STATISTICAL ANALYSIS PLAN

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"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"

CRF Date: 06-FEB-2018

STUDY DRUG:

KRX-0502 (FERRIC CITRATE)

SPONSOR:

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1. LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this statistical analysis plan.

Table 1: Abbreviations and Special Terms

Abbreviation	Term
ADaM	Analysis data model
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
BID	Twice Daily
BMI	Body mass index
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCP	Complete Chemistry Profile
CI	Confidence Interval
CKD	Chronic Kidney Disease
cm	Centimeter
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DD-CKD	Dialysis-Dependent Chronic Kidney Disease
DILI	Drug Induced Liver Injury
dL	Deciliter

Abbreviation	Term
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ESA	Erythropoiesis-Stimulating Agents
ET	Early Termination
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FGF23	Fibroblast growth factor 23
g	Gram
HCT	Hematocrit
Hgb	Hemoglobin
IDA	Iron deficiency anemia
iPTH	Intact parathyroid hormone
IV	Intravenous
IWRS	Interactive Web and Voice Response System
kg	Kilogram
L	Liter
LSM	Least square mean
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MEq	Milliequivalents
MDRD	Modification of Diet in Renal Disease
mg	Milligram
min	Minute
ml	Milliliter
ML	Maximum likelihood
mmHg	Millimeters of mercury
MMRM	Mixed Model Repeated Measures

Abbreviation	Term
mPP	Modified Per Protocol
N	Total Sample Size
NDD-CKD	Non-Dialysis Dependent Chronic Kidney Disease
ng	Nanogram
PP	Per Protocol
PT	Preferred term
Q1	First quartile
Q3	Third quartile
RBC	Red Blood Cell
REML	Residual Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Standard Data Tabulation Model
SOC	System organ class
TEAE	Treatment emergent adverse event
TIBC	Total iron binding capacity
TID	3 times daily
TLF	Tables, listings and figures
TSAT	Transferrin saturation
UIBC	Unsaturated iron-binding capacity
ULN	Upper Limit of Normal
WBC	White Blood Cell Count
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment
yr	Years

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the specifics of the statistical analyses to be performed for the planned 24-Week and final analyses for this study based on Protocol KRX-0502-402. The data displays to be included in the Clinical Study Report (CSR) for Protocol KRX-0502-402 are described in the document, KRX-502-402 Phase IV TLFs Shells.

Protocol Revision Chronology:		
Protocol	DD-MMM-YYYY	Description
Version 0.1	03-APR-2017	Original
Amendment 1	13-Dec-2017	Changes to eligibility criteria and screening processes that will facilitate subject enrollment. Incorporate the correct FACIT Fatigue Scale.

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding an analysis, as defined in this SAP document, will be made prior to Database Freeze/Lock of the study data. Further information can be found in the protocol.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study 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 (NDD-CKD)

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoints

The secondary endpoints of this study are as follows:

1. Change in Hgb from Baseline at Week 48
2. Time from randomization to first increase from Baseline Hgb of at least 0.5 g/dL
3. Change in transferrin saturation (TSAT) from Baseline at Weeks 24 and 48
4. Change in ferritin from Baseline at Weeks 24 and 48
5. Change in serum phosphate from Baseline at Weeks 24 and 48
6. Change in estimated glomerular filtration rate (eGFR) from Baseline at Weeks 24 and 48
7. Change in bicarbonate from baseline at Weeks 24 and 48
8. Change in intact parathyroid (iPTH) from baseline at Weeks 24 and 48
9. Change in C-terminal fibroblast growth factor 23 (FGF 23) from baseline at Weeks 24 and 48
10. Change in intact fibroblast growth factor from baseline at Weeks 24 and 48
11. Change in score for Work Productivity and Activity Impairment (WPAI) questionnaire adapted for anemia associated with chronic kidney disease from Baseline at Weeks 24 and 48 (A copy of the questionnaire is in Section 11.1.)
12. Change in score on the FACIT Fatigue Scale (Version 4) from Baseline at Weeks 24 and 48 (A copy of the questionnaire is in Section 11.3.)
13. Number of hospitalizations and duration (days)

3.2.3. Safety Endpoints

Safety evaluations are based on the following:

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

4. STUDY DESIGN

4.1. Summary of 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. 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

A scheduled study drug dose adjustment will occur at Week 12 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 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 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

Unscheduled dose adjustments can be made at any time during the study for adverse events (AEs) or abnormal laboratories. The unscheduled dose adjustments may involve a sequence of dose decreases, interruptions, no changes and/or increases based on various laboratory test results. (See the Test product, dose and mode of administration section of the Synopsis in this SAP and Section 7.5.2 of the protocol for details.)

4.2. Definition of Study Drugs

The term "study drug" refers to KRX-0502 (ferric citrate).

4.3. Sample Size Considerations

4.3.1. Sample Size Justifications

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 subgroups 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 standard deviation

(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 (Keryx Study KRX-0502-306).

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 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 (i.e., 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 (i.e., 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 subgroups of interest are deemed sufficient for the analyses proposed below including the longitudinal analyses.

4.3.2. Sample Size Re-estimation

Not Applicable.

4.4. Randomization

In this open-label study, eligible subjects will be randomized 1:1 to one of the two KRX-0502 starting dose 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

4.5. Clinical Assessments

The complete schedule of assessments for this study is presented in Table 2 of the protocol.

Data from the central laboratory will be used for efficacy and safety analyses including analyses for supportive and exploratory endpoints. The following laboratory evaluations will be performed at the central laboratory:

- 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, calcium adjusted for albumin, chloride, carbon dioxide/bicarbonate, glucose, blood urea nitrogen [BUN], creatinine, estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) Study equation, 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, transferrin, unsaturated iron-binding capacity [UIBC], total iron-binding capacity [TIBC] and serum iron) will be performed at Visit 1A (Screening) and Visit 1B (Re-screening), if applicable, 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.

The laboratory parameters used in the assessment of efficacy are:

- Hgb,
- TSAT,
- Ferritin and
- Serum phosphate

The schedule for the additional efficacy assessments is as follows:

- Work Productivity and Activity Impairment (WPAI) Questionnaire and FACIT Fatigue Scale Questionnaire will be administered at Visit 2 (Randomization); Visit 9 (Week 24); Visit 12 (Week 48); and the ET visit.
- Number of hospitalizations and duration (days) will be assessed at each visit.

In addition to the laboratory assessments listed above, the safety assessments schedule includes the following:

- AEs will be collected starting at the time of informed consent.
- 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.

- 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.
- Spot urine protein-to-creatinine ratio will be measured at Visit 2 (Randomization).
- Serum pregnancy test for all women of childbearing potential will be performed at Visit 1A (Screening) and, if applicable, Visit 1B (Re-screening).

Further, serum samples that will be frozen for future analysis of biomarkers of CKD will be obtained at Visit 2 (Randomization), Visit 9 (Week 24), Visit 12 (Week 48), and the ET visit from only those subjects who provided informed consent specifically for their collection.

5. PLANNED ANALYSES

The following analyses are planned for this trial:

- A 24-Week Analysis (to be performed after all Screening and Dose Titration Period data are available for all subjects)
- The Final Analysis (to be performed after Database lock, based on data from the entire study).

There will be two analyses; a 24-Week analysis after all subjects complete the 24-Week Dose Titration Period or have been withdrawn from the study and a Final analysis after all subjects either complete or have been withdrawn from the 48-Week study. Both analyses will be done at the end of the study.

Additionally, a "snapshot" of the data for the 24-Week analysis will be presented for publication. This publication will be based on clean data through Week 24 for key safety and efficacy measurements. This will be referred to as the "24-Week analysis snapshot".

5.1. 24-Week Analysis

The 24-Week analysis will be based on the data for all visits up to and including the Week 24 visit, (i.e. it will cover the Dose Titration Period). Data for screen failure subjects will not be cleaned for this analysis.

Data for this analysis are the data for those subjects who completed the Week 24 visit or had Early Termination from the study prior to Week 24. This will be done at the end of the study.

The 24-Week analysis snapshot will be used for a publication. The subset of data will be cleaned and summarized in an abstract after all subjects have completed the 24-Week Dose Titration Period or have been withdrawn from the study. The following variables will be summarized:

- Efficacy analyses for hemoglobin, transferrin saturation, ferritin, serum phosphorus, and estimated glomerular filtration rate (eGFR) will be analyzed using a MMRM model. Additionally, hemoglobin, intact parathyroid hormone (iPTH), C-Terminal fibroblast growth factor 23, and intact fibroblast growth factor 23 will be analyzed using an ANCOVA model. Analyses will use the modified PP Analysis Set.
- Summary statistics for safety analyses, including demographic, baseline characteristics, adverse events, and hematology, chemistry and miscellaneous laboratory tests will be performed. Analyses will use the Safety Analysis Set and modified PP Analysis Set (demographics and baseline characteristics only).

