≥2.0 to <2.5 mg/dL, reduce the dose again.
  - If serum phosphorus is <2.0 mg/dL, interrupt dosing.
- Decisions about resuming or increasing dosing and at which dose should take into consideration the absolute levels and trends of the serum phosphorus in the context of the prior dose changes as well as Hgb and TSAT.
- After resolution of a low serum phosphorus, an attempt should be made to increase the dose to the highest dose tolerated prior to the dose interruption or reduction, if supported by the Investigator's clinical judgement.

TSAT ≥50%:

- If TSAT is ≥50%, repeat laboratory tests with care to assure that the blood draw is performed before dosing with KRX-0502.
  - If the repeat TSAT is ≥70%, interrupt dosing.
  - If the repeat TSAT is ≥50 and <70%, the response should consider the Hgb level.
    - If Hgb is ≥12 g/dL, interrupt dosing.
    - If Hgb is <12 g/dL, reduce the dose.
  - If the repeat TSAT is <50%, continue current dose and repeat laboratory tests at the next scheduled visit.
- After a dose reduction, repeat laboratory tests at the next scheduled visit.
- Two weeks after interrupting dosing, repeat laboratory tests.
  - If the repeat TSAT is ≥70%, continue dose interruption and repeat laboratory tests after 2 weeks.
  - If TSAT is <70%, consult the Medical Monitor.
- Decision about resuming and increasing dosing and at which dose should take into consideration the absolute levels and trends of the TSAT and Hgb in the context of the prior dose changes, as well as serum phosphorus levels.
- After resolution of an elevated TSAT, an attempt should be made to increase the dose to the highest dose tolerated prior to the dose interruption or reduction, if supported by the Investigator's clinical judgement.

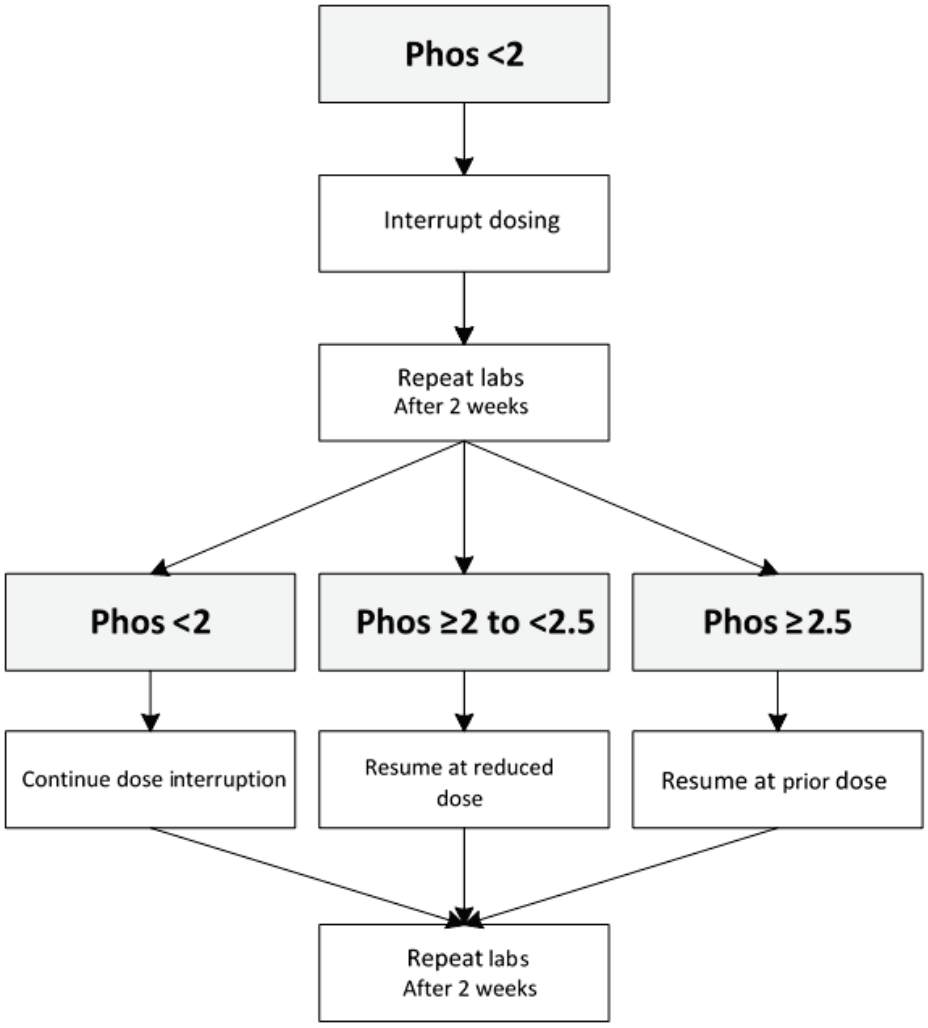
Elevated ferritin:

An elevated ferritin level alone (ie, ferritin >1000 ng/mL) does not require dose interruption or dose reduction because it is a poor indicator of iron stores in patients with CKD. However, an elevated ferritin level should prompt clinical evaluation for inflammation or infection and, in review together with the Hgb and TSAT, may lead an Investigator to the decision to interrupt or reduce dosing.

Other laboratory abnormalities or AEs:

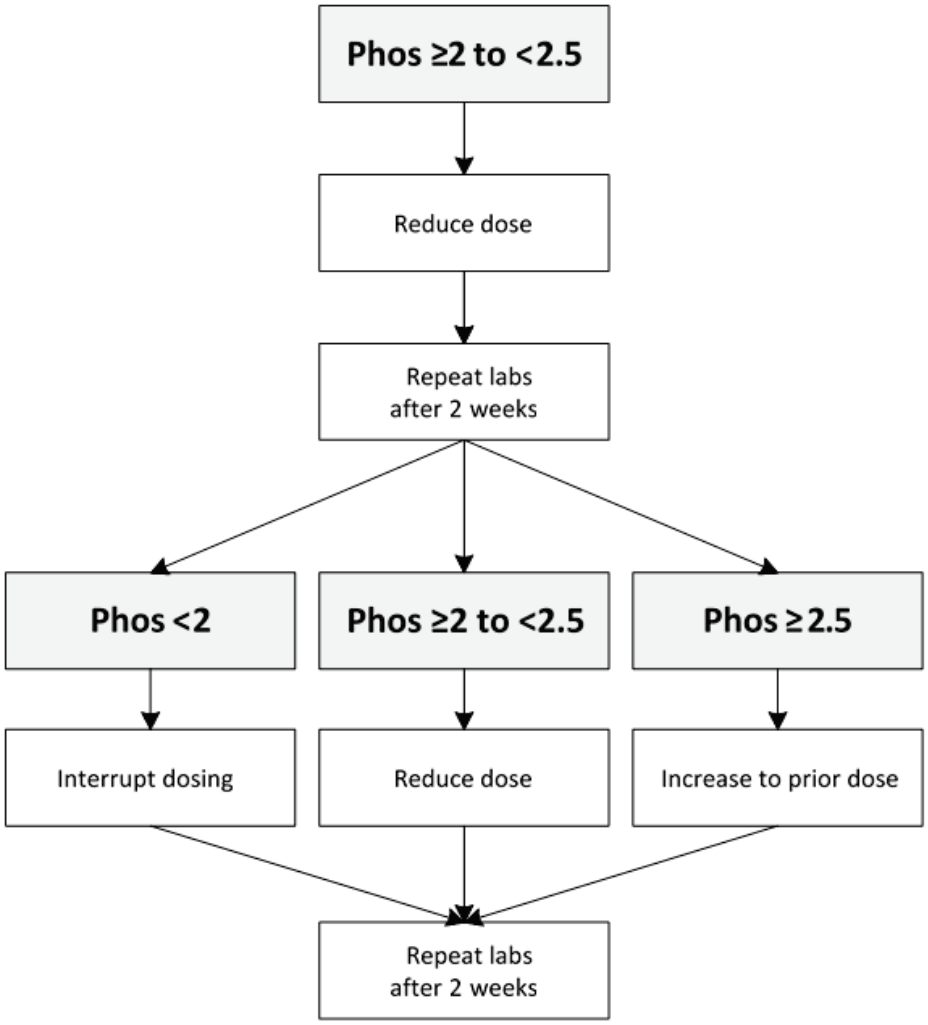
If an unscheduled dose reduction or interruption is necessary due to another laboratory abnormality or AE, upon resolution of the laboratory abnormality or AE the dose should be resumed and/or subsequently increased to the highest dose tolerated prior to dose reduction or interruption, if supported by the Investigator's clinical judgement.

