STATISTICAL ANALYSIS PLAN

Protocol:	Phase 2, randomized, open-label, active-controlled, pharmacokinetics / pharmacodynamics and dose optimization study of oral vadadustat for the treatment of anemia in hemodialysis subjects converting from epoetin alfa
Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0025
US IND Number:	102,465
Phase:	Phase 2
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Version:	Final 2.0
Release Date	July 02, 2020
NCT Number:	NCT03799627

Revision History

Version	Version Date	Author	Summary of Changes Made
Draft 0.1	09 July 2018	[redacted]	New Document
Draft 0.2	20 July 2018		Per sponsor's comments
Draft 0.3	11 August 2018		Per sponsor's comments
Draft 0.4	13 January 2019		Per sponsor's comments
Draft 0.5	27 February 2019		Per sponsor's comments
Draft 0.6	16 April 2019		Added new QoL assessment
Draft 0.7	19 July 2019		Per sponsor's comments
Final 1.0	24 July 2019		Added section 9.5 for any potential sensitivity analyses. Modified the definition of PK population per Rishi.
Final 2.0	02 July 2020		Updated based on Protocol amendment 2, no IA analyses for the study. Added sensitivity analyses by excluding some HB data due to the Eurofins Ransomware Attack

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Contents

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{inf}	area under concentration-time curve from dosing to infinity
AUC_{last}	area under concentration-time curve from dosing to last measurable concentration
BLQ	below the limit of quantification
BP	blood pressure
CBC	complete blood count
CKD	chronic kidney disease
CL/F	apparent total body clearance
C_{max}	maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	common terminology criteria for adverse events
CVD	cardiovascular disease
DD-CKD	dialysis dependent chronic kidney disease
ECG	electrocardiogram
EDC	electronic data capture
EOT	end-of-treatment
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FAS	Full Analysis Population
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Hb	hemoglobin
HF	heart failure
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl-hydroxylase
HIF-PHI	hypoxia-inducible factor prolyl-hydroxylase inhibitor
HR	heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web Response System
LFT	liver function test
LPO	last patient out

MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MCS	mental component score
NDD-CKD	non-dialysis dependent chronic kidney disease
PCS	physical component score
PD	pharmacodynamics(s)
PGI-C	patient global impression of change
PGI-S	patient global impression of severity
PHD	prolyl 4-hydroxylase domains
PI	Package Insert
PK	pharmacokinetic(s)
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SO2	oxygen saturation
TIW	three times a week
T_{max}	time to reach Cmax
TSAT	transferrin saturation
U	unit
ULN	upper limit of normal
US	United States
Vd/F	apparent volume of distribution
VEGF	vascular endothelial growth factor
λz	elimination rate constant

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical analysis methods that will be used to analyze, and report results for Akebia Protocol AKB-6548-CI-0025.

This document is prepared based on the final study protocol Amendment 2, version 3 (dated April 05, 2019). Reader can refer to the study protocol, the case report form (CRF), and general CRF completion guidelines for details of study design, conduct and data collection. Specifications of tables, figures, and data listings are contained in a separate document.

2 STUDY OBJECTIVE AND DESIGN

2.1 Study Objectives

2.1.1 Primary Objective

To assess the efficacy and safety of daily dosing of vadadustat compared to epoetin alfa for 12 weeks in hemodialysis subjects.

2.1.2 Secondary Objectives

- To assess the efficacy and safety of TIW dosing of vadadustat in selected hemodialysis subjects who have been successfully managed with daily dosing of vadadustat through Week 12.
- To evaluate the PK/PD of daily and TIW dosing of vadadustat in hemodialysis subjects compared to epoetin alfa.
- To assess the efficacy and safety of several dosing strategies of vadadustat compared to epoetin alfa during a 20-week Treatment Period in hemodialysis subjects.