5.2. Final Analysis

The final analysis will be based on the full set of cleaned data for all visits up to and including the Week 48 visit (i.e. it will cover the Dose Titration Period and the Dose Maintenance Period).

Data for this analysis are the data for those subjects who completed the Week 48 visit or had Early Termination from the study prior to Week 48.

Some tables, listings and figures produced for the final analysis will display statistics for both the Dose Titration and the Dose Maintenance treatment periods.

5.3. Ad Hoc Analysis

There is no ad hoc analysis planned. If an ad hoc analysis is deemed necessary, the SAP will be updated accordingly.

5.4. Chronic Kidney Disease Biomarker Analysis

Analyses for the CKD biomarkers from the frozen samples are not covered in this SAP. The analyses and report will be specified in an addendum to the final analysis report.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

Data management will transfer the raw data that were recorded in the eCRF and those data sets from external vendors that contain data to be used in the analyses to Biostatistics for creating the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets. These derived datasets will be created using (SAS®) software. All data analyses will be conducted and summary tables generated using SAS version 9.4 or above.

6.1. Data Collection, Processing and Reporting

Keryx will provide the study sites with secure access to, and training on, the Electronic Data Capture (EDC) application sufficient to permit study site personnel to enter or correct information in the eCRFs on the subjects for which they are responsible. Creation and validation of the clinical database, entry and management of data, and transfer of central laboratory data will be maintained by the Contract Research Organization (CRO) and conducted in accordance with 21 CFR Part 11 [1] and the Guidance for Industry on Computerized Systems Used in Clinical Investigations [2].1. U.S. Department of Health and Human Services, Food and Drug Administration. 21 CFR Part 11.2. U.S. Department of Health and Human Services, Food and Drug Administration. Computerized Systems Used in Clinical Investigations, May 2007.

An eCRF will be completed for each enrolled study subject. Data processed at the central laboratory will be transferred electronically. 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.

Where corrections to an eCRF are needed after the eCRF has been submitted to EDC, the Investigator or appropriate staff member will have to respond with the correct answer. The audit trail entry will show the user's identification information and the date and time of any correction. Details of the data correction (query) process will be specified in the Data Management Plan.

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. CRFs will be completed for all subjects enrolled to study.

6.2. Data Presentation Conventions

Unless otherwise stated, all analyses will be performed using SAS® Version 9.4 or higher.

The following formats apply to all tables, figures and listings:

1. p-values will be presented with 3 decimals; p-values that are less than 0.001 will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. All date information in listings will be presented using 9 character alphanumeric formats (e.g., 01JAN2008).
2. Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum. Given that the 25th and 75th percentiles are the 1st and 3rd quartiles, respectively, they will be labelled as Q1 and Q3, respectively.
3. Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation and coefficient of variation will be displayed to two extra decimal places compared to the raw data.
4. Frequencies and percentages will be used to summarize categorical (discrete) data. If there are missing values, the number missing will be presented.
5. Percentages will be based on the non-missing values. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts.
6. Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level.
7. For binomial variables, the confidence intervals will be constructed using the normal approximation without continuity correction due to the relatively large sample size.
8. Wherever possible, data will be decimal aligned.
9. Some laboratory values may be reported as <x, <=x, >x, or >=x due to the limits of detection for a specific assay, where x is the lower or upper limit of detection. For analysis purposes, these values will be treated as x, and for the listings they will be transcribed as from the raw data. (e.g., <x, <=x, >x, or >=x).
10. The listings that display Study Day will have its numeric value, with 'Day' appended as a prefix and a suffix (if applicable) that is:
    - F, if Study Day is the subject's first study medication dose date,

- L, if Study Day is the subject's last study medication dose date and
- P, if Study Day is after the subject's last study medication dose date.

The derivation of study day is outlined in section 6.5.2.

11. In the listings, any subject who is a 'protocol permitted ESA rescue therapy user' will be identified with an asterisk.

6.3. Analysis Sets

Keryx's agreement and authorization of subjects included/excluded from each analysis set will be obtained prior to the 24-Week Analysis snapshot and the Final Analysis database lock.

6.3.1. Screened Subjects

A screened subject is a person who signs an informed consent form, attends a Screening visit and is assigned a screening ID in IWRS.

6.3.2. Screen Failures

Subjects who do not meet all the inclusion and exclusion criteria will be considered screen failures. 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. A subject can be rescreened only once and informed consent must be obtained no more than 7 days before the rescreening. Re-screening will include re-evaluation of all inclusion and 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).

6.3.3. Safety Analysis Set

All subjects who take at least 1 dose of study medication will be included in the Safety Analysis Set. The Safety Analysis Set will be used in the assessment and reporting of safety data.

The only study medication to be used is KRX-502. Therefore, treatment groups for the safety analyses will be based on the starting dose of KRX-502 to which subjects were randomized, irrespective of the dose used during the study.

6.3.4. 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 and have the corresponding baseline data will be included in the Full Analysis Set (FAS).

6.3.5. Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will include all subjects in the FAS who have no major protocol deviations that affect the validity of the efficacy measurements (see section 7.2) and have not received additional treatment that affect the validity of the efficacy measurements.

The following criteria exclude a subject from the PP Analysis Set:

- Receive red blood cell transfusions within 4 weeks prior to screening or at any time during the study.
- Receive ESAs (permitted or non-permitted) within 4 weeks prior to screening or at any time during the study.
- Receive IV Iron within 4 weeks prior to screening or at any time during the study.
- Pregnancy during screening or at any time during the study.
- Overall drug compliance < 50% i.e., from randomization to the Week 48 Visit date or to Early Termination date (whichever is earlier). (See section 7.4.1 Compliance Calculation)
- Major violations of eligibility criteria as determined by review prior to database lock.

The PP analysis set will be used for the 24-Week and Final analyses.

6.3.6. Modified Per Protocol Analysis Set

The modified Per Protocol (mPP) Analysis Set will include all subjects in the FAS who have no important, i.e., major protocol deviations that affect the validity of the efficacy measurements (see section 7.2).

The following criteria exclude a subject from the mPP Analysis Set:

- Receive red blood cell transfusions within 4 weeks prior to screening or at any time during the study.
- Receive ESAs (permitted or non-permitted) within 4 weeks prior to screening or at any time during the study.
- Receive IV Iron within 4 weeks prior to screening or at any time during the study.
- Pregnancy during screening or at any time during the study.
- Major violations of eligibility criteria as determined by review prior to the snapshot.

The mPP analysis set will be used for the 24-Week analysis snapshot only. The only difference between the PP and mPP is the mPP analysis set is not considering compliance as a criterion for exclusion.

6.4. Baseline Definition

The baseline value for each variable, except age, for the 24-Week analysis and the final analysis is the last non-missing value observed prior to administration of the first dose of study medication, irrespective of whether it was a scheduled visit, or unscheduled visit or retest observation.

Unless otherwise indicated, measurements taken on the same day as the first dose are considered to have been taken prior to the first dose.

Each subject's first dose of study medication is prescribed to be consumed on the next day after the Date of Randomization. Because the actual date that the subject takes the first dose may differ from what was prescribed the actual start date will be recorded in the eCRF.

First Dose Date = Study Medication Actual Start Date recorded in the eCRF.

6.5. Derived and Transformed Data

6.5.1. Baseline Age

Baseline Age (years) will be calculated as

the integer part of [(date of informed consent – date of birth + 1) / 365.25].

CKD Initial Diagnosis Age (years) will be calculated as

the integer part of [(CKD initial diagnosis date – date of birth + 1) / 365.25],

where the CKD initial diagnosis date is imputed using the rule in section 6.6.4, if it contains any missing parts.

6.5.2. Study Day

If the date of interest occurs on or after randomization date and on or before treatment end date, then study day will be calculated as

(date of interest – date of randomization) + 1.

If the date of interest occurs prior to randomization date, then study day will be calculated as

(date of interest – date of randomization).

If the date of interest occurs after treatment end date, then study day will be calculated as

(date of interest – treatment end date) + 1.

In this study, there is no Study Day 0 and Study Day 1 is the subject's Randomization Day.

6.5.3. Change from Baseline

Change from baseline is calculated as

(post-baseline result – baseline result).

If either the baseline or the post-baseline result is missing, the change from baseline and percentage change from baseline are both set to missing.

6.5.4. Visit Windows

Except for the Randomization Visit, which is designated as Study Day 1, all originally planned visits given in the protocol schedule of assessments from the Screening visit (Visit 1A) through the End of Study visit (Visit 12: Week 48) have a specified visit window. The table below gives the window for each of these visits.