Figure 2: KRX-0502 Dosing Algorithm: Serum Phosphorus <2.0 mg/dL



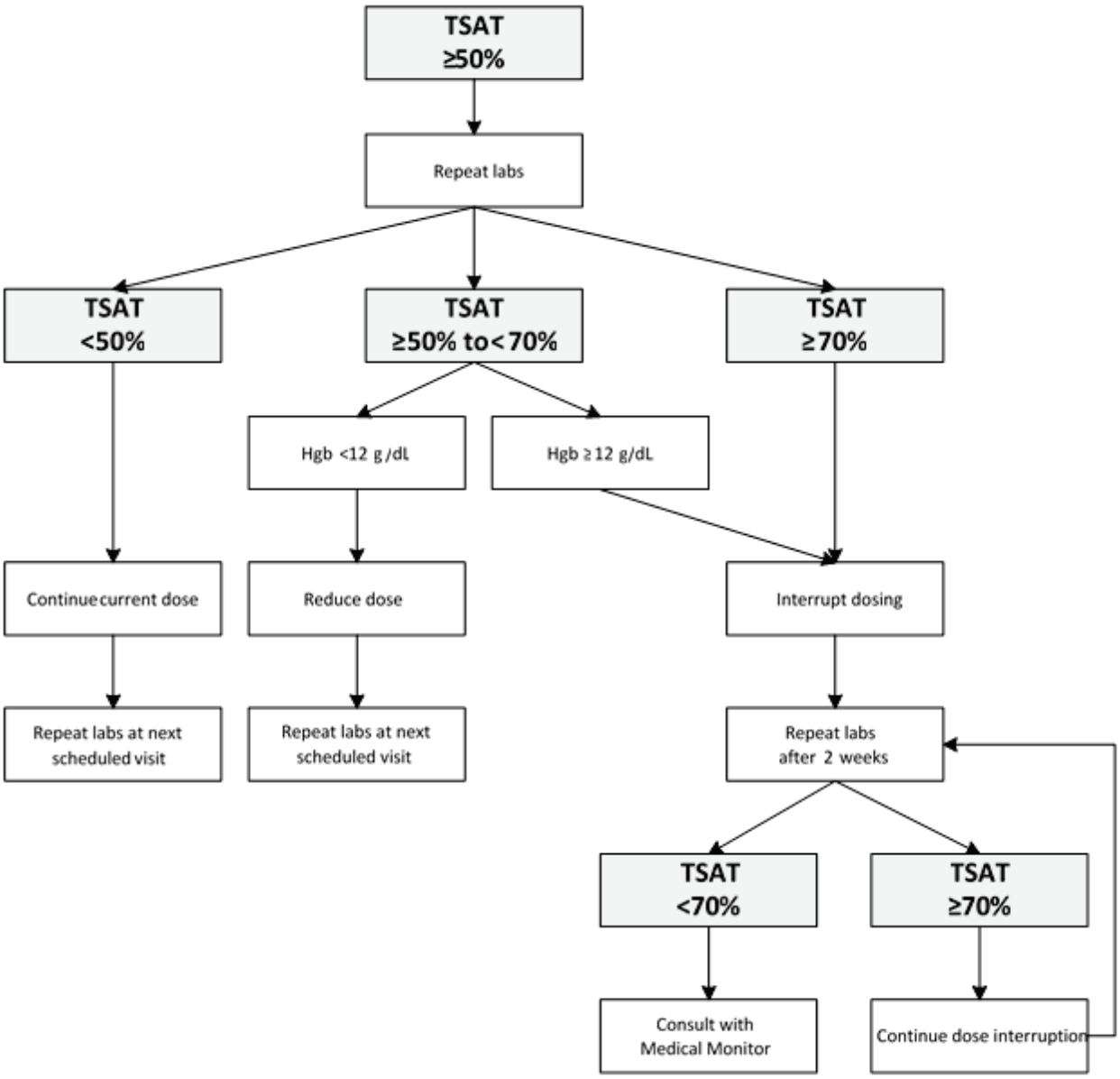
Phos=serum phosphorus.
Note: All serum phosphorus values are presented in mg/dL.
Decisions about resuming or increasing dosing, and at which dose, should take into consideration the absolute levels and trends of the serum phosphorus in the context of the prior dose changes as well as Hgb and TSAT.
To discuss any dosing decisions, including extended dose interruption, Investigators should contact the Medical Monitor.

Figure 3: KRX-0502 Dosing Algorithm: Serum Phosphorus ≥2.0 to<2.5 mg/dL



Phos=serum phosphorus.
Note: All serum phosphorus values are presented in mg/dL.
Decisions about resuming or increasing dosing, and at which dose, should take into consideration the absolute levels and trends of the serum phosphorus in the context of the prior dose changes as well as Hgb and TSAT.
To discuss any dosing decisions, including extended dose interruption, Investigators should contact the Medical Monitor.

Figure 4: KRX-0502 Dosing Algorithm: TSAT ≥50%



Hgb=hemoglobin; TSAT=transferrin saturation.
Decision about resuming and increasing dosing, and at which dose, should take into consideration the absolute levels and trends of the TSAT and Hgb in the context of the prior dose changes, as well as serum phosphorus levels. To discuss any dosing decisions, including extended dose interruption, Investigators should contact the Medical Monitor.

7.6. Study Commencement

Upon satisfactory receipt of all necessary paperwork, Keryx or its official designee will arrange for all study material to be delivered to the study center. Subjects must not undergo study procedures, that is, sign a consent form, until appropriate initiation activities have occurred. Initiation activities will include the training of personnel expected to be involved in the study conduct and will include review of the study protocol, instructions for electronic Case Report

Form (eCRF) completion and serious adverse event (SAE) reporting, and overall responsibilities, including those for drug accountability and Study Master File maintenance.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible to participate in this study:

1. Age ≥18 years
2. Men and women. Women of childbearing potential must have a negative serum pregnancy test at Screening
3. eGFR ≥20 mL/min and <60 mL/min at Screening
4. Hgb ≥8.5 g/dL and ≤11.5 g/dL at Screening
5. Serum ferritin ≤500 ng/mL and TSAT ≤25% at Screening
6. Serum iPTH ≤600 pg/mL at Screening
7. Must consume a minimum of 2 meals per day
8. Willing and able to give written informed consent
9. Female subjects who are not surgically sterile (by bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or postmenopausal (no menstrual period within 1 year of Screening) must agree to use adequate contraception throughout the study and for at least 4 weeks following their final study visit. Adequate contraception is defined as:
    a. Total abstinence from sexual intercourse starting at least 1 complete menstrual cycle prior to Screening visit, or
    b. Having a vasectomized partner, or
    c. Use of hormonal contraceptives (oral, parenteral, or transdermal) for at least 3 months prior to study drug administration or intrauterine contraception/device, or
    d. Use of a double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap *together with* spermicidal foam/gel/film/suppository) starting at Screening

There is no restriction for female partners of male subjects.

8.2. Subject Exclusion Criteria

Subjects will be excluded if they meet any of the following criteria:

1. Serum phosphate <3.0 mg/dL at Screening
2. Liver transaminases (ALT or AST) >3× upper limit of normal at Screening
3. IV iron administered within 4 weeks prior to Screening or during the Screening Period
4. ESA administered within 4 weeks prior to Screening or during the Screening Period
5. Blood transfusion within 4 weeks prior to Screening or during the Screening Period

6. Treatment with any investigational drug within 4 weeks prior to Screening or during the Screening Period
7. Cause of anemia other than iron deficiency anemia of CKD
8. Symptomatic gastrointestinal bleeding within 12 weeks prior to Screening or during the Screening Period
9. Symptomatic inflammatory bowel disease within 12 weeks prior to Screening or during the Screening Period
10. Dialysis within 12 weeks prior to Screening or during the Screening Period, or initiation of dialysis planned within 6 months following Screening
11. Kidney transplant recipient or kidney transplant scheduled within 6 months following Screening
12. Planned surgery or hospitalization (anticipated to last >72 hours) in the 6 months following Screening other than dialysis access-related surgery
13. Requires treatment with myelosuppressive therapy and/or immunosuppressive therapy at Screening or during the Screening Period
14. Requires treatment with oral corticosteroids at Screening or during the Screening Period (use of low-dose oral corticosteroids, eg, ≤5 mg/day prednisone or the relative equivalent dose of another corticosteroid, is not an exclusion); IV corticosteroids administered within 2 weeks prior to Screening or during the Screening Period.
15. Active infection requiring treatment with antibiotics at Screening or during the Screening Period
16. Malignancy except for subjects that have been disease-free for at least 2 years after curative therapy or non-melanoma skin cancer regardless of treatment
17. History of hemochromatosis
18. Subjects who are pregnant or breast feeding
19. Active drug or alcohol dependence or abuse (excluding tobacco use or medicinal or recreational marijuana use where legal unless there is evidence of abuse) within the 12 months prior to Screening or evidence of such abuse (in the opinion of the Investigator)
20. Subjects with known allergic reaction to previous oral iron therapy
21. Prior treatment with KRX-0502
22. Any other medical condition that, in the opinion of the Investigator, renders the subject unable or unlikely to complete the study or that would interfere with optimal participation in the study or produce significant risk to the subject

8.3. Subject Withdrawal Criteria

8.3.1. Discontinuation From Study Drug

Discontinuation from study drug is defined as a permanent termination of treatment with KRX-0502. Subjects may be discontinued from the study drug at any time for any of the following reasons:

- Adverse event
- Lack of efficacy (see Section 9.2.2)
- Pregnancy
- Withdrawal by subject
- Other

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study drug.

Whenever study drug is discontinued prematurely, Keryx and the Medical Monitor must be notified. The subject should return for the ET visit and exit the study.

8.3.2. Discontinuation From Study

Subjects may discontinue from the study for the following reasons:

- Discontinuation from study drug (see Section 8.3.1)
- Subject withdrawal of consent
- Lost to follow-up
- Study drug non-compliance
- Investigator judgment
- Use of certain prohibited therapies (see Section 9.2.1 and Section 9.2.2)
- Start of chronic dialysis or kidney transplantation
- Death
- Sponsor termination of study
- Other

The Investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product, request the subject to return for a final ET Visit as soon as possible to undergo the assessments specified for the visit, and follow-up with the subject regarding any unresolved AEs. For ETs that occur on or after the day of study drug initiation, every effort should be made to document the subject's outcome, regardless of cause. Whenever a subject is discontinued prematurely, Keryx and the Medical Monitor must be notified.