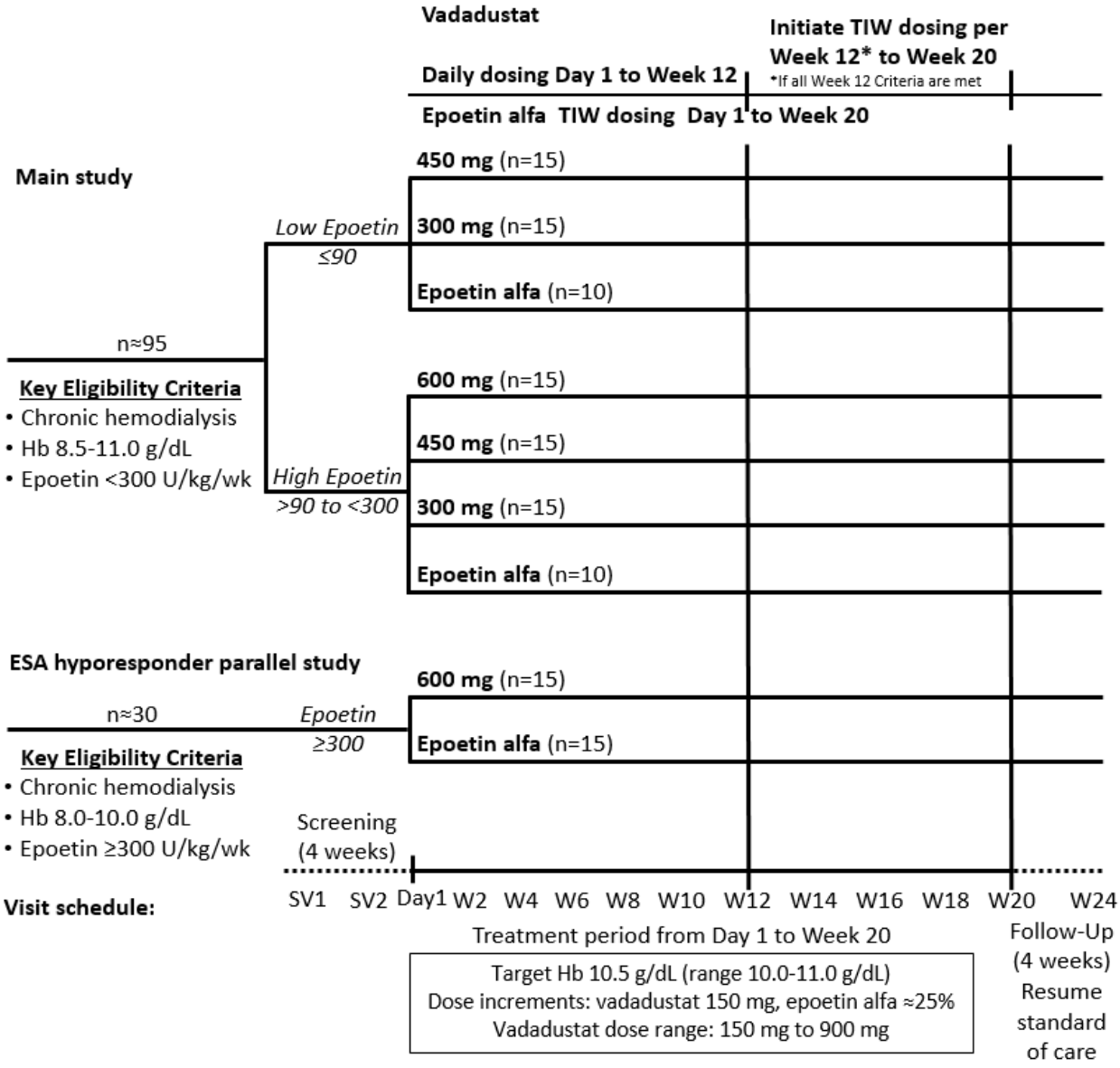
3 STUDY DESIGN

This is a Phase 2, randomized, open-label study to evaluate vadadustat for the treatment of anemia in hemodialysis subjects converting from epoetin alfa therapy.

For all subjects (Main study and ESA hyporesponder parallel study), the study (as shown in Figure 1) will include a Screening Period, a study Treatment Period, and a Safety Follow-Up Period as described below.

The aim is to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range.