During the first screening episode, subjects may be re-tested for specific inclusion and exclusion criteria that were not met at the initial testing. The re-test must take place within 10 days of the original screening date. Subjects who do not meet all the eligibility criteria within 21 days of the screening visit are considered screen failures.

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. Subjects who are to be re-screened must give informed consent again no more than 7 days prior to rescreening.

Table 2: Visit Windows (Study Days)

Visit Number: Visit Name	Analysis Visit Name	Relative Target Day (Study Day)	Visit Window (Study Day Interval)
Visit 1A: Screening [a]	Screening	-14	<1
Visit 1A: Retest[a]	Screening	-9[a]	<1
Visit 1B: Rescreen[b]	Screening	-14[b]	<1
Visit 1B: Retest[b]	Screening	-9[a]	<1
Visit 2: Randomization	Baseline	1	1
Visit 3: Week 2	Week 2	15	[2, 22]
Visit 4: Week 4	Week 4	29	[23, 43]
Visit 5: Week 8	Week 8	57	[44, 71]
Visit 6: Week 12	Week 12	85	[72, 99]

Visit Number: Visit Name	Analysis Visit Name	Relative Target Day (Study Day)	Visit Window (Study Day Interval)
Visit 7: Week 16	Week 16	113	[100, 127]
Visit 8: Week 20	Week 20	141	[128, 155]
Visit 9: Week 24	Week 24	169	[156, 197]
Visit 10: Week 32	Week 32	225	[198, 253]
Visit 11: Week 40	Week 40	281	[254, 309]
Visit 12: Week 48	Week 48	337	>309
Visit Early Termination: Early Termination (ET) [c]	Early Termination		

[a] Any retest for specific inclusion and exclusion criteria that were not met at the initial testing may occur within 10 days of the original screening date. Therefore, the visit window, including start and end dates, for the retest is the same visit window as that for the original screening visit. A subject can have only 1 retest based on the original screening results.

[b] Visit window for the rescreen visit has a study day interval relative to Day 1, equivalent to that for the original screening visit but because rescreening of a subject must be at least 14 days after the subject's original screen failure date the actual start and end dates on a subject's Screening Visit window and the Re-Screening Visit window differ. A subject can have only 1 retest based on the re-screening results. Any retest for specific inclusion and exclusion criteria that were not met at re-screening may occur within 10 days of the re-screening date.

[c] Early Termination visits may fall within a visit window corresponding to a planned study visit. If this is the case, the ET visit will be labeled and summarized with the analysis visit name corresponding to the visit window.

Multiple assessments may occur within the same window for a variety of reasons, for example, assessments to determine if the study drug dose should be adjusted. While there is only one planned scheduled dose adjustment, unscheduled dose adjustments for a subject may be necessary at any time during the study.

The protocol includes guidance on making dosing adjustments which are dependent on specific central laboratory results. Laboratory values will be checked at each scheduled visit 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.

Given the time lag in obtaining lab results and communicating the desired dose adjustment to the subject via telephone the time that the new prescription is to start and the subsequent follow-up blood draws for testing may or may not be in a single window for an originally planned visit given in the protocol's schedule of assessments. There may be multiple assessments falling in the same window and multiple assessments related to a single event may be taken during the window for more than one scheduled visit.

Additionally, when a subject discontinues from the study, the assessments made at the Early Termination visit may fall within a window for one of the originally planned visits given in the protocol's schedule of assessments.

When multiple assessments occur within the same window, the one whose date of assessment is the largest study day in the window will be considered as the observed assessment value for that scheduled visit study day.

6.6. Handling of Missing Data

6.6.1. Missing Efficacy Endpoints

Subjects who discontinue will not be replaced. If efficacy endpoint data are missing, they will not be imputed.

Mixed models will be used to analyze the repeated measures data for visits up to and including Week 24 and Week 48. The Mixed Model Repeated Measures (MMRM) models described in section 8.2 implicitly adjust for missing data under the assumption of missing at random.

6.6.2. Missing Start and Stop Dates for Prior and Concomitant Medications and Medical Conditions

Prior and concomitant medication missing start and stop dates will be imputed in accordance with the rules specified in section 7.5. Imputed dates will only be used to determine whether a medication is concomitant or not.

The rules for imputing medical history and medical conditions start and stop dates to identify those present at entry are equivalent to the rules given in section 7.5 for prior and concomitant medications, respectively.

6.6.3. Missing Start and Stop Dates for Adverse Events

Missing stop dates for adverse events will not be imputed. Missing start dates for adverse events will be imputed in accordance with the rules specified in section 9.2.2. Imputed dates will only be used to determine whether an adverse event is treatment emergent or not.

6.6.4. Missing CKD Initial Diagnosis Date

If the year part of the CKD diagnosis date is missing, it will not be imputed and CKD Initial Diagnosis Age (years) will be missing. If the year part of the CKD diagnosis date is not missing and either the month or day is missing, then the missing part of the date will be imputed as follows for the analysis:

- If the month is missing, then the month will be imputed as January.

- If the day is missing, then the day will be imputed as 01.

The imputed CKD diagnosis date will be concatenated with subject number and other subject characteristics on some of the by subject listings.

7. STUDY POPULATION

7.1. Subject Disposition

Each subject who provided informed consent will be accounted for in this study.

A table displaying the number and percentage of randomized subjects in each analysis set by starting dose treatment group and the two treatment groups combined will be provided for the 24-Week Analysis and the Final Analysis. For the Final analysis, this table will also include these counts and percentages on subjects who enter the Dose Maintenance Period, as there may be subjects who do not return after the Dose Titration Period, i.e., after their Week 24 visit.

A summary of subject accountability by treatment period and treatment group will also be presented. The summary will include the number of subjects screened, number of screen failures, number of subjects randomized, number subjects that were randomized but did not receive a dose of study drug and the number of subjects and percentage of randomized subjects in the Safety, Full and Per Protocol/modified Per Protocol analysis sets.

The subject disposition table for the 24-Week Analysis will display statistics for the Dose Titration Period. The subject disposition table for the Final Analysis will display statistics for the 48-Week treatment period (i.e. both the Dose Titration and the Dose Maintenance treatment periods).

These tables will display by treatment group and overall the number and percentage of randomized subjects with each of the following two statuses at the end of the specific treatment period:

- Completed the treatment period;
- Discontinued from the study.

The number and percentage of those who discontinued the study during the treatment period will be displayed by reason for non-completion.

One of the following 15 reasons for non-completion should have been recorded in the eCRF for each subject who did not complete the study:

- Discontinuation from study drug
- Subject withdrawal of consent
- Lost to follow-up
- Study drug non-compliance
- Investigator judgment

- Prohibited Therapy
- Start of chronic dialysis or kidney transplantation
- Death
- Sponsor termination of study
- Protocol violation
- Adverse event
- Pregnancy
- Administrative reasons
- Two consecutive Hgb values of < 8.0 g/dL (< 8.5 g/dL per original protocol) and patient does not qualify for ESA Rescue Therapy
- Other

A by subject listing, showing the subject disposition information, including the analysis set flags for all screened subjects, sorted by subject number within treatment group will be produced. For the Final analysis only, if there are less than 3 subjects in the 'Permitted' ESA Rescue Therapy subgroup, a separate disposition listing for only those subjects will be provided instead of a table.

7.1.1. Discontinuation from Study for Use of Prohibited Therapies

A table displaying the number and percentage of subjects in the Safety analysis set who discontinued the study with use of each of the following prohibited therapies as the primary reason will be provided:

- IV iron
- Blood transfusion
- ESA with the exception of ESA Rescue Therapy under the conditions permitted by protocol.
- Oral iron therapy other than KRX-0502 as treatment for iron deficiency except for multivitamins containing iron
- Phosphate binder other than KRX-0502
- Commercial ferric citrate
- Aluminum-containing therapies
- Investigational drug other than the KRX-0502

The statistics in this table will be shown for each of the starting dose treatment groups and the two treatment groups combined.

7.1.2. Discontinuation from Study Drug

A table will display the number and percentage of subjects in the Safety Analysis set whose primary reason for discontinuation of treatment with the study drug was as follows:

- Adverse event
- Two consecutive Hgb below 8.0 g/dL (below 8.5 g/dL per original protocol) more than 3 days apart and subject does not qualify for ESA Rescue Therapy
- Pregnancy
- Withdrawal by subject
- Other

The statistics will be displayed by starting dose treatment group and the two treatment groups combined for the Dose Titration treatment period and the Dose Maintenance treatment period.

7.2. Protocol Deviations

Protocol deviations (PDs) will be collected on a PD log.

Protocol deviations will be reviewed by the Keryx Team, and their status confirmed by the time that all data are cleaned for the 24-Week analysis and the Final Analysis.