8.3.3. Deviations From the Protocol

A protocol deviation is defined as an event where the Investigator or site personnel do not conduct the study according to the investigational plan or the Study Site Investigator agreement. Protocol deviations are neither encouraged nor allowed unless there are special circumstances. The Sponsor or the Medical Monitor will not grant waivers for eligibility criteria.

Investigators are required to obtain prior approval from the Sponsor or the Medical Monitor before initiating deviations from the investigational plan or protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (eg, subject did not attend scheduled follow-up visit or clinical sample lost by laboratory); however, the event is still considered a deviation.

Keryx will not assume responsibility or liability for any unauthorized deviation from, or change to the protocol.

The Per Protocol (PP) population will exclude subjects with major protocol deviations. Details of the criteria for exclusion from the PP population will be provided in the Statistical Analysis Plan (SAP).

8.4. Termination of Study

Throughout the course of the study, the Investigator shall make every effort to maintain the enrollment rate of appropriate subjects at a level previously determined by Keryx as reasonable. Should the enrollment rate lag or significant numbers of clearly non-evaluable subjects be entered, the Sponsor may elect to terminate the study.

The Sponsor also has the right at any time to terminate the study at specific sites for subject safety, non-adherence to the protocol, unavailability of Investigators or study staff for monitoring visits, or administrative reasons.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

The term "study drug" refers to KRX-0502 (ferric citrate). All subjects will be initiated on a fixed dose of KRX-0502 as determined at Randomization.

Study drug titration will occur at Week 12 as described in Section 7.5.

9.2. Concomitant Medications

All prescription and over-the-counter medications taken at Visit 1A (Screening) and thereafter must be noted on the eCRF as confirmed with the subject.

9.2.1. Prohibited Therapy

Administration of any of the following therapies to subjects enrolled in the study starting with the Screening visit is not permitted:

1. IV iron
2. Blood transfusion
3. ESA with exception specified in Section 9.2.2
4. Oral iron therapy other than KRX-0502 as treatment for iron deficiency (multivitamins containing iron are permitted)
5. Phosphate binder other than KRX-0502
6. Commercial ferric citrate
7. Aluminum-containing therapies
8. Investigational drug other than the KRX-0502

If a subject receives a dose of IV iron or a blood transfusion (items 1 and 2 listed above), the subject will immediately discontinue study drug, complete the ET Visit assessments, and exit the study.

If a subject is to receive or has received any prohibited medication listed under items 3 to 8 above, the subject should be discussed with the Medical Monitor as soon as possible to determine the most appropriate course of action.

9.2.2. ESA Rescue Therapy

ESA use is not permitted during the study. The exception is a scenario in which all of the following conditions for ESA rescue therapy are met:

1. A subject has had 2 consecutive Hgb values of <8.0 g/dL more than 3 days apart.
2. The Investigator decides to treat the subject with ESA as per standard of care.
3. The Investigator deems it appropriate for the subject to continue in the study.
4. The subject continues in the study on study drug.

Any subject who is to receive or has received ESA therapy regardless of whether its use constitutes permitted ESA rescue therapy or not should be discussed with the Medical Monitor as soon as possible to decide whether the subject may remain in the study.

Subjects who received ESA during the study and who remain in the study will be excluded from the PP analysis set. Subgroup analyses will be conducted for these subjects.

Subjects who have had 2 consecutive Hgb values of <8.0 g/dL more than 3 days apart but do not meet the other criteria of ESA rescue therapy should complete the ET visit and discontinue from the study.

9.3. Treatment Compliance

Study personnel will instruct the subjects on the correct number of tablets to take each day with their meals or snacks. Subjects will be given a diary to record daily drug intake. Subjects will be instructed to return with their bottle(s) of medication and their diary at each visit so that compliance may be assessed.

9.4. Randomization and Blinding

As described in Section 7.2, in this open-label study, eligible subjects will be randomized 1:1 to 1 of the 2 KRX-0502 groups with approximately 100 subjects per group:

- Group 1: KRX-0502 1 tablet TID (total of 3 tablets/day) with meals
- Group 2: KRX-0502 2 tablets BID (total of 4 tablets/day) with the largest 2 daily meals

10. STUDY VISITS AND PROCEDURES

10.1. Visit 1A (Screening)

Iron-deficient anemic subjects with NDD-CKD who have an Hgb ≥8.5 g/dL and ≤11.5 g/dL will be approached to participate in this study. Subjects must sign an informed consent form prior to the initiation of any study-related activities and must qualify based on all inclusion criteria (Section 8.1) and exclusion criteria (Section 8.2) to be eligible for this study. Visit 1 (Screening) must occur within 7 days of signing the informed consent form.

To be eligible for the study, the test results from Visit 1A must include an Hgb ≥8.5 g/dL and ≤11.5 g/dL, serum ferritin ≤500 ng/mL, TSAT ≤25%, iPTH ≤600 pg/mL, and a negative serum pregnancy test (if applicable). The subject must also meet all other eligibility criteria. The subject, if eligible, will then be instructed to proceed to Randomization (W0, Day 1). Subject randomization should occur as soon as possible, but no later than 21 days from the date of Visit 1A (Screening).

10.1.1. Procedures for Visit 1A (Screening)

- Obtain informed consent form (no more than 7 days before Screening)
- Review and record inclusion and exclusion criteria including but not limited to the following:
  - Confirming subject has not been administered IV iron, ESA, or blood transfusions in the last 4 weeks prior to Screening
- Obtain clinically significant medical history (pre-existing medical conditions including ongoing signs and symptoms)
- Obtain demographic information
- List current medications
- Instruct subject to stop any oral iron treatment (multivitamin containing iron is permitted) and oral phosphate binder
- Instruct subject about non-permitted medications (Section 9.2.1)
- List current non-drug therapies
- Record weight and height
- Record vital signs (seated heart rate and blood pressure after at least 5 minutes of rest)

- Obtain blood samples:
  - CBC
  - Iron studies
  - CCP
  - iPTH
  - Serum pregnancy test for women of childbearing potential
- Record AEs since signing informed consent and ensure that no recent event has impacted the subject's ability to participate in the study
- Enroll subject using Interactive Web and Voice Response System (IWRS) to obtain unique subject number based on site number and sequential screening order of subject
- Schedule next visit

At this and each subsequent visit, the Investigator will ensure that the procedures used for blood collection and processing are completed in accordance with guidelines provided in this protocol (see Section 7.1 for instructions on timing of trough blood draws). All laboratory samples will be sent to the Sponsor-designated Central Laboratory. The Central Laboratory will provide all materials and procedures for the collection of laboratory samples sent to the Central Laboratory.

It is the Investigator's decision, in consultation with the Medical Monitor if needed, to re-test or re-screen a subject. A subject will maintain the original screening ID for re-testing or re-screening.

10.1.1.1. Re-testing for Specific Inclusion/Exclusion Criteria

During screening and/or re-screening (if applicable), subjects may be re-tested for specific inclusion and exclusion criteria that were not met at the initial testing. If a re-test is conducted, it needs to occur within 10 days of Screening (Visit 1A) or Re-screening (Visit 1B). For example, a subject with a TSAT above the eligibility threshold may be re-tested after discontinuation of an oral iron medication that the subject received up to the Screening visit, or, a subject with a phosphorus level below the eligibility threshold may be retested after discontinuation of an oral phosphate binders that the subject received up to the Screening visit. Retesting for an iron parameter should be done by retesting all iron studies, retesting for phosphorus should be done for phosphorus only. The results from the second test should be used to assess eligibility. However, results from both the first test and the second test should be recorded in the eCRF.

10.2. Visit 1B (Re-screening)

Depending on the reason for screen failure, subjects may be re-screened for study entry at least 2 weeks after their original screen failure date. Re-screening will include re-evaluation of all inclusion and exclusion criteria.

10.2.1. Procedures for Visit 1B (Re-screening)

- Obtain informed consent form (no more than 7 days before Re-screening)
- Review and record inclusion and exclusion criteria including but not limited to the following:
  - Confirming subject has not been administered IV iron, ESA, or blood transfusions in the last 4 weeks prior to Screening
- Obtain clinically significant medical history (pre-existing medical conditions including ongoing signs and symptoms)
- Obtain demographic information
- List current medications
- Instruct subject to stop any oral iron treatment (multivitamin containing iron is permitted) and oral phosphate binder
- Instruct subject about non-permitted medications (Section 9.2.1)
- List current non-drug therapies
- Record weight and height
- Record vital signs (seated heart rate and blood pressure after at least 5 minutes of rest)
- Obtain blood samples:
  - CBC
  - Iron studies
  - CCP
  - iPTH
  - Serum pregnancy test for women of childbearing potential
- Record AEs since signing informed consent and ensure that no recent event has impacted the subject's ability to participate in the study
- Enroll subject using previously obtained unique subject number assigned by IWRS
- Schedule next visit

Retesting for specific inclusion/exclusion criteria may be conducted during re-screening, as detailed in Section 10.1.1.1.

10.2.1.1. Screen Failures

After screening (i.e. a maximum of 21 days after the Screening visit), subjects who do not meet all the inclusion and exclusion criteria will be considered screen failures. Screen failure eCRFs will be completed and the subject's screen failure status will be captured on the appropriate log.