Figure 1: Overview of Study Design



3.1 Screening Period (up to 28 days; Day -28 to Baseline/Day 1)

For all subjects (Main study and ESA hyporesponder parallel study), the Screening Period starts at the time the informed consent is signed and will be a maximum of 28 days in duration. Baseline/Day 1 will be performed within 28 days of the start of Screening. Subjects who meet all eligibility criteria will be randomized to a vadadustat treatment arm or an epoetin alfa treatment arm. Subjects will be required to stop epoetin alfa treatment for a minimum duration of 5 days before Baseline/Day 1 in the Main study and for a minimum of 2 days before Baseline/Day 1 in the ESA hyporesponder parallel study. In the Main study, randomization will be stratified by the mean weekly epoetin dose calculated over a period of 8 weeks prior to Screening Visit 2 (SV2):

- Low epoetin alfa dose group (≤90 U/kg/week)
- High epoetin alfa dose group (>90 to <300 U/kg/week)

3.2 Study Treatment Period (Baseline/Day 1 to Week 20)

For all subjects (Main study and ESA hyporesponder parallel study), the Treatment Period will run from Baseline/Day 1 to Week 20. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range.

3.3 Vadadustat Treatment

Subjects in the Main study randomized to vadadustat:

- Subjects in the low epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300 or 450 mg daily.
- Subjects in the high epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300, 450, or 600 mg daily.

Subjects in the ESA hyporesponder parallel study randomized to vadadustat:

- Subjects will receive a starting dose of vadadustat 600 mg daily.

Transition to TIW for all subjects randomized to vadadustat:

All subjects randomized to vadadustat (Main study and ESA hyporesponder parallel study), who complete the 12-week once daily dosing regimen and who meet all the Week 12 transition criteria for switching from daily to TIW dosing, will initiate TIW dosing at a starting dose one tablet greater (+150 mg) than the final dose in the daily dosing.

Note: Subjects who are not eligible to switch from daily vadadustat to TIW dosing at Week 12 will remain on daily dosing for the remainder of the study.

3.4 Epoetin Alfa Treatment

Subjects in both the Main study and ESA hyporesponder parallel study randomized to epoetin alfa:

All subjects randomized to epoetin alfa will receive TIW dosing for the entire Treatment Period based on the subject's central laboratory Hb value and the approved epoetin alfa US Package Insert (PI) for adult patients with CKD on dialysis. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range.

3.5 Safety Follow-Up Period (Weeks 20 to 24)

For all subjects (Main study and ESA hyporesponder parallel study), the 4-week Safety Follow-Up Period starting at Week 20 will be followed by a post-treatment safety assessment conducted at the beginning of Week 24.

3.6 Study Medication Stopping Rules

Study medication must be permanently discontinued if a subject meets one of the following criteria:

- ALT **or** AST >3x Upper Limit of Normal (ULN) **and** total bilirubin >2x ULN
- ALT **or** AST >3x ULN **and** international normalized ratio (INR) >1.5
- ALT **or** AST >8x ULN
- ALT **or** AST remains >5x ULN over 2 weeks
- ALT or AST >3x ULN with symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash) or eosinophilia.

4 CHANGES FROM THE PROTOCOL

No changes in planned analyses were done compared to the protocol in this SAP. But due to the Eurofins Ransomware Attack, the change from baseline in Hemoglobin (Hb, g/dL) with excluding subjects who were randomized before July 23, 2019 for vadadustat group will be provided as sensitivity analyses.

5 PRIMARY AND SECONDARY ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary endpoint will be the mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 10 to 12).

5.2 Key Secondary Efficacy Endpoints

- Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12).
- For subjects who transitioned to TIW vadadustat dosing, mean change in Hb from primary evaluation period (average Hb from Weeks 10 to 12) to the secondary evaluation period (average Hb from Weeks 18 to 20).

5.3 Other Secondary Efficacy Endpoints

- Mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 18 to 20)
- Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20)
- For subjects who transitioned to TIW vadadustat dosing, proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20)
- Proportion of subjects with a mean increase in Hb from Baseline to the primary evaluation period ≥0.5 g/dL (average Hb from Weeks 10 to 12) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12)
- Proportion of subjects with a mean increase in Hb from Baseline to the secondary evaluation period ≥0.5 g/dL (average Hb from Weeks 18 to 20) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20)
- Intravenous (IV) iron supplementation
- ESA rescue
- RBC transfusion

5.4 Exploratory Endpoints

[redacted]

[redacted]

5.5 PK/PD Endpoints

The PK parameters will include (but not limited to) the following:

- Area under concentration-time curve from dosing to last measurable concentration (AUC_{last})
- Area under concentration-time curve from dosing to infinity (AUC_{inf})
- Maximum concentration C_{max}
- Time to reach C_{max} (T_{max})
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal half-life (t1/2)

The PD parameters will include (but are not limited to) the following:

- EPO
- Reticulocytes
- Iron
- Ferritin
- TIBC
- Hepcidin

5.6 Safety Endpoints

Safety endpoints in this study include the following:

- AEs
- Vital sign measurements and clinical laboratory values
- Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
- Hb <8.0 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (Main Study);
- Hb <7.5 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (ESA hyporesponder parallel study)
- Hb increase >1.0 g/dL within any 2-week interval

6 GENERAL ANALYSIS DEFINITION

Data collected throughout the study will be summarized using descriptive statistics and listed in the by-subject listings. The continuous variables will be summarized by descriptive statistics (n, mean, SD, median, minimum, and maximum). Categorical variables will be summarized with frequency and percentage. Summaries will be provided by treatment group within appropriate analysis populations, and by time point/time period, as appropriate. Baseline is defined as the last observation before the first dose of study drug administration except for the parameters specified below.

Primary evaluation period is defined as Weeks 10 to 12 and the secondary evaluation period is defined as Weeks 18 to 20.

Study day is defined as follows:

Study Day= [Event date – First dosing date + 1] if after first dosing date

[Event date – First dosing date] if before first dosing date.

Note that with the definition above, days of "0" will not be used. As such, the study day can be interpreted as the number of days before or after first day of dosing. Event date refers to the date associated with the result being summarized. In some cases, this is the date of an assessment or measurement; in other cases, this is the onset date of an adverse or outcome event.

Assessments will be assigned to analysis visits based on the date the assessment took place regardless of the CRF page completed (i.e., scheduled visit number). Assessments will be mapped to visits based on Study Day.

If more than 1 Hb result is available in an analysis time period post-baseline, the average of all observed values will be assigned to that period. When more than 1 assessment is made for other measures within a given visit window post-baseline, the value of the assessment closest to the scheduled visit should be used. If the assessments are equally close, the value from the last assessment should be used.

If the central laboratory uses assays that have lower limits of detection (LLD), all laboratory results below the LLD will be imputed with the LLD. Results reported as greater than a value (i.e., "> value") will be imputed as 1.5 × that value.

For subjects whose reference date is missing, the study day will also be categorized as missing.

Adverse event onset

- If onset date is completely missing, 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 31.
  - If year > year of first dose, then set month and day to January 1.
- If month and year are present and day is missing:
  - If year = year of first dose and
    - month = month of first dose, then set day to day of first dose date.
    - month < month of first dose, then set day to last day of month.
    - month > month of first dose, then set day to first 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 first day of month.
- For all other cases, set date to date of first dose.

Adverse event end date

- If year is present and month and day are missing or year and day are present and month is missing, set end month and day to December 31.
- If month and year are present and day is missing, set the day to last day of the month.
- If fatal event, date is set to minimum of imputed end date and death date.
- For all other cases, set date to missing.

The following table provides the convention to classify assessment dates into protocol-defined visits. The time windows reflect the administrative range around each visit. These windows are wider than those stated in the protocol.

Table 1. Classification of assessments at every visit during the study

Target week / day	Actual visit day	Visit / Week classification
Week 0 / Day 1	Day 1	Visit 1 / Week 0
Week 1 / Day 8	Day 2-11	Visit 2 / Week 1
Week 2 / Day 15	Day 12-21	Visit 3 / Week 2
Week 4 / Day 29	Day 22-35	Visit 4 / Week 4
Week 6 / Day 43	Day 36-49	Visit 5 / Week 6
Week 8 / Day 57	Day 50-63	Visit 6 / Week 8
Week 10 / Day 71	Day 64-74	Visit 7 / Week 10
Week 11 / Day 78	Day 75-81	Visit 8 / Week 11
Week 12 / Day 85	Day 82-88	Visit 9 / Week 12
Week 13 / Day 92	Day 89-95	Visit 10 / Week 13
Week 14 / Day 99	Day 96-105	Visit 11 / Week 14
Week 16 / Day 113	Day 106-119	Visit 12 / Week 16
Week 18 / Day 127	Day 120-133	Visit 13 / Week 18
Week 20 / Day 141	Day 134 - (last dose day + 7)	Visit 14 / Week 20
Follow up / Day last dose day + 28	≥ last dose day + 8	Visit 15 / Week 24 (Follow up)

Note: Week 20 is the end of treatment.