Section 6.3.5 lists PDs that affect the validity of the efficacy measurements and result in exclusion of subjects from the PP Analysis Set.

A listing of PDs for subjects who are excluded from the PP analysis set will be generated.

7.3. Demographic and Other Baseline Characteristics

Baseline demographic and other baseline characteristics for subjects in the PP analysis and Safety analysis sets will be summarized by starting dose group and these two treatment groups combined, as well as by dosing sequence group, using descriptive statistics and by subject listings of these data will be presented by starting dose group. In addition, comparable summary tables and by subject listings will be provided for the subgroup of FAS who received ESA rescue therapy under the conditions permitted by the protocol given that there will be efficacy analyses performed for this subgroup. For the Final analysis only, if the subgroup includes less than 3 subjects, by subject listings of the data for these subjects will be provided instead of tables.

Note, no comparisons of the baseline demographic and other baseline characteristics between treatment groups are carried out for this study.

The demographic characteristics include:

- Age (years)
- Age Category
- Sex
- Ethnicity
- Race
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI kg/m^2)

Age (years) is the Baseline Age derived using the expression in section 6.5.1.

Age Category is this calculated value, Age (years), categorized into the groups:

- < 65 years
- ≥ 65 years

Race is recorded in the eCRF by choosing all of the following classifications that apply:

- Asian
- Black/African-American
- White/Caucasian
- American Indian or Alaska Native
- Native Hawaiian or Other Pacific Islander
- Unknown
- Other

The subjects' choices will be summarized to show the number and percentage of subjects in the following categories for each of the starting dose groups and these two treatment groups combined:

- Asian Only
- Black/African-American Only

- White/Caucasian Only
- American Indian or Alaska Native Only
- Native Hawaiian or Other Pacific Islander Only
- More Than One Race
- Unknown
- Other

Only those categories with at least 1 subject will be displayed in the Baseline Demographic tables.

Subjects with more than 1 of the 5 categories, Asian, Black/African-American, White/Caucasian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander selected on the eCRF Demography page are to be counted in the "Multiple" category.

Calculate Baseline BMI using the expression below where the values for weight and height values are baseline values.

$$\text{BMI (kg/m}^2\text{)} = [\text{Weight (kg)}] / [\text{height (m)}]^2.$$

Since height and weight are recorded in inches and pounds, respectively, note that

$$\text{Weight (kg)} = \text{Weight (lb)}/2.2046$$

$$\text{Height (m)} = 0.0254*\text{height (in)}.$$

Round weight and height to one decimal place before calculating BMI and round BMI to one decimal place.

Descriptive statistics of the following CKD characteristics will be presented in a table separate from the other characteristics:

- Age (years) at CKD Diagnosis
- CKD Primary Cause
- Baseline CKD Stage

Age at CKD Diagnosis is the CKD initial diagnosis age derived using the expression in section 6.5.1.

Other baseline characteristics include:

- Work Productivity and Activity Impairment Scores (See section 11.2 for scoring instructions.)

- Percent work time missed due to anemia associated with CKD
- Percent impairment while working due to anemia associated with CKD
- Percent overall work impairment due to anemia associated with CKD
- Percent activity impairment due to anemia associated with CKD

- FACIT-Fatigue Subscale Score (See section 11.4 for scoring instructions.)
- Number of hospitalizations
- Duration of hospitalization stay (days)
- The baseline evaluation for the following parameters reported by the central laboratory:
  - Hemoglobin (Hgb)
  - Estimated glomerular filtration rate (eGFR)
  - eGFR category: <30, 30 - 44, and >=45 ml/min/1.73m^2
  - Transferrin saturation (TSAT)
  - Ferritin
  - Phosphorus, i.e., serum phosphate
  - Intact parathyroid hormone (iPTH)
  - Intact Fibroblast growth factor 23 (iFGF23
  - C-terminal Fibroblast growth factor 23 (cFGF23)
  - Spot urine protein-to-creatinine ratio

Descriptive statistics of the laboratory parameters will be displayed in conventional units.

7.4. Medical History and Medical Conditions Present at Entry

No table showing the number and percentage of subjects who had each medical history condition coded to MedDRA version 20.0 system order class (SOC) and preferred term (PT) or by subject data listings will be presented. The missing start and stop dates will be imputed as described in section 6.6.2 and included in the ADaM dataset.

7.5. Prior and Concomitant Medications and Non-Drug Therapies

All prescription and over-the-counter medications and non-drug therapies used by subjects at Visit 1A (Screening) and thereafter through the last study visit will be recorded in the eCRF.

WHO-DD version 01Jun2017 B2 format will be used to code the medications. Non-drug therapies will not be coded.
Prior medications and therapies are defined as any that were started and stopped prior to the date the subject used the first dose of the study drug. Concomitant medications and therapies are defined as any that were started or were ongoing on or after the study drug first dose date up to and including the last study visit date.

No by subject data listings or tables showing the prior or concomitant medications recorded in the eCRF will be presented.

Incomplete start and/or stop dates for the medications and therapies recorded in the eCRF will be imputed as follows:

- If either the start of medication or other therapy date is completely missing, or the month and/or year of the start date is missing, the start date will be set to the first dose date.
- If only the day is missing, the day will be set to the first day of the month except if the start month is the same as the first dose month. If the latter is true, the start day will be set to the first dose day.
- If stop date is completely missing, it will be assumed that use of the medication is ongoing, and it will be classified as a concomitant medication with a missing stop date.
- If stop date is partially missing, then impute as the latest possible date given date parts that are not missing. (I.e., if only day is missing then impute as last day of the given month and if month and day are missing then impute as Dec. 31st of the given year.

8. EFFICACY

8.1. General Considerations

Efficacy analyses will be based on the PP Analysis Set data for the 24-Week and Final analyses (mPP Analysis Set for 24-Week analysis snapshot). Additionally, efficacy of the study drug in the FAS subgroup of subject who received rescue therapy under the conditions specified in section 9.2.2 of protocol will be assessed.

Table 3 lists the efficacy endpoints of special focus for the 24-Week Analysis snapshot and the 24-Week and Final Analyses showing the analysis method and analysis set to be used in assessing them. See section 8.2 for any special conditions to be explored for implementation of the analysis method or alternatives that will necessitate implementation of an alternative method.

Table 3: Analysis Method and Analysis Set for Special Focus Efficacy Endpoints

Efficacy Parameter	24-Week Analysis (Study Period: Dose Titration Period)	Final Analysis (Study Period: Entire Study)	Analysis Method	Analysis Set
Hgb	Change from Baseline to Week 24*	Change from Baseline to Week 48	MMRM	PP[1]
Hgb	Change from Baseline at Week 24	Change from Baseline at Week 48	ANCOVA	PP[1] Completers
Hgb	Time from Randomization to First Increase from Baseline Hgb >= 0.5 g/dL	Not Applicable	Kaplan-Meier	PP[1]
TSAT, ferritin, phosphate, bicarbonate, eGFR	Change from Baseline to Week 24	Change from Baseline to Week 48	MMRM	PP[1]
PTH, c-terminal and intact FGF-23	Change from Baseline to Week 24	Change from Baseline to Week 48	ANCOVA	PP[1]
FACIT score	Change from baseline at Week 24	Change from Baseline to Week 48	Descriptive	PP[1]
WPAI	Change from Baseline to Week 24	Change from Baseline to Week 48	Descriptive	PP[1]
Hospitalizations	Number and Duration (days)	Number and Duration (days)	Descriptive	PP[1]

Hgb, TSAT, ferritin, phosphate	Change from Baseline to Week 24	Change from Baseline to Week 48 Change from Baseline to Week 24	MMRM	FAS subjects who received permitted ESA Rescue Therapy
Hgb, TSAT, ferritin, phosphate		Change from Baseline to Week 48 Change from Baseline to Week 24	MMRM	PP Dosing sequence groups

* Hgb change from baseline to Week 24 is the primary endpoint.

[1] The analysis set used will either be the modified PP Analysis Set (24-Week Analysis snapshot) or PP Analysis Set (24-Week and Final Analysis).

8.2. Primary Efficacy Analysis

The primary efficacy endpoint is change from Baseline Hgb value at Week 24. A two-sided 95% confidence interval will be constructed for the mean change from Baseline in Hgb at Week 24 for each of the starting dose treatment groups, for subjects in the PP/mPP analysis set.

Results obtained using the Mixed Model Repeated Measures (MMRM) model will be used to construct the confidence intervals. The SAS procedure PROC MIXED with method specified as residual maximum likelihood (REML) will be used to fit the model and obtain the least squares mean, the associated standard error and two-sided 95% confidence interval for each treatment.