10.3. Visit 2 (Randomization/Week 0, Day 1/Baseline) – First Visit of Dose Titration Period

Randomization should occur within 3 weeks after Screening. Prior to randomizing a subject into the study, it should be verified that the subject still meets all eligibility criteria, and did not develop an intercurrent issue, start a prohibited medication, or require hospitalization since Screening. If the subject is not eligible, the subject will be considered a screen failure.

On the first visit of the 24-week Dose Titration Period, eligible subjects will be randomized in a 1:1 ratio to receive 1 of 2 dosing regimens of KRX-0502.

The starting dose of study drug is determined at Randomization as described in Section 9.4.

The site will contact the IWRS for randomization for each subject at Visit 2 (Randomization) at which time the randomization number will be assigned by the IWRS.

Subjects who consume only 2 meals a day and who are randomized to the TID dosing group should be instructed to take the third daily dose with a snack.

10.3.1. Procedures for Visit 2

- Review and record inclusion/exclusion criteria confirming that the subject meets all eligibility criteria
- Record weight
- Record vital signs
- Record AEs (ensure that AEs have not impacted the subject's ability to participate in the study)
- Record hospitalizations and duration (ensure that the hospitalization has not impacted the subject's ability to participate in the study)
- Record changes in concomitant medications or non-drug therapies
- Instruct subject about non-permitted medications (see Section 9.2.1 and Section 9.2.2)
- Obtain blood samples:
  - CBC
  - CCP
  - Iron studies
  - iPTH
  - FGF23 (intact and C-terminal)
  - Serum sample for freezing
- Obtain spot urine for protein-to-creatinine ratio
- Administer FACIT Fatigue Scale
- Administer the WPAI questionnaire

- Assign randomization number through IWRS
- Dispense study drug and diary and instruct on use of diary
- Instruct subjects on the number of tablets to take each day and how they are to be taken with meals or snacks (see Section 7.5)
- Schedule next visit for AM and instruct subject to hold KRX-0502 on visit day until blood is drawn (see Section 7.1)

Additional information regarding drug-drug interactions is provided in Section 14. For dosing and dose adjustment criteria, see Section 7.5.

10.4. Visits 3 to 8 (Weeks 2 to 20) – Dosing Titration Period

During the Dose Titration Period, Hgb will guide dose titration at Visit 6 (Week 12). Provided the subject's increase in Hgb from Baseline is <0.5 g/dL or Hgb <10 g/dL, the subject's dose will be increased at this visit as described in Section 7.5. If a subject's Hgb increase from Baseline is ≥0.5 g/dL and Hgb >10 g/dL, the subject's dose will not be titrated.

The maximum dose of study drug will be 3 or 4 tablets/day up to Visit 6 (Week 12), and the maximum dose thereafter will be the dose determined by the dose titration at Week 12. At any time, the Investigator can reduce, interrupt, or discontinue the dose of study drug due to an AE or other safety reason. If there are any questions regarding titration of the dose of KRX-0502, the Investigator should contact the Medical Monitor. For additional guidance, refer to Section 7.5.

If an unscheduled dose reduction or interruption is necessary due to a laboratory abnormality or an AE, upon resolution of the laboratory abnormality or AE the dose should be resumed and/or subsequently increased to the highest dose tolerated prior to dose reduction or interruption, if supported by the Investigator's clinical judgement.

Visits need to occur in the morning, non-fasted and subjects instructed to hold KRX-0502 until blood is drawn. The morning dose can be taken after the blood draw with a snack or with the next meal.

It is expected that dose adjustments will be communicated via telephone to the subject as soon as possible after receipt of laboratory values to ensure the longest possible amount of time on the new dose prior to the next scheduled visit.

10.4.1. Procedures for Visits 3 to 8

- Record vital signs
- Review laboratory results from previous visit
- Record AEs
- Record hospitalizations and duration
- Record changes in concomitant medications and non-drug therapies
- Review whether any non-permitted medications were administered since the last visit and instruct subject about non-permitted medications (see Section 9.2.1 and Section 9.2.2)

- Obtain blood samples:
  - CBC (every visit)
  - Iron studies (every visit)
  - CCP (every visit)
- Record study drug dosing, review diary, and assess study drug compliance
- Dispense study drug
- Schedule next visit for AM and instruct subject to hold KRX-0502 on visit day until blood is drawn (see Section 7.1)
- At Visit 6 (Week 12), assess the subject for scheduled dose titration (see Section 7.5.1 and Table 3). If necessary, notify the subject (via telephone) as soon as possible following receipt of laboratory results to titrate study drug dose

For dosing and dose adjustment criteria, see Section 7.5.

10.5. Visit 9 (Week 24) – End of Dose Titration Period

Visit 9 (Week 24) is the final visit of the Dose Titration Period for all subjects.

Only subjects who complete Visit 9 (Week 24) on study drug will enter the Dose Maintenance Period.

10.5.1. Procedures for Visit 9

- Record weight
- Record vital signs
- Review laboratory results from previous visit
- Record AEs
- Record hospitalizations and duration
- Record changes in concomitant medication and non-drug therapies
- Review whether any non-permitted medications were administered since the last visit and instruct subject about non- permitted medications (see Section 9.2.1 and Section 9.2.2)
- Obtain blood samples:
  - CBC
  - CCP
  - Iron studies
  - iPTH
  - FGF23 (intact and C-terminal)

  - Serum sample for freezing
- Record study drug dosing, review diary, and assess study drug compliance
- Dispense study drug
- Administer WPAI questionnaire
- Administer FACIT Fatigue Scale
- Schedule next visit for AM and instruct subject to hold KRX-0502 on visit day until blood is drawn (see Section 7.1)

For dosing and dose adjustment criteria, see Section 7.5.

10.6. Visits 10 to 12 (Weeks 32 to 48) – Dose Maintenance Period

Only subjects who complete the 24-week Dose Titration Period will be eligible to enter the Dose Maintenance Period following Week 24.

During the Dose Maintenance Period, subjects will continue on the dose determined during the Dose Titration Period. There will be no scheduled dose adjustment other than that on Week 12. If an unscheduled dose reduction or interruption is necessary due to an AE or abnormal laboratory value, the dose may be subsequently increased back to the previous dose upon resolution of the event/laboratory abnormality.

Instructions for unscheduled dose interruption (Section 7.5.2) and reduction, dose resumption, and dose increase (Section 7.5), as the case may be, apply also to the Dose Maintenance Period.

If an unscheduled dose reduction or interruption is necessary due to an AE or an abnormal laboratory value, upon resolution of the laboratory abnormality or AE the dose should be resumed and/or subsequently increased to the highest dose tolerated prior to dose reduction or interruption, if supported by the Investigator's clinical judgement.

Visits need to occur in the morning, non-fasted and subjects instructed to hold KRX-0502 until blood is drawn. The morning dose can be taken after the blood draw with a snack or with the next meal.

10.6.1. Procedures for Visits 10 and 11

- Record vital signs
- Review laboratory results from previous visit
- Record AEs
- Record changes in concomitant medications or non-drug therapies
- Review whether any non-permitted medications were administered since the last visit (see Section 9.2.1 and Section 9.2.2)
- Instruct subject about non-permitted medications (see Section 9.2.1 and Section 9.2.2)
- Record hospitalizations and duration
- Obtain blood samples:

  - CBC (every visit)
  - CCP (every visit)
  - Iron studies (every visit)
- Record study drug dosing, review diary, and assess study drug compliance (every visit)
- Dispense study drug
- Schedule next visit for AM and instruct subject to hold KRX-0502 until blood is drawn (see Section 7.1)

For dosing and dose adjustment criteria, see Section 7.5.

10.6.2. Procedures for Visit 12 (Week 48) and ET Visit

- Record weight
- Record vital signs
- Review laboratory results from previous visit
- Record AEs
- Record hospitalizations and duration
- Review whether any non-permitted medications were administered since the last visit (see Section 9.2.1 and Section 9.2.2)
- Record changes in concomitant medication and non-drug therapies
- Obtain blood samples:
  - CBC
  - CCP
  - Iron studies
  - iPTH
  - FGF23 (intact and C-terminal)
  - Serum sample for freezing
- Record study drug dosing, review diary, and assess study drug compliance
- Collect study drug and diary
- Administer WPAI questionnaire
- Administer FACIT Fatigue Scale

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

KRX-0502 (ferric citrate) will be supplied as tablets containing 1g ferric citrate (210 mg of ferric iron).

11.2. Study Drug Packaging and Labeling

KRX-0502 will be supplied to subjects in bottles of 200 tablets. The following information will be provided on the label:

- protocol number
- Sponsor name and address
- compound/code/name of investigational drug
- number of tablets
- Investigational New Drug statement
- instructions for use and storage
- blank space for site number, subject number, and date opened
- lot number
- expiration date

Study personnel will instruct the subjects on the correct number of tablets to take with their meals or snacks. Subjects will be instructed to return with their bottle(s) of medication at each visit so that compliance may be assessed. Unused medication will be re-dispensed to the subjects at the end of each visit. When needed, a new bottle of medication will also be dispensed to ensure that the subjects have enough medication to last until their next visit.

KRX-0502 packaging will be labeled to indicate that the drug is to be used only for investigational purposes and is to be kept out of the reach of children.

11.3. Administration

Keryx or its official designee will supply study drug. The study drug is to be prescribed by only the Investigator or his/her designee. Under no circumstances will the Investigator allow the study drug to be used other than as directed by the protocol without prior Keryx approval.

Subjects will be instructed to return all unused study drug to the Investigator at each visit or upon discontinuation of participation (for any reason).

11.4. Study Drug Accountability

Keryx or its official designee will supply a Drug Accountability Record (DAR) to the Principal Investigator (PI). The PI and his/her designee must maintain the DAR or a suitable site substitute for this record. The site will complete the DAR with dates and quantities of all drug shipments received from Keryx or its official designee, as well as the dates and quantities of all

drug supplies returned to Keryx or its official designee. The DAR must be made available for inspection by authorized representatives of Keryx, its official designee, and the FDA or appropriate regulatory authorities.

Study personnel are responsible for the accountability of used and unused study drug.

11.5. Study Drug Storage, Handling, and Disposal

All study drug, used and unused, must be stored in the original containers in a secure area at the study site (eg, locked cabinet or pharmacy) protected from light and moisture. Storage temperature should be between 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Temperature excursions out of this range should be promptly reported to Keryx for determination of product use and recording of any necessary protocol deviations. Upon completion of the study, the PI must return all used containers and unused drugs to Keryx or its official designee for destruction.

12. ASSESSMENT OF EFFICACY

The primary efficacy endpoint is the change in Hgb from Baseline at Week 24.

The secondary endpoints for this study are as follows:

1. Change in Hgb from Baseline at Week 48
2. Change in TSAT from Baseline at Weeks 24 and 48
3. Change in ferritin from Baseline at Weeks 24 and 48
4. Change in serum phosphate from Baseline at Weeks 24 and 48
5. Change in scores of WPAI questionnaire from Baseline at Weeks 24 and 48
6. Change in FACIT Fatigue Scale from Baseline at Weeks 24 and 48
7. Number of hospitalizations and duration (days)

13. ASSESSMENT OF SAFETY

13.1. Safety Parameters

13.1.1. Demographic/Medical History

Subject demographic and clinically significant medical history information will be collected at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening).

13.1.2. Vital Signs

Vital signs (seated heart rate and blood pressure after at least 5 minutes of rest) will be recorded at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); and all subsequent visits.

13.1.3. Weight and Height

Subject weight and height will be measured at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening). Weight will also be measured at Visit 2 (Randomization), Visit 9 (Week 24), Visit 12 (Week 48), and ET Visit.

13.1.4. Laboratory Assessments

All laboratory values for this study will be determined by a Sponsor-designated Central Laboratory. The Central Laboratory will provide all materials and procedures for the collection of laboratory samples to be sent to the Central Laboratory. Decisions regarding study drug dosing should be based on Central Laboratory test results only. If local laboratory tests are conducted as part of routine care and there are discrepancies between the Central Laboratory and local laboratory test results, the Investigator should use their clinical judgment and consult the Medical Monitor as needed.

Only Central Laboratory test results will be used for statistical analyses.

13.1.4.1. Hematology

A CBC (WBC count, WBC differential, RBC count, HCT, Hgb, RBC indices, platelet [thrombocyte] count) will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); and all subsequent visits.

13.1.4.2. Blood Chemistry

A CCP (sodium, potassium, phosphorus, calcium, calcium [adjusted for albumin], chloride, carbon dioxide/bicarbonate, glucose, BUN, creatinine, eGFR, AST, ALT, ALP, total bilirubin, total protein, and albumin) will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); and all subsequent visits

13.1.4.3. Iron Tests

Iron studies (TSAT, ferritin, UIBC, TIBC, and serum iron) will be performed at Visit 1 A (Screening) and, if applicable, Visit 1B (Re-screening); Visit 2 (Randomization); and all subsequent visits.

13.1.4.4. Other Tests

FGF23 (intact and C-terminal) will be performed at Visit 2 (Randomization), Visit 9 (Week 24), Visit 12 (Week 48), and the ET visit.

iPTH will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-Screening); Visit 2 (Randomization); Visit 9 (Week 24); Visit 12 (Week 48); and the ET visit.

13.1.4.5. Spot Urine Protein-to-Creatinine Ratio

Spot urine protein-to-creatinine ratio will be measured at Visit 2 (Randomization)

13.1.4.6. Frozen Serum Samples

For subjects that provide informed consent specifically for collection of serum samples for freezing, serum samples will be obtained at Visit 2 (Randomization), Visit 9 (Week 24), Visit 12 (Week 48), and the ET visit. The serum samples obtained will be frozen for future analysis of biomarkers of CKD. One candidate biomarker is Klotho for which efforts are underway to develop a better standard assay [Hu 2013]. Thus, the testing is deferred. The future analysis will only be for biomarkers of CKD such as Klotho, there will be no genetic testing done with the frozen specimens at any point.

13.1.4.7. Pregnancy Screen

Serum pregnancy test for all women of childbearing potential will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening). Post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.

13.2. Adverse and Serious Adverse Events

13.2.1. Definition of Adverse Events

All AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation, regardless of treatment group or suspected causal relationship to the study drug, will be recorded on the AE eCRF.

13.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical study subject administered a medicinal (investigational) product and which does not necessarily have a causal relationship with the study treatment.

An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any worsening of a pre-existing condition that is temporally associated with the use of the study drug (ie, occurs after the first dose of study drug) is also considered an AE and should be captured as “worsening” of the pre-existing condition.

13.2.1.2. Serious Adverse Event

The definitions and reporting requirements to which full adherence will be ensured during the conduct of the study are: 1) ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting Topic E2A; 2) Code of Federal Regulations 312.12 IND Safety Reporting.

The Investigator or the Sponsor may determine the seriousness of an AE based on the criteria below.

An AE is considered **serious** if at least one of the following conditions apply:

- Death: An AE that results in the death of a subject. The cause of death or AE that resulted in a fatal outcome should be recorded and reported as the SAE
- Life-threatening: An AE that places the subject in the view of the Investigator or the Sponsor, at immediate risk of death from the event as it occurred (ie, this does not include an event that, had it occurred in a more severe form, might have caused death).
- Disability/Incapacity: An AE that results in a persistent or significant disability/incapacity or substantial disruption of the subject's ability to conduct normal life functions.
- Hospitalization/Prolongation of Hospitalization: An AE that results in subject hospitalization or prolongation of an existing hospitalization. Hospitalization refers to admission of a subject to a hospital for any length of time.

  The following instances do not constitute hospitalization for the purposes of SAE reporting:

  - Routine treatment or monitoring of the studied indication, not associated with any worsening in the baseline condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing of the informed consent
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in a hospital admission for patient care
  - Social reasons and respite care in the absence of any worsening in the patient's baseline condition
- Congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth in the offspring of a study subject
- Important Medical Event: Medical and scientific judgment should be exercised in determining whether an event is an important medical/medically significant event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other outcomes listed in the

SAE definition provided above, the important medical event should be reported as serious/SAE. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization

13.2.2. Recording Adverse Events/Serious Adverse Events

All AEs/SAEs will be collected for all randomized subjects from the date informed consent was signed to completion of the study or to the last administration of study drug or the Investigator/subject decision to discontinue treatment, whichever occurs later. Subjects will be followed for a 28-day follow-up period that begins with completion of the study or after the last administration of study drug, or after the Investigator/subject decision to discontinue treatment, whichever occurs later.

An SAE that occurs during the 28-day follow-up period must be collected regardless of relationship to study drug.

Any SAE reported to the Investigator following completion of the 28-day follow-up period must be promptly reported to the study's Sponsor if it is considered "related" by the Investigator.

The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the following:

- Seriousness
- Relationship to study drug
- Action taken with the study drug
- Onset date
- Ongoing or resolution date
- Outcome
- Intensity (if applicable)

For all AEs, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE (Section 13.2.1.2) requiring immediate action.

Changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However abnormal values that are deemed clinically significant, lead to discontinuation of administration of study drug, or constitute an SAE must be reported and recorded as an AE.

13.2.2.1. Intensity

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal day-to-day activities)
- Severe (incapacitating, with inability to perform normal day-to-day activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.2. An AE of severe intensity may not be considered serious if it does not meet any of the seriousness criteria listed in Section 13.2.1.2.

13.2.2.2. Relationship to Study Drug

An Investigator who is licensed in medicine must make the determination of causal relationship to the study drug for each AE.

The Investigator should use his/her knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered unrelated or related to study drug.

The following factors should be taken into consideration for determination of relationship to study drug:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering the effects of dose reduction
- The effects of study drug discontinuation or re-introduction (if applicable)
- Known association of the AE to ferric citrate therapy or with similar treatments
- Known association of the AE with the disease under study
- Presence of risk factors for the AE in the subject or use of concomitant medications known to be associated with the AE
- Presence of non-treatment-related factors that are anticipated or known to be associated with the occurrence of the AE (eg, conditions associated with the progress of the underlying disease)

Unrelated: The AE is considered "unrelated" to ferric citrate (study drug) if:

- there is evidence that clearly indicates an alternative explanation,
- the subject has not received study drug,
- the timing of the exposure to study drug and the onset of the AE are not reasonably associated in time, or
- other facts, evidence or arguments exist that suggest an alternative cause or explanation

Related: The AE is considered "related" to ferric citrate (study drug) if:

- administration of study drug and the AE are considered reasonably associated in time,
- the AE could be explained by exposure to study drug or by other causes, or no alternative has been identified,

- there is biological plausibility for the causal relationship between the AE and the study drug, and
- there is no alternative cause identified for the AE to occur.