Under an assumption that the missing observations are missing at random, change from baseline Hgb at Week 24 will be analyzed by using a MMRM model with an intercept term, baseline Hgb as a covariate, starting dose treatment group effect, visit, visit by starting dose treatment group interaction, baseline Hgb by visit interaction and a random error term.

For the MMRM model, the Kenward-Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. This will be achieved by specifying the DDFM = KR option in the MODEL statement within PROC MIXED. An unstructured variance-covariance matrix will be used to model the within-subject covariance. If the unstructured covariance configuration results in a lack of convergence, then the following variance-covariance matrix will be used, in the order listed below, stopping with the first that converges:

- Heterogeneous Toeplitz
- Heterogeneous first-order autoregressive
- Heterogeneous compound symmetry

- Toeplitz
- First Order Autoregressive
- Compound symmetry

If all variance-covariance matrices selected fail to converge, variance components will be used as the next attempt at convergence.

To check the model assumption regarding normality for residuals and to detect potential outliers a normal probability plot of residuals and a plot of the residuals versus the fitted values will be used. If necessary, transformations and/or dropping of outliers to obtain data that meet the model assumptions will be implemented.

A table displaying, by visit and starting dose, the descriptive statistics for Hgb and the change from Baseline Hgb, the least squares mean (LSM) change from Baseline Hgb obtained using the MMRM described above and the corresponding 95% confidence interval of the mean change from baseline Hgb for each starting dose treatment group and these two groups combined will be presented for the 24-Week Analysis.

8.3. Secondary Efficacy Analyses

For the Final Analysis, the secondary efficacy endpoint, change from Baseline Hgb at Week 48 will be assessed in the same manner, using data for all visits up to and including the Week 48 visit, as described in section 8.2 for the Week 24 visit.

The 95% CI for the mean change from baseline will be obtained for each of the following secondary efficacy endpoints by using an MMRM:

1. Change in transferrin saturation (TSAT) from Baseline at Weeks 24 and 48
2. Change in ferritin from Baseline at Weeks 24 and 48
3. Change in serum phosphate from Baseline at Weeks 24 and 48
4. Change in eGFR from Baseline to Weeks 24 and 48
5. Change in bicarbonate from Baseline to Weeks 24 and 48

The same type statistics as described in Section 8.2 for Hgb will also be provided for the endpoints listed above where the change from Baseline to Week 24 results and the change from Baseline to Week 48 results will be presented in tables for the 24-Week analysis and the Final analysis, respectively.

Ninety-five percent CIs will be constructed for mean change from Baseline Hgb at Week 24 and mean change from Baseline Hgb at Week 48 based on the data for the PP analysis subjects who complete their Week 24 visit and data for the PP analysis subjects who complete their Week 48

visit, respectively, by starting dose treatment group and these two groups combined. The parametric analysis of covariance (ANCOVA) model for change from baseline in Hgb at Week 24 and at Week 48 with an intercept term, baseline Hgb as a covariate, starting dose treatment group effect, and a random error will be used to obtain the least squares mean (LSM), the associated standard error and associated 95% confidence intervals. To check the model assumption regarding normality for residuals and to detect potential outliers a normal probability plot of residuals and a plot of the residuals versus the fitted values will be used. If necessary, transformations and/or dropping of outliers to obtain data that meet these assumptions will be implemented.

Intact parathyroid hormone (iPTH), C-terminal fibroblast growth factor 23 and intact fibroblast growth factor 23 are only measured at Randomization Day, Week 24 and Week 48. Therefore, the type of ANCOVA model as described above for change for Baseline Hgb in the PP/mPP analysis subjects who complete the Week 24 visit and those who complete the Week 48 visit will be used to obtain the 95% confidence intervals for the means of the following:

1. Change in intact parathyroid hormone (iPTH) from Baseline to Weeks 24 and 48
2. Change in C-terminal fibroblast growth factor 23 from Baseline to Weeks 24 and 48
3. Change in intact fibroblast growth factor 23 from Baseline to Weeks 24 and 48.

Box plots over time of the observed value and the change from Baseline for each of the efficacy parameters, Hgb, TSAT, ferritin and serum phosphate will be provided. The box plots will be constructed based on observations made during the window of time designated for each visit given in section 6.5.4. If there are visits that are out of window, a scatter plot of the in-window and out of window observations will be used along with the box plots to explore the question of the stability of Hgb, TSAT, ferritin and serum phosphate during treatment with the study medication.

The Kaplan-Meier estimator of the survival function of time from randomization to first increase from Baseline Hgb of at least 0.5 g/dL for each of the two starting dose treatment groups will be obtained. The Kaplan-Meier plot of the functions for the two starting doses will be presented on a single figure.

A table will be presented that shows for the PP/mPP analysis set by treatment group the following for the event, time from randomization to first increase from Baseline Hgb of at least 0.5 g/dL, during the Dose Titration Period:

- Estimated median time in days;
- Number and percentage of subjects who had at least one event;

- Number and percentage of subjects with time to the event censored (Censoring occurs if a subject does not have the event prior to either completing the Week 24 visit or discontinuing from the study prior to the Week 24 visit.).

Tables displaying descriptive statistics will be provided for the Week 24 analysis and the Final analysis for the following secondary efficacy endpoints:

- Change in FACIT Fatigue Scale from Baseline at Weeks 24 and 48;
- Change in WPAI questionnaire specific health problem score from Baseline at Weeks 24 and 48

where the change from Baseline at Week 24 results and the change from Baseline at Week 48 results will be presented in tables for the 24-Week analysis and the Final analysis, respectively.

Descriptive statistics will also be provided for the number of hospitalizations and duration of hospital stay in days during the Dose Titration Period and the entire study for the 24-Week Analysis and Final Analysis, respectively.

8.4. Subgroup Analyses

For the 24-Week analysis, the change from baseline at Week 24 in Hgb, TSAT, ferritin, and phosphorus will be assessed for subjects who received 'Permitted' ESA therapy during the Dose Titration Period. For the Final analysis, the change from baseline at Week 24 and at Week 48 in Hgb, TSAT, ferritin, and phosphorus will be assessed for subjects who received 'Permitted' ESA therapy during the study.

Data in the Full Analysis Set for this subgroup of subjects will be used for the analyses. If at least 30 subjects are in the subgroup descriptive statistics and the two-sided 95% confidence intervals for the mean change from Baseline will be obtained as described in section 8.2 for the change from Baseline Hgb. If this subgroup includes at least 3 subjects but less than 30 subjects, only descriptive statistics will be presented for each of the starting dose treatment groups. For the Final analysis only, if less than 3 subjects are in the subgroup by subject listings of disposition, demographics, and laboratory tests (hematology, chemistry, urine chemistry, and miscellaneous) will be provided instead of summary tables.

It is expected that after the planned dose titration at Week 12 there will be about 35 subjects in each of the 4 dosing sequence groups,

(Starting Dose Group Daily Dose (pills/day) – Week 12 Titrated Daily Dose (pills/day), i.e.:

- 3 pills/day – 3 pills/day,
- 3 pills/day – 6 pills/day,

- 4 pills/day – 4 pills/day and
- 4 pills/day – 6 pills/day.

For the Final analysis, additional subgroup analyses will be conducted for change from baseline in Hgb, TSAT, ferritin, and phosphorus in these dosing sequence groups. The 95% confidence interval for the mean change from baseline for each dosing sequence will be obtained by using dosing sequence rather than starting dose treatment group in the MMRM model described in section 8.2. Each subject's dosing sequence group will be based on the actual dose prescribed at baseline and the Week 12 dose titration assignment. If the subgroups include at least 3 subjects but less than 30 subjects, the MMRM analysis will not be performed and only descriptive statistics will be presented. For the Final analysis only, if there are less than 3 subjects in any subgroup, only by subject listings will be provided instead of tables.

9. SAFETY AND TOLERABILITY

Safety and tolerability evaluation will be included in the 24-Week Analysis and the Final Analysis.

The safety data includes adverse events, vital signs and clinical laboratory measurements.

Adverse events that begin after the first administration of study medication or pre-existing conditions that worsen after the first dose of study medication are considered TEAEs. If, based upon the data recorded in the eCRF and/or the procedure for imputing the start date given in section 9.2.2, it is not possible to classify an AE as treatment emergent or not, then classify the AE as a TEAE.

For the 24-Week Analysis, since any table, listing or figure produced will only include statistics based upon the Screening period and Dose Titration treatment period:

- No adverse event that starts or worsens after the Week 24 visit date will be included in summaries of TEAEs and
- In calculating the subject months of study drug exposure only those days of treatment prior to the Week 24 visit will be counted since subjects are to delay taking their study drug on the day of planned site visits until after the site visit.

For the Final Analysis, all observations up to and including those for the Week 48 visit date will be included in identifying TEAEs and calculating subject months of study drug exposure.