13.2.2.3. Follow-up of Adverse Events

There should be routine follow-up of AEs in all subjects. Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated and per standard of care, should be instituted. Appropriate consultation and follow-up evaluations should be carried out.

All SAEs and related AEs will be followed until the event is resolved, clinically stable, or otherwise explained by the Investigator (eg, returned to baseline, is chronic/irreversible).

After the 28-day follow-up period, only unresolved SAEs should be followed at least every 4 weeks until they resolve, improve to baseline level (for "worsening of a pre-existing condition"), or are clinically stable and chronic/irreversible.

Any related SAE occurring after the 28-day follow-up period should be followed at least every 4 weeks until it is resolved, clinical stable, or otherwise explained by the Investigator (eg, has returned to baseline, is chronic/irreversible)

The Medical Monitor or Sponsor may specify a longer period of follow-up time for AEs if required to assure the safety of the subject.

13.2.3. Reporting of Serious Adverse Events

All SAEs must be reported on the AE eCRF to the study Sponsor within 24 hours of becoming aware of the SAE.

The Sponsor will notify all Investigators of all reportable SAEs that are unexpected per Investigator's Brochure and considered related to the study drug. This notification will be in the form of an expedited safety report. Upon receiving such notices, the Investigator must review and retain the notice with other study-related documentation.

For all SAEs, the Investigator is obligated to pursue and provide information to the study Sponsor. In addition, the Investigator may be requested by the study Sponsor to obtain specific information in an expedited manner. This information may be more detailed than that captured on the AE eCRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causal relationship. Information on other possible causes such as concomitant medications and concurrent illnesses must be provided as applicable.

The Investigator, Sponsor, and Institutional Review Board (IRB) will determine if the informed consent requires revision. The Investigator will comply with the IRB or the Independent Ethics Committee (IEC) procedures for reporting any other safety information.

Suspected serious adverse reactions and other significant safety issues reported from the study shall be reported to the relevant regulatory authorities by the study Sponsor in full adherence to the guidelines and regulations.

13.2.4. Pregnancy

All pregnancies must be reported and recorded on Keryx's pregnancy form. Pregnancy itself is not regarded as an AE unless there is an AE associated with the pregnancy and/or pregnancy outcome and a suspicion that the study drug may have caused or have been associated with this AE.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous abortions/miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be recorded as AEs.

13.3. Medical Emergency Unblinding Procedures

This is an open-label study.

14. CLINICAL PHARMACOLOGY

An interaction with KRX-0502 was seen with doxycycline and ciprofloxacin. Doxycycline should be taken at least 1 hour before KRX-0502. Ciprofloxacin should be taken at least 2 hours before or after KRX-0502.

The following drugs, by drug category, did not show an interaction with KRX-0502:

- Antibiotics: levofloxacin
- Anticoagulants/antiplatelets: aspirin, clopidogrel, and warfarin
- Antidiabetics: sitagliptin
- Antihyperlipidemics: atorvastatin, fluvastatin and pravastatin
- Antihypertensives: amlodipine, enalapril, metoprolol, and propranolol
- Cardiac glycoside: digoxin
- Vitamin D analogues: calcitriol and doxercalciferol

Consider separation of the timing of the administration of KRX-0502 with drugs where a reduction in their bioavailability would have a clinically significant effect on safety or efficacy. Monitor blood levels of concomitant medications that have a narrow therapeutic range.

15. STATISTICAL METHODS AND PLANNED ANALYSES

15.1. General Considerations

All statistical analyses will be performed using Version 9.4 or later of Statistical Analysis Software (SAS®).

Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency and percentage for categorical and ordinal variables. If there are missing values, the number missing will be presented but without a percentage. All data collected will be included in by-subject data listings.

15.2. Determination of Sample Size

Because this is an open-label Phase 4 study designed to estimate within-group changes from Baseline and describe time trends of iron parameters in sub-groups of subjects, it is appropriate to conduct a precision-based sample size estimation as opposed to a power-based calculation. The primary endpoint of interest is change in Hgb from Baseline at Week 24. The SD for that endpoint is estimated as 0.9 g/dL based on the Week 16 data in a prior Phase 3 study in a similar population (Study 306).

Assuming a population SD of 0.9 g/dL, with a sample size of 140 subjects, the 95% confidence intervals (CIs) for mean change in Hgb from Baseline to Week 24 can be estimated, allowing for a of CI half-width of 0.149 g/dL.

It is assumed that 30% of the subjects in this study will drop out or be otherwise excluded from the PP population. Hence, 200 subjects will be randomized to ensure that there will be sufficient subjects at the end of the study for the longitudinal analyses (ie, 70 evaluable subjects in each randomized treatment group). Based on prior clinical trial experience, it is estimated that half of the subjects will stay on their starting dose, and the other half will increase their dose after 12 weeks of treatment. Hence, it is expected that the 4 dosing sequence groups that will arise will have approximately equal numbers of subjects (ie, 35 subjects are expected in each of the four dosing sequence groups (3-3, 3-6, 4-4, and 4-6 tablets/day).

The proposed sample size and the sizes of the sub-groups of interest are deemed sufficient for the analyses proposed below including the longitudinal analyses.

15.3. Analysis Sets

15.3.1. Safety Analysis Set

All subjects who are randomized and take at least 1 dose of study medication will be included in the Safety Analysis Set. Safety analyses will be based on the medication that was actually dispensed to each subject.

15.3.2. Full Analysis Set

All subjects who are randomized, take at least 1 dose of study medication, and have at least 1 post-randomization efficacy measurement will be included in the Full Analysis Set (FAS). Analyses of the FAS will be based on each subject's randomized assigned dose group.

15.3.3. Per Protocol Analysis Set

The PP Analysis Set will include all subjects in the FAS who meet the study eligibility requirements and have no major protocol deviations that affect the validity of the efficacy measurements. Protocol violations that may result in exclusion from the PP Analysis Set will include, but may not be limited to: violations of entry criteria deemed to impact efficacy results, usage of prohibited medications deemed to impact efficacy results, and lack of compliance with study medication to an extent that is deemed to impact efficacy results. The SAP will include specific criteria for exclusion from the PP analysis set.

15.4. Demographics and Baseline Characteristics

Demographic data and baseline characteristics for the FAS, PP, and Safety Analysis Sets will be summarized overall and by dose group using descriptive statistics. These data include sex, age (years), race/ethnicity, weight (kg), height (cm), and calculated body mass index. Baseline characteristics include baseline Hgb, eGFR, TSAT, ferritin, and phosphorus. The baseline value is the last non-missing value observed prior to the first dose of study medication date/time.

15.5. Subject Accountability

Frequencies and percentages will be displayed for the number of subjects screened, failed screening, randomized, completed the study, and dropped out from the study, overall and by dose group. Similarly, the number and percentage of subjects in each analysis set will be summarized.

15.6. Study Treatment Usage and Compliance

Study treatment usage will be assessed based on the numbers of tablets dispensed and returned. Percent compliance will be calculated and analyzed using descriptive statistics. Percent compliance is defined as the ratio of the number of actual study medication tablets taken to the number of study medication tablets that should have been taken during the dosing period multiplied by 100.

15.7. Efficacy Analyses

All efficacy analyses will be performed based on both the FAS and the PP analysis sets. The PP analyses will be considered primary and the FAS analyses will be considered as sensitivity analyses to assess the impact of subject exclusions.

15.7.1. Primary Efficacy Endpoint Analyses

The change in Hgb from Baseline is the primary endpoint of interest. Ninety-five percent CIs will be constructed for change from Baseline at Week 24 and change from Baseline at Week 48 based on the entire sample and by randomized dose groups. No imputation will be performed for these analyses.

15.7.2. Secondary Efficacy Analyses

A Mixed Model Repeated Measures (MMRM) model will be fitted to the change from Baseline Hgb incorporating all visits at which Hgb is measured for each subject. Baseline Hgb and randomized dose group will be applied as fixed effects, as will time (in weeks) and time-by-dose group interaction. An unstructured within-subject covariance structure will be assumed.

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As a sensitivity analysis to MMRM fitted to observed-case data, missing Hgb data will be imputed using multiple imputation (MI) methods described in Section 15.10.3.

TSAT, ferritin, and serum phosphorus will be analyzed in a manner similar to the primary endpoint stated above.

Changes in scores for the WPAI questionnaire and the FACIT Fatigue Scale, and frequency of hospitalizations and hospital days will be analyzed descriptively.

Efficacy analyses will be repeated, substituting the dosing sequence groups for the randomized dose groups if appropriate, based on the distribution in the 4 dosing sequence groups (3-3, 3-6, 4-4, and 4-6 tablets/day). The dosing sequence groups will be determined based on actual doses received by each subject.

15.8. Safety Analyses

All safety analyses will be conducted based on the Safety Analysis Set.

Safety data will include AEs, vital signs, and clinical laboratory measurements. Observed data will be listed by subject and summarized using descriptive statistics overall and by dose group based on the Safety Analysis Set. Selected safety analyses (including AE analyses) will be repeated substituting the dosing sequence groups for the randomized dose groups, if appropriate, based on the distribution in the 4 dosing sequence groups.