9.1. Overall Summary of Tolerability

An overall summary of tolerability table by treatment group and the two treatment groups combined for all subjects in the Safety Analysis Set will be produced.

The following statistics for the set of treated subjects will be displayed in this table:

- Subject months of study drug exposure descriptive statistics
- Number and percentage of subjects with treatment emergent adverse events (TEAEs)
- Number of TEAEs
- Number and percentage of subjects with serious adverse events (SAEs)
- Number and percentage of subjects with serious TEAEs
- Number and percentage of subjects requiring a dose alteration due to adverse events
- Number and percentage of subjects discontinuing the study due to adverse events
- Number and percentage of subjects who died

Another table displaying the same statistics by dosing sequence will be produced.

Subject months of drug exposure =

total number of days of treatment for each subject summed over all subjects divided by 30.4375

=

total duration of exposure in days for each subject summed over all subjects divided by 30.4375

See section 9.3 for the procedure used to calculate each subject's total duration of exposure (days) in this study.

To determine the number of adverse events, count all unique events reported at the preferred term level. Multiple events with the same preferred term are considered unique if the event onset dates are different.

9.2. Adverse Event Summary Tables

Adverse events will be mapped to system organ class (SOC) and preferred term (PT) using MedDRA version 20.0.

An adverse event subject data listing providing a complete disclosure of adverse events as recorded in the CRF will be produced for each of the starting dose treatment groups.

To determine the number of adverse events, count all unique events reported at the preferred term level. Multiple events with the same preferred term are considered unique, if the event onset dates are different.

9.2.1. Summaries of All Treatment Emergent Adverse Events

The summaries described below will be provided for the 24-Week Analysis and the Final Analysis.

1. The number and percentage of subjects with TEAEs will be summarized by MedDRA system organ class and preferred term within each starting dose treatment group and all treated subjects without regard to severity (intensity) or relationship to study drug. The SOCs will appear in descending order of number of subjects in the two treatment groups, i.e., all treated subjects, with at least one TEAE mapped to the SOC. The PTs within each SOC will appear in descending order of number of subjects in the two treatment groups with at least one TEAE mapped to the PT within that SOC
2. A table summarizing TEAE by intensity will be produced. The table will display the number and percentage of subjects with TEAEs summarized by MedDRA system organ class, preferred term, intensity level within each starting dose treatment group and all

treated subjects. The SOCs and PTs will appear in the same order as in the table described in #1 above.

3. A table summarizing TEAE by relationship to study drug will be produced. This table will display the number and percentage of subjects with TEAEs summarized by MedDRA SOC, PT and relationship to study drug within each starting dose treatment group and all treated subjects. The SOCs and PTs will appear in the same order as in the table described in #1 above.
4. Tables as described in #1, #2 and #3 above where, instead of the summaries for the two starting dose treatment groups, summaries are presented for the four dosing sequence treatment groups, Starting Dose Group Daily Dose (pills/day) – Week 12 Titrated Daily Dose (pills/day), i.e., 3 pills/day – 3 pills/day, 3 pills/day – 6 pills/day, 4 pills/day – 4 pills/day and 4 pills/day – 6 pills/day.
5. Tables displaying the number and percentage of subjects reporting serious AEs and the number and percentage of subjects reporting AEs leading to treatment discontinuation for all treated subjects and for each randomized dose group by MedDRA system organ class and preferred term.

Severity (Intensity on the eCRF) is classified as mild, moderate or severe where these categories denote increasing intensity, respectively. TEAEs starting after the first dose of study drug with a missing intensity will be classified as severe. If a subject has more than one TEAE within the same SOC/ PT, the AE with the worst case intensity will be used in the corresponding intensity summaries.

The only relationships of AE to study drug used in this study are "unrelated" and "related". An AE's relationship to study drug is based on the Investigator's assessment. TEAEs with the relationship to study drug missing will be classified as "related" to study drug. If a subject has more than one AE within the same SOC and PT, the AE with the worst case relationship to study drug will be used in the corresponding relationship summaries.

9.2.2. Missing and Partial AE Start Dates

Completely missing or partially missing AE start (onset) dates will be imputed as follows:

- If onset date is completely missing, onset date is set to date of first dose.
- If (year is present and month and day are missing) or (year and day are present and month is missing):
    - If year = year of first dose, then set month and day to month and day of first dose
    - If year < year of first dose, then set month and day to December 31st

- If year > year of first dose, then set month and day to January 1st

- If month and year are present and day is missing:
  - If year=year of first dose and
    - if month = month of first dose then set day to day of first dose date
    - if month < month of first dose then set day to last day of month
    - if month > month of first dose then set day to 1st day of month
  - if year < year of first dose then set day to last day of month
  - if year > year of first dose then set day to 1st day of month
- For all other cases, set onset date to date of first dose

Note, adverse event listings will display start and end dates as collected, not imputed.

9.2.3. Summaries of Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

For the 24-Week Analysis and the Final Analysis the number and percentage of subjects with serious treatment emergent AEs reported will be summarized by MedDRA system organ class and preferred term within each starting dose group and all treated subjects without regard to intensity or relationship to study drug. The SOCs will appear in descending order of number of subjects in the two treatment groups combined, i.e., all treated subjects, with at least one SAE mapped to the SOC. The PTs within each SOC will appear in descending order of number of subjects in the two treatment groups combined with at least one SAE mapped to the PT within that SOC.

The same types of tables as described for SAEs will be produced for:

- TEAEs leading to treatment discontinuation and
- TEAEs leading to deaths

A by subject adverse events listing will be produced to support these three tables. The list for the 24-Week Analysis will show all AEs for subjects who had at least one SAE or had treatment discontinued due to a TEAE or had a TEAE that led to death during the Dose Titration Period by starting dose group and subject number with the subject's AEs listed in chronological order of AE start date. Similarly, the list for the Final Analysis will be produced to show the AEs for subjects who experienced the same types of AEs either in the Dose Titration or Dose Maintenance period.

A listing of all adverse events of each deceased subject will be produced.

9.3. Total Duration of Therapy, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

For the 24-Week Analysis, a table will be provided that shows the descriptive statistics for subject's total duration of exposure in days, average and maximum daily dose attained, final daily dose taken, and the number and percentage of subjects with overall compliance during the Dose Titration Period in the two categories, < 50% and >=50%, by starting dose treatment groups and for the four dose sequence treatment groups.

A by subject listing for exposure, dosing and compliance will be provided for support in determining members of the PP Analysis set for the Final analysis.

For the Final Analysis, a table will be provided corresponding to that described for the 24-Week Analysis except that along with the descriptive statistics for the Dose Titration Period those for the Dose Maintenance Period and the entire study will be included. The Final Analysis listing will include the data for all visits within the study and total duration of exposure at Week 48 and overall compliance for the entire study along with the other variables on the listing produced for the 24-Week Analysis.

9.3.1. Total Duration of Exposure Calculation

A subject's total duration of exposure in days is the total number of days that the subject was prescribed to be taking more than zero pills per day.

For this study, duration of exposure in days for a subject is defined as the subject's first dose date minus last dose date plus 1day minus the number of days that the subject was using a prescribed study drug interruption, i.e., using a dose of zero pills per day as prescribed.

For the Dose Titration Period a subject's:

duration of exposure (days) during the Dose Titration Period

=

([minimum of the subject's Week 24 visit date and date of last dose in the period] – first dose date + 1 day)

$$- \sum_{i=1}^{k} \left([actual\ stop\ date]_i - [actual\ start\ date]_i + 1\right)$$

where i denotes the i^{th} time during the Dose Titration Period that the subject was prescribed zero pills per day, the i^{th} actual start date and i^{th} actual stop date are the first and last dates that the subject was taking zero pills during the period for which the i^{th} prescription of zero pills per day was in effect.

For the Dose Maintenance Period a subject's:

duration of exposure (days) during the Dose Maintenance Period

=

(last dose date – Dose Maintenance Period first dose date + 1)

$- \sum_{i=1}^{k} ([actual\ stop\ date]_i - [actual\ start\ date]_i + 1)$

where i denotes the i^{th} time during the Dose Maintenance Period that the subject was prescribed zero pills per day, the i^{th} actual start date and i^{th} actual stop date are the first and last dates that the subject was taking zero pills during the period for which the i^{th} prescription of zero pills per day was in effect.

Total duration of exposure (days) for the entire study

=

Total duration of exposure (days) during the Dose Titration Period

+

Total duration of exposure (days) during the Dose Maintenance Period.

Note: Duration of exposure in months = duration of exposure in days divided by 30.4375.

9.3.2. Compliance Calculation

A subject's compliance to treatment during a specific time period expressed as a percentage is equal to 100 times the amount of study drug taken by the subject during the specific time period divided by the amount that was prescribed to be taken by the subject during the specific time period.

The number of pills recorded in the eCRF drug accountability pages as the number of pills dispensed and/or the number of pills returned at each site visit are based on a count of the physical pills in the bottle(s) dispensed and/or returned during the visit, respectively.

A subject's prescription may be changed at any time during the course of this study based on adverse events or certain laboratory test results observed or reported at any scheduled visit or any unscheduled visit. Additionally, it is planned that each subject will get the study drug dose titrated at the scheduled Week 12 visit. The prescribed amount to be taken starting after the scheduled Week 12 visit will depend on the Week 12 Hgb value.

The results of some laboratory tests will be required to make the decision regarding each study drug prescription during the study but these results will not be immediately available to the site on the visit day. Therefore, it may not be possible to confirm the number of pills actually in the bottle at the time that a new dose is prescribed to start. (Instructions with respect to a prescribed dose change may be delivered via telephone.)

The general expression for calculating a subject's compliance (%) over a specific time period X,

$$100 * \frac{amount\ of\ study\ drug\ taken\ during\ the\ specific\ time\ period, X}{amount\ of\ study\ drug\ prescribed\ to\ be\ taken\ during\ the\ specific\ time\ period, X}$$

using the drug accountability data recorded in the eCRF is expressed as

$$100 * \frac{(\#\ of\ pills\ dispensed\ at\ start\ of\ period\ X\ -\ \#\ of\ pills\ returned\ at\ end\ of\ the\ period\ X)}{(\#\ days\ in\ period\ X) * (\#\ pills\ prescribed\ to\ be\ taken\ per\ day\ during\ the\ period\ X)}$$

This expression for compliance will take one of three forms depending on the number of dose adjustments made between two successive site visits, i.e., zero, one or m greater than one dose adjustments.

To define compliance (%) for these three cases, the following notation and assumptions are made:

- Let the subscript $k \geq 2$ denote the site visit number where:

  k = 2 for the Randomization Visit, i.e., Visit 2 in the Schedule of Assessments (See protocol section 7 Table 2.);

  k = 3 for the subject's next site visit, scheduled or unscheduled, after Visit 2;

  k = 4 for the subject's next site visit, scheduled or unscheduled, after $Visit_{(k=3)}$;

  k = 5 for the subject's next site visit, scheduled or unscheduled, after $Visit_{(k=4)}$;

  ...

  k = j for the subject's next site visit, scheduled or unscheduled, after $Visit_{(k=j-1)}$.

- First dose on a new prescription issued on date of site visit is to be taken on the day after the site visit. E.g., a subject's 1st bottle of pills is dispensed on the Date of Visit 2 but the first pill is prescribed to be taken on the day after Visit 2.

- In general, because visits should be scheduled to occur in the morning, non-fasted and subjects are instructed to hold study drug until blood is drawn, assume that pills

consumed on the date of a site visit are at the dose level last prescribed before the site visit.

To calculate compliance between any two successive site visits one of the three cases described below are applicable.

Case 1:

Zero dose adjustments were prescribed to start during the period between last date study drug was dispensed which was Visit$_{(k-1)}$, and the date of the current visit, which is Visit $_{(k)}$.

Compliance (%) =

100 times (# pills dispensed at Visit$_{(k-1)}$ – # pills returned at Visit$_{(k)}$)

divided by

([# pills prescribed to be taken on the day of Visit$_{(k-1)}$] + {[date of Visit$_{(k)}$ – 1 day – date of Visit$_{(k-1)}$] times [# pills prescribed to be taken per day on 1 day after date of Visit$_{(k-1)}$ thru the day before Visit$_{(k)}$]}),

where if day of Visit$_{(k-1)}$ is day of Randomization,

then [# pills prescribed to be taken on the day of Visit$_{(k-1)}$] = 0

Case 2:

Only one dose adjustment was made during the period between last date study drug dispensed which was Visit$_{(k-1)}$ and the date of the current visit at which study drug was returned, which is Visit $_{(k)}$.

Compliance (%) =

100 times (# pills dispensed at Visit$_{(k-1)}$ – # pills returned at Visit$_{(k)}$)

divided by

([date new dose was prescribed to start – date of Visit$_{(k-1)}$] times [# pills prescribed to be taken per day starting on date of Visit $_{(k-1)}$ thru the day before the new dose was prescribed to start],

plus

[date of Visit$_{(k)}$ – date the new dose was prescribed to start] times [total # pills prescribed to be taken per day starting on date the new dose was prescribed to start thru the day before the Visit$_{(k)}$])

where if date of Visit$_{(k-1)}$ is date of Randomization,

then let date of Visit$_{(k-1)}$ = {1 + date of Visit$_{(k-1)}$}

Case 3:

A total of m >1 dose adjustments were made during the period between last date study drug was dispensed which was Visit $_{(k-1)}$, and the date of the current visit at which study drug was returned, which is Visit$_{(k)}$,

Compliance (%) =

100 times (# pills dispensed at Visit $_{(k-1)}$ – # pills returned at Visit $_{(k)}$)

divided by

([prescribed start date at dose level for dose adjustment #1 – date of Visit$_{(k-1)}$] times [# pills prescribed to be taken per day starting on date of Visit $_{(k-1)}$ thru the day dose adjustment #1 was prescribed to start]

plus

[the sum over i for i = 1 to (m -1) of {date new dose # (i+1) was prescribed to start – date new dose # i was prescribed to start] times [# pills prescribed to be taken per day starting on date that new dose # i was prescribed to start thru the day before the new dose # (i+1) was prescribed to start}]

plus

[date of day before Visit$_{(k)}$ – date new dose # m was prescribed to start] times [total # pills prescribed to be taken per day starting on date the new dose # m was prescribed to start thru the day before the Visit$_{(k)}$]),

where if date of Visit$_{(k-1)}$ is date of Randomization,

then let date of Visit$_{(k-1)}$ = {1 + date of Visit$_{(k-1)}$}

Special Case:

Missing Value for Number of Pills Returned and/or Number of Pills Dispensed

- For all three cases, Case 1, Case 2 and Case 3 described above:
  - If (# pills returned at Visit$_{(k)}$) is a missing value then Number of Pills Used Since Last Visit and Compliance Since Last Visit will be missing.
  - If (# pills dispensed at Visit$_{(k-1)}$) is a missing value,

    let (# pills dispensed at Visit$_{(k-1)}$) = # pills dispensed at Visit$_{(n)}$, where n is the largest site visit number less than k – 1 where (# pills dispensed at Visit$_{(n)}$) is a non-missing value and

calculate compliance (%) using Visit(k - 1)) = Visit(n), where n is the largest site visit number less than k – 1 where (# pills dispensed at Visit(n)) is a non-missing value.

Compliance Over Period Spanning More Than Two Consecutive Site Visits:

To calculate compliance for any period X that spans more than the period between two consecutive site visits note that the numerator in the expression,

Compliance (%) =

$$100 * \frac{amount\ of\ study\ drug\ taken\ during\ the\ specific\ time\ period, X}{amount\ of\ study\ drug\ prescribed\ to\ be\ taken\ during\ the\ specific\ time\ period, X}$$

is 100 times $\sum_{k=3}^{n}$ (# pills dispensed at Visit(k – 1) – # pills returned at Visit(k)), where n -1 is the number of site visits the subject had during the period X and the denominator is

$$\sum_{k=3}^{n} (\text{the number of pills } \textit{prescribed to be taken from } \text{Visit(k} - 1) \text{ thru the day before Visit(k))}$$

where (the number of pills *prescribed to be taken from* Visit(k – 1) thru the day before Visit(k)

is the denominator of the expression given above for Case 1, Case 2 or Case 3 depending on the number of dose adjustments between Visit(k – 1) and Visit(k) .

9.4. Routine Laboratory Data

Tables for three groups of laboratory parameters, hematology, clinical chemistry and urine chemistry will be provided. All laboratory tests will be listed. Laboratory test results for all subjects in the safety analysis set will be summarized using descriptive statistics. For the continuous laboratory parameters descriptive statistics will be displayed for the actual values and for the change in value from baseline to each scheduled post-baseline visit. Tables and listings for the 24-Week Analysis will only display statistics for visits during the Dose Titration period. Tables for the Final Analysis will show those visits during the Dose Maintenance period in addition to the Baseline visit but listings for the Final Analysis will be based on observations over the entire study.

Subject's laboratory results for the following laboratory parameters:

- Ferritin
- TSAT
- Hemoglobin
- Serum Phosphorous

are of special interest. Their values will be classified as low or where relevant one of its sub-categories, normal, or high or where relevant one of its sub-categories given the range of values used to identify clinically meaningful abnormalities in a patient with CKD.