15.8.1. Vital Signs

Vital signs (seated heart rate and blood pressure after at least 5 minutes of rest) will be summarized as changes from Baseline and will be classified as low, normal, or high based on reference ranges pre-specified in the SAP. Vital sign abnormalities will be summarized using shift tables for all subjects and by randomized dose group.

15.8.2. Clinical Laboratory Tests

Clinical and laboratory parameters will be measured at baseline and post-baseline visits. Each continuous laboratory variable will be summarized as changes from Baseline for all subjects and by randomized dose group.

Laboratory data will also be classified as low, normal, or high relative to the parameter's reference range for a population with CKD stage 3 to 5. Laboratory abnormalities for all subjects and for each dose group will also be summarized using shift tables.

15.8.3. Adverse Events

AEs will be mapped to preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA). AEs that begin after the first administration of study medication or a pre-existing condition that worsens after the first dose of study medication are considered treatment-emergent adverse events (TEAEs). The number and percentage of subjects reporting TEAEs will be summarized overall and for each randomized dose group by MedDRA system organ class and preferred term, then by severity, and by relationship to study treatment. The number and percentage of subjects reporting serious AEs and the number and percentage of subjects reporting AEs leading to treatment discontinuation will also be summarized overall and for each randomized dose group by MedDRA system organ class and preferred term.

15.9. Other Analyses

Concomitant medications will be coded using the World Health Organization Drug Dictionary. A by-subject listing of concomitant medications will include all medications taken during the study regardless of the timing for the start of the medication. All medications started prior to the administration of study drug will be included in the data but will be identified as prior in the listing. Only the continuing/ongoing concomitant medication use will be summarized for all subjects and by randomized dose group.

15.10. Other Statistical Issues

15.10.1. Significance Levels

Unless otherwise specified, all tests will be 2 tailed using a 0.05 level of significance. All CIs will be 2-sided 95% CIs.

15.10.2. Multiple Comparisons/Multiplicity

No multiplicity adjustments are required for this Phase 4 trial.

15.10.3. Missing or Invalid Data

Subjects who discontinue will not be replaced. To the extent possible, attempts will be made to minimize the amount of missing data through measures planned in the study conduct. However, if missing data are present, they will be handled as follows.

As the primary longitudinal analysis, only available data will be analyzed using the MMRM model described above. This model implicitly adjusts for missing data through a variance-covariance structure.

As a sensitivity analysis, missing endpoint information will be imputed via an MI linear regression approach. A total of 10 imputed datasets will be generated, and the MMRM analyses will be carried out on each imputed dataset; the analyses results will be combined across the 10 datasets using the standard techniques for multiple imputed datasets to yield overall dose group comparisons based on the imputed data.

15.11. Interim Analysis

When all subjects complete their Week 24 visit, an interim analysis will be conducted based on an interim database lock for all subject data through Week 24 visit. As this is a long-term open label Phase 4 trial, it is considered appropriate to conduct a descriptive interim analysis for the primary endpoint (Hgb) and key secondary endpoints (TSAT and ferritin) based on cleaned data through Week 24 using the methods described above including CIs and MMRM analyses. Further details regarding the interim analysis will be provided in the SAP.

16. STUDY MANAGEMENT

16.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Keryx will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Keryx or its representatives. This will be documented in a Clinical Study Agreement between Keryx and the Investigator.

During the study, a monitor from Keryx or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm proper storage of study drug.
- Review drug accountability logs.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and study drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Keryx.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Keryx and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

16.2. Audits and Inspections

Authorized representatives of Keryx, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Keryx audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact Keryx immediately if contacted by a regulatory agency about an inspection.

16.3. Electronic Data Capture

Keryx will provide the study sites with secure access to, and training on, the Electronic Data Capture application sufficient to permit study site personnel to enter or correct information in the eCRFs on the subjects for which they are responsible.

An eCRF will be completed for each enrolled study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations and subject status.

The Investigator or designated representative, will complete the eCRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The Investigator will provide formal approval of all the information in the eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the Investigator is responsible.

Keryx will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be placed in the Investigators study file.

17. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Keryx may conduct a quality assurance audit. Please see Section 16.2 for more details regarding the audit process.

18. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE CONSIDERATIONS

18.1. Ethics Review

The Investigator must obtain IRB approval for the investigation. A copy of written IRB approval or favorable opinion of the protocol, informed consent form, and advertising (if applicable) must be provided to Keryx prior to initiation of the study. Initial IRB approval and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection. The PI is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Investigator is responsible for obtaining continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not exceeding 1 year or otherwise specified by the IRB. Keryx must be supplied with written documentation of continued review of the clinical research. The Investigator must promptly inform their IRB of all SAEs or other safety information reported from Keryx/CRO in accordance with applicable laws and regulations.

18.2. Ethical Conduct of the Study

This study will be conducted in compliance with all U.S. FDA regulations including 21 CFR, Parts 11, 50, 54, 56, and 312, as well as other guidelines for GCP, and applicable local regulatory requirements and laws. This study will also comply with the Declaration of Helsinki, ICH/GCP and all subsequent international agreements for subjects' rights and safety. This study will receive IRB approval prior to its commencement at each study site.

The clinical database at the Sponsor-designated Clinical Research Organization complies with the regulation in 21 CFR Part 11.

18.3. Written Informed Consent

The study personnel shall obtain written informed consent from each subject prior to performing any study assessments. The consent form must be approved by Keryx and the IRB according to the IRB's requirements. The consent must also indicate that, by signature, the subject permits access to relevant medical records by designated auditors and representatives of the Regulatory Authority. This document must be written in a language understandable to an individual with an eighth grade education. The consent form must be written and explained in the subject's primary language. Subjects must be given time to consider the information fully and be encouraged to ask questions about their study participation. The Investigator must also inform the subject that s/he is free to refuse to enter the study and to withdraw from the study at any time, for any reason, and that such refusal will not compromise the care s/he is rendered. All consent forms must be signed and dated by the study personnel and the subject. For subjects not qualified to give legal consent, written consent must be obtained from the next of kin or legal guardian. A copy of the signed document will be given to the subject, and the Investigator will retain the original with the subject files.

18.4. Patient Confidentiality

Keryx will preserve the confidentiality of subjects taking part in this study. Keryx, its official designee, the IRB, and the FDA will use records from the study only in connection with this research project. These medical records will not be disclosed to any other parties and will otherwise be kept completely confidential. In the event of subject names inadvertently appearing on study documentation, this information will not be entered into the computer database for the study. Representatives of Keryx will seek access to clinical information only after the subject or subject's legal guardian so has given approval to do.

The study will comply with Health Insurance Portability and Accountability Act.

18.5. Study Master File

All study correspondence and administrative documentation (eg, protocol, consent form, and IRB information) should be filed by the Investigator in an organized and easily retrievable manner for review during monitoring, an audit, or an inspection. This Investigator Site File will be open for inspection by monitors, to ensure that all relevant documents are present and easily retrievable.

18.6. Laboratory Accreditation

Laboratories used for analysis of samples required for this protocol must show evidence of adequate licensure or accreditation. A copy of the accreditation certificate(s) for all laboratories will be provided for retention in the Investigator Site File.

18.7. Independent Medical Monitor

The Sponsor delegates the responsibility of medical monitoring to a contracted Medical Monitor. Contact information for the Medical Monitor is provided in the Study Contacts page (see page 4).

The Medical Monitor will be available 24 hours per day to provide assistance for

- Interpretation of protocol and eligibility criteria,
- Dosing decisions (see Section 7.5),
- Discussion of any subject who is to receive or has received ESA therapy (see Section 9.2.2),
- Discussion of any subject who is to receive or has received prohibited therapy (see Section 9.2.1),
- Questions regarding AEs,
- Discussion of any subject with extended dose interruption, and
- Discussion or notification regarding any subject who is considered for or has undergone study drug discontinuation or study discontinuation (see Section 8.3.1 and Section 8.3.2).

The medical care of a subject remains the sole responsibility of the Investigator.

In case a subject has to be withdrawn from the trial, the Medical Monitor will be informed immediately, who will then inform the Sponsor.

19. DATA HANDLING AND RECORDKEEPING

19.1. Inspection of Records

Keryx will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, DARs, subject charts and study source documents, and other records relative to study conduct.

19.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Keryx or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

If the Investigator relocates, retires, or for any reason withdraws from the study, Keryx should be prospectively notified. The study records must be transferred to an acceptable designee. The Investigator must retain Keryx's written permission before disposing of any records, even if retention requirements have been met.

19.3. Financial Disclosure

By signing this protocol, the Investigator agrees to provide Keryx accurate financial information to allow Keryx to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Keryx. The Investigator will update this information if there are any relevant changes during the conduct of the study and for 1 year after completion of the study. This requirement also extends to sub-investigators.

20. PUBLICATION POLICY

Individual subject medical information obtained as a result of this study is to be considered confidential, and disclosure to third parties other than the FDA or regulatory authorities and/or other persons or organizations designated by Keryx is prohibited. Any medical information may be provided to the subject's personal physician or to appropriate medical personnel responsible for the subject's care. Additionally, data generated from this study are to be provided, upon request, to FDA auditors, and Keryx's monitors, as well as to the local IRB. Subject confidentiality is to be further assured by utilizing subject identification code numbers to identify subject data.