The thresholds for potentially significant abnormalities are based upon Common Terminology Criteria for Adverse Events v4.0 (CTCAE) grades and/or clinically meaningful abnormalities in a CKD stage 3- 4 patient. The thresholds are listed in Table 4 below. Table 4 also includes these categories for impaired liver function, i.e., the categories of total bilirubin, ALT and AST as related to identification of potential Hy's Law cases.

Shift tables, for the laboratory parameters of special interest will be produced showing the number and percentage of subjects with Baseline result in each of the categories, low or where relevant the sub-categories of low, normal and high or where relevant the sub-categories of high, whose result at the post-baseline visit is in each of these categories. The shift tables will be provided by starting dose group and the two treatment groups combined. A by subject listing by visit of the subject's values with their classification relative to potentially significant abnormality for each laboratory parameter of special interest will be provided.

By subject listings for every laboratory parameter collected will be provided. Each value will be identified in the by subject listings as being low, normal or high based on the central laboratory reference ranges. For the Final analysis only, if less than 3 subjects received permitted ESA rescue therapy, comparable by subject listings will be provided for this FAS subgroup.

An additional by subject listing by starting dose will be provided of subjects who have a total serum bilirubin value > 2xULN. This listing will include the date of first elevated bilirubin; an indicator for ALT >3xULN and an indicator for AST >3xULN along with the baseline identifying characteristic variables that are displayed on all other by subject listings.

Table 4: Clinical Laboratory Potentially Clinically Significant Criteria

Parameter	Threshold (Low Criterion/ High Criterion)	Low Criterion (Subcategories)	High Criterion (Subcategories)
Iron Parameter (unit)			
Ferritin (ng/mL)	Clinical	NA	High 1: > 500 to 1000, High 2: > 1000
Transferrin saturation (%)	Clinical	NA	High 1: > =50 to <70 High 2: > =70
Hematology			
Hemoglobin (g/dL)	CTCAE grade 3 /Clinical	< 8.0	> 13
Chemistry			
Phosphorous (mg/dL)	CTCAE grade 2 /Clinical	Low 1: ≥2.0 to <2.5, Low 2: < 2.0	> 9.0
Liver Function			
Hy's Law (Impaired Liver Function)	CTCAE grade 2 /DILI*	NA	High 1: ALT or AST > 3 x ULN to 5 x ULN High 2: ALT or AST >5 x ULN
Total serum bilirubin value	DILI*	NA	> 2xULN

*DILI = Drug Induced Liver Injury

9.5. Vital Signs

No tables of descriptive statistics or by subject listings for the vital signs, i.e., seated systolic and diastolic blood pressures (mmHg), heart rate (bpm) and weight, values and change from baseline will be presented.

Each value's classification of low, normal or high based on the parameter's central laboratory reference range and the following clinical significance and CTCAE classifications will be included in an ADaM dataset:

- Diastolic Blood Pressure < 50 mmHg, Systolic Blood Pressure < 80 mmHg (based on clinical significance),
- Diastolic Blood Pressure ≥100 mmHg, Systolic Blood Pressure ≥160 mmHg (based on CTCAE grade 3)
- Pulse < 55 beats/min, Pulse >110 beats/min (based on clinical significance).

9.6. Summary of Changes from Protocol-Specified Analyses

- The protocol states that "All subjects who are randomized and take at least 1 dose of study medication will be included in the Safety Analysis Set." However, the Safety Analysis Set is being defined as the set of all subjects who receive at least one dose of study medication, to allow for the highly unlikely possibility that some subject (s) may receive a dose of medication prior to being randomized.
- The protocol did not discuss the potential for an ad hoc analysis. The analysis is acknowledged in this SAP and more details will be added to an amended SAP if an analysis is performed.
- The protocol did not discuss the modified Per Protocol Analysis Set. This analysis set is described in section 6.3.6 and is used for the 24-Week analysis snapshot only.
- The SAP describes analyses for the following secondary efficacy endpoints which were not included in the protocol:
    - Time from randomization to first hemoglobin increase of ≥ 0.5 g/dL from Baseline.
    - Change from the baseline value for each of the following:
        - eGFR
        - serum bicarbonate
        - intact parathyroid hormone
        - C-terminal fibroblast growth factor 23
        - intact fibroblast growth factor
    - Inclusion of box and scatter plots over time of the observed value and the change from Baseline for each of the iron parameter efficacy variables, TSAT and ferritin to explore the question of their stability over time on treatment.
- The protocol specified analyses of vital signs is not included in the SAP, since no related safety concerns are anticipated.

- The protocol states that all efficacy analyses will be performed based on both the FAS and the PP/mPP analysis sets, however only the PP/mPP analyses sets will be considered. Subjects are excluded from the PP/mPP analysis sets due to confounders of efficacy and thus the FAS is not appropriate for efficacy analyses. The FAS will be used for the efficacy analysis for the 'Permitted' ESA Rescue Therapy subgroup.
- The protocol did not include the baseline by visit interaction term in the efficacy model. This interaction term is included in the SAP and will be included in the model.
- Missing endpoint observations will not be imputed using a multiple imputation (MI) linear regression approach for use in an additional sensitivity analysis as specified in the protocol sections 15.7.2 and 15.10.3.
- The protocol discusses an Interim Analysis after all subjects have completed the 24-Week Visit or Early Termination Visit. This analysis will no longer be performed. Instead, a 24-Week analysis snapshot will be performed. A selective group of data (disposition, demographic, laboratory test, and adverse events) will be cleaned and presented in a publication. The 24-Week analysis and Final analysis will be done at the end of the study.

10. REFERENCES

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

Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Version 4), http://www.facit.org/FACITOrg/Questionnaires.

11. APPENDIX

11.1. Work Productivity and Activity Impairment (WPAI) 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 while you were working?

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

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

11.2. WPAI:SHP QuestionnaireV2.0

The instructions given by **REILLY ASSOCIATES Health Outcomes Research** at http://www.reillyassociates.net/WPAI_Scoring.html and inserted below will be used to score the WPAI:SHP questionnaires completed by each subject. Questions 1, 2, 3, 4,5, and 6 in those instructions correspond to the questions with the same number in the questionnaire given above that subjects will complete during this study.

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

1 = currently employed

2 = hours missed due to specified problem

3 = hours missed other reasons

4 = hours actually worked

5 = degree problem affected productivity while working

6 = degree problem affected regular activities

Scores:

Multiply scores by 100 to express in percentages.

Percent work time missed due to problem: Q2/(Q2+Q4)

Percent impairment while working due to problem: Q5/10

Percent overall work impairment due to problem:Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]

Percent activity impairment due to problem: Q6/10

11.3. Functional Assessment of Chronic Illness Therapy (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 past 7 days.**

		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 starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing 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

English (Universal)
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11.4. FACIT-Fatigue Subscale Scoring

The instructions for the FACIT-Fatigue Subscale Scoring Guidelines (Version 4) below were copied from the link to **FACIT-Fatigue:** Functional Assessment of Chronic Illness Therapy-Fatigue; a 13-item FACIT Fatigue Scale Scoring and Interpretation found at http://www.facit.org/FACITOrg/Questionnaires. These instructions for scoring will be used as described below and if less than 7 of the 13 FACIT Fatigue Subscale items are missing the Total Score will be missing.

Instructions:*

1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale,

then divide by the

number of items answered. This produces the subscale score.

4. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?	Item response	Item Score
	HI7	4 -	_____	=_____
FATIGUE	HI12	4 -	_____	=_____
	An1	4 -	_____	=_____
SUBSCALE	An2	4 -	_____	=_____
	An3	4 -	_____	=_____
Score range: 0-52	An4	4 -	_____	=_____
	An5	0 +	_____	=_____
	An7	0 +	_____	=_____
	An8	4 -	_____	=_____
	An12	4 -	_____	=_____
	An14	4 -	_____	=_____
	An15	4 -	_____	=_____
	An16	4 -	_____	=_____

Sum individual item scores: _____

Multiply by 13: _____

Divide by number of items answered: _____**=Fatigue Subscale score**

*See the instructions related to missing data in FACIT subscales within the FACIT Administration and Scoring Guidelines on the FACIT.org website.

11.4.1. **Handling Missing Items on FACIT Fatigue Subscale**

Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all FACIT scales and symptom indices, the higher the score the better the QOL.

If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done by using the formula below:

Prorated subscale score = [Sum of item scores] x [N of items in subscale] □□[N of items answered]

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (i.e, more than 7 of the 13 FACIT Fatigue Subscale items).

11.5. Tables, Listings and Figures

See the document, KRX-502-402 Phase IV TLFs Shells_v1.1_03APR2019 for a list of the tables, listings and figures that will be produced for this study. In addition to the shell for each table, listing and figure, this document will include a section which describes the conventions to which the TLFs discussed in this SAP will adhere.

pmeneses

AKEBIA

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