Primary data resulting from all centers participating in this study are to be published as 1 or 2 articles following Good Publication Practices including ICMJE authorship criteria [Graf 2009; Battisti 2015]. After submission of the primary data, Keryx may produce publications addressing secondary analyses, post-hoc analyses and/or sub-analyses following all good publication practices. Additionally, individual centers may request permission from Keryx to submit manuscripts addressing secondary analyses, post-hoc analyses and/or sub-analyses. In this case, Keryx will be granted a period of 60 days to review all final drafts and make suggestions.

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22. APPENDICES

APPENDIX A. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT (WPAI) QUESTIONNAIRE

Work Productivity and Activity Impairment Questionnaire:

Specific Health Problem V2.0 (WPAI:SHP)

The following questions ask about the effect of your Anemia associated with Chronic Kidney Disease on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your Anemia associated with Chronic Kidney Disease? *Include hours you missed on sick days, times you went in late, left early, etc., because of your Anemia associated with Chronic Kidney Disease. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your Anemia associated with Chronic Kidney Disease affect your productivity <u>while you were working?</u>

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Anemia associated with Chronic Kidney Disease affected your work only a little, choose a low number. Choose a high number if Anemia associated with Chronic Kidney Disease affected your work a great deal.

Consider only how much Anemia associated with Chronic Kidney Disease affected productivity while you were working

Anemia associated with Chronic Kidney Disease had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Anemia associated with Chronic Kidney Disease completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your Anemia associated with Chronic Kidney Disease affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If Anemia associated with Chronic Kidney Disease affected your activities only a little, choose a low number. Choose a high number if Anemia associated with Chronic Kidney Disease affected your activities a great deal.

Consider only how much anemia associated with chronic kidney disease affected your ability to do your regular daily activities, other than work at a job

Anemia associated with Chronic Kidney Disease had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Anemia associated with Chronic Kidney Disease completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993; 4(5):353-365.

APPENDIX B. FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) FATIGUE SCALE QUESTIONNAIRE

FACIT-Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX C. AMENDMENT 1 DETAILED SUMMARY OF CHANGES

Purpose: Change the lower limit of eGFR for eligibility from >20 to ≥20 mL/min (Inclusion #3).

The primary change occurs in Section 8.1, Subject Inclusion Criteria:

Formerly read: 3. eGFR ~~>~~20 mL/min and <60 mL/min at Screening

Now reads: 3. eGFR **≥**20 mL/min and <60 mL/min at Screening

Section 2, Synopsis, also contains this change.

Purpose: Change the Hgb range for eligibility, from ≥9 and ≤11.0 g/dL, to ≥8.5 and ≤11.5 g/dL (Inclusion # 4).

The primary change occurs in Section 8.1, Subject Inclusion Criteria:

Formerly read: 4. Hgb ≥~~9.0~~ g/dL and ≤~~11.0~~ g/dL at Screening

Now reads: 4. Hgb ≥**8.5** g/dL and ≤**11.5** g/dL at Screening

Sections that also contain this change are:

- Section 2, Synopsis
- Section 10.1, Visit 1A (Screening)

Purpose: Revise the Hgb level for allowing ESA therapy, or for withdrawing the subject from the study if all ESA rescue therapy requirements are not met, from <8.5 to <8.0 g/dL.

The change occurs in Section 9.2.2, ESA Rescue Therapy

Formerly read: ESA use is not permitted during the study. The exception is a scenario in which all of the following conditions for ESA rescue therapy are met:

1. A subject has had 2 consecutive Hgb values of <~~8.5~~ g/dL more than 3 days apart.
2. …

Subjects who have had 2 consecutive Hgb values of <~~8.5~~ g/dL more than 3 days apart but do not meet the other criteria of ESA rescue therapy should complete the ET visit and discontinue from the study.

Now reads:	ESA use is not permitted during the study. The exception is a scenario in which all of the following conditions for ESA rescue therapy are met: 1. A subject has had 2 consecutive Hgb values of <**8.0** g/dL more than 3 days apart. 2. … Subjects who have had 2 consecutive Hgb values of <**8.0** g/dL more than 3 days apart but do not meet the other criteria of ESA rescue therapy should complete the ET visit and discontinue from the study.

Purpose: Raise the serum ferritin eligibility requirement from ≤200 ng/mL to ≤500 ng/mL (Inclusion #5).

The primary change occurs in Section 8.1, Subject Inclusion Criteria

Formerly read:	5. Serum ferritin ≤~~200~~ ng/mL and TSAT ≤25% at Screening
Now reads:	5. Serum ferritin ≤**500** ng/mL and TSAT ≤25% at Screening

Sections that also contain this change are:

- Section 2, Synopsis
- Section 10.1, Visit 1A (Screening)

Purpose: Allow subjects on low-dose oral corticosteroids (eg, ≤5 mg/day prednisone or the relative equivalent dose of another corticosteroid) to enter the study (Exclusion #14).

The primary change occurs in Section 8.2, Subject Exclusion Criteria

Formerly read:	14. Requires treatment with oral corticosteroids at Screening or during the Screening Period; IV corticosteroids administered within 2 weeks prior to Screening or during the Screening Period.
Now reads:	14. Requires treatment with oral corticosteroids at Screening or during the Screening Period **(use of low-dose oral corticosteroids, eg, ≤5 mg/day prednisone or the relative equivalent dose of another corticosteroid, is not an exclusion)**; IV corticosteroids administered within 2 weeks prior to Screening or during the Screening Period.

Section 2, Synopsis, also contains this change.

Purpose: Allow re-testing for specific inclusion/exclusion criteria during a re-screening episode, if applicable, as well as during the first screening episode.

The primary change occurs in Section 10.1.1.1, Re-testing for Specific Inclusion/Exclusion Criteria

Formerly read:

10.1.1.1 Retesting for Specific Inclusion/Exclusion Criteria During Screening

During ~~the first~~ screening ~~episode~~, subjects may be re-tested for specific inclusion and exclusion criteria that were not met at the initial testing. ~~Re-test may~~ occur within 10 days of ~~the original screening date~~.

Now reads:

10.1.1.1 Re-testing for Specific Inclusion/Exclusion Criteria

During screening **and/or re-screening (if applicable)**, subjects may be re-tested for specific inclusion and exclusion criteria that were not met at the initial testing. **If a re-test is conducted, it needs to** occur within 10 days of **Screening (Visit 1A) or Re-screening (Visit 1B)**.

Sections also affected by this change are:

- Table 2: Schedule of Assessments (footnote d)
- Section 10.1.1, Procedures for Visit 1A (Screening)
- Section 10.2.1, Procedures for Visit 1B (Re-screening)

Purpose: Clarify that Medical Monitor consultation is not required when the Investigator decides to re-test or re-screen a subject. (Note, this is a clarification of initial intent, not a change to protocol procedures).

The change occurs in 10.1.1, Procedures for Visit 1A (Screening)

Formerly read:

It is the Investigator's decision, in consultation with the Medical Monitor, to re-test or re-screen a subject. ~~There may only be 1 re-testing or re-screening for a subject.~~ A subject will maintain the original screening ID for re-testing or re-screening.

Now reads:

It is the Investigator's decision, in consultation with the Medical Monitor **if needed**, to re-test or re-screen a subject. A subject will maintain the original screening ID for re-testing or re-screening.

Purpose: Increase the number of clinical sites from approximately 25 to approximately 30.

The primary change occurs in 7.3, Study Sites:

Formerly read:

There will be approximately ~~25~~ sites in the US participating in this study. Each site may randomize a maximum of 25 subjects.

Now reads: There will be approximately **30** sites in the US participating in this study. Each site may randomize a maximum of 25 subjects.

Section 2, Synopsis, also contains this change.

Purpose: Replace the incorrect FACIT Scale questionnaire with the correct FACIT Fatigue Scale questionnaire in Appendix B.

The primary change occurs in Appendix B, Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale Questionnaire:

This change required the deletion of 3 pages of the FACIT scale and replacement of 1 page; these changes are not shown here for brevity/clarity.

Purpose: Incorporate a description of the FDA approval (on 06 November 2017) for the use of ferric citrate as "an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis".

The primary change occurs in Section 5.2, KRX-0502 (Ferric Citrate) Known Potential Benefits and Risks:

Formerly read: ~~Based on these data, Keryx submitted a sNDA for treatment of IDA in NDD-CKD to the FDA in January 2017.~~

Now reads: **As of 06 November 2017, KRX-0502 (ferric citrate) is approved in the US as "an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease not on dialysis."**

Section 5.1, Background is also affected by this change.

Purpose: Revise the Signature Page with the current Study Biostatistician information.

The change occurs on the Protocol Signature Page:

Formerly read: [redacted]
~~PROMETRIKA, LLC~~
~~Cambridge, MA~~

Now reads: [redacted]
Biostatistics
IQVIA™
United States

Purpose: Change "Quintiles" to "IQVIA™" to reflect the integration of IMS Health and Quintiles under this new organization name.

The change occurs on the Study Contact Information page:

Formerly read:

[redacted]
Immunology & Internal Medicine,
Medical Strategy & Science
Therapeutic Science & Strategy Unit

~~QuintilesIMS~~
10188 Telesis Court, Suite 400
San Diego, CA 92121

Contact directly on mobile phone, for urgent issues:
Mobile: [redacted]
Email: [redacted]

Now reads:

[redacted]
Immunology & Internal Medicine,
Medical Strategy & Science
Therapeutic Science & Strategy Unit

IQVIA™
10188 Telesis Court, Suite 400
San Diego, CA 92121

Contact directly on mobile phone, for urgent issues:
Mobile: [redacted]
Email: [redacted]