It is expected that some subjects will discontinue Follow-Up. The reasons for any missing data will be summarized by treatment arm. The primary analysis will be based upon observed data without imputation. As a sensitivity analysis for primary efficacy endpoint, missing Hb in weeks 10 to 12 will be imputed using last observation carried forward (LOCF). Similarly, for certain secondary efficacy endpoints, missing Hb in weeks 18-20 will be imputed using LOCF.

7 SAMPLE SIZE JUSTIFICATION

Sample size is not based on a power analysis. Sample size reflects the exploratory nature of this study.

Approximately 95 subjects are planned for enrollment in the Main study with 40 and 55 subjects randomized to the low epoetin alfa dose group and the high epoetin alfa dose group, respectively. Approximately 30 subjects are planned for enrollment in the ESA hyporesponder parallel study.

Enrollment may be increased by up to approximately 20 additional subjects in the Main study and by up to approximately 30 additional subjects in the ESA hyporesponder parallel study to ensure adequate data are captured for the primary, PK/PD, and safety endpoints.

8 STUDY ANALYSES

8.1 General Consideration

The following rules will be adopted when summarizing the data:

1. The Main Study and the ESA Hyporesponder Parallel Study will be summarized separately, but in an analogous manner, for all endpoints.
    a. For the Main study, the low epoetin dose group (≤90 U/kg/week), 450 mg of vadadustat, 300 mg of vadadustat and epoetin will be displayed side by side. In addition, the total vadadustat will be presented as well.

    b. For the Main study, the high epoetin dose group (>90 and < 300 U/kg/week), 600 mg, 450 mg, 300 mg of vadadustat and epoetin will be displayed side by side. In addition, the total vadadustat will be presented as well.

    c. For the Main study, a summary of total vadadustat vs. epoetin will be presented as well. For the background information, a total column for all randomized patients will be presented except certain PK/PD parameters.

    d. For the ESA Hyporesponder Parallel Study (≥300 U/kg/week), 600 mg and epoetin will be displayed side by side.

2. For efficacy data analysis, 3 tables will be presented for some selected efficacy endpoints:
    a. Overall summary by week including the first weeks and post Week 12 by treatment group which is based on the randomized dose group.
    b. For subjects who switched Vadadustat dosing from QD to TIW dosing.
    c. For subjects who did not switch from QD to TIW dosing after Week 12.

3. For safety data analysis, 5 sets of tables will be presented for some selected safety parameters:
    a. Overall summary for all weeks including the first 12 weeks and post Week 12 by treatment group
    b. Overall summary for the first 12 weeks of treatment.
    c. Overall summary for Weeks 12 to the end of study for both switched and not switched patients at Week 12
    d. Overall summary for Weeks 12 to the end of study for switched patients
    e. Overall summary for Weeks 12 to the end of study for not switched patients

4. For patients who switched Vadadustat dosing from QD to TIW dosing at week 12, and then switched back to QD, if there are less than or equal to 20 subjects, only patient

listings/profiles will be created. If there are more than 20 patients, summary tables will be created by treatment groups for efficacy and safety.

8.2 Analysis Population

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects. Analyses of this population will be based on the randomized treatment.

- Full Analysis Population (FAS): all subjects in the randomized population who received at least one dose of study drug and had at least one Hb assessment during the primary efficacy evaluation period. Analyses of this population will be based on the randomized treatment.

- Safety Population: all subjects in the randomized population who received at least one dose of study treatment. Analysis of this population will be based on the actual treatment received. Subjects who received in error some vadadustat and some epoetin alfa will be classified by the more frequently received drug.

- Per protocol (PP) population: all randomized subjects who received study drug during the primary evaluation period, had at least one Hb assessment during the primary efficacy evaluation period, received no rescue therapy (with ESA or transfusion) prior to the evaluation period, and had no major protocol deviation affecting the primary endpoint analyses. Major protocol deviations leading to exclusion from the PP population will be specified prior to database lock on a blinded basis and recorded in a separate document. Analyses of this population will be based on actual treatment received.

- Pharmacokinetic (PK) population: will include all randomized subjects who received study medication (vadadustat or EPO) and had enough drug concentrations to estimate AUC and Cmax. Analysis of this population will be based on the dose amount taken at the date of PK sampling for vadadustat group.

Efficacy analyses will utilize the Randomized, FAS, and PP Populations while safety analyses will utilize the Safety Population. PK analyses will utilize the PK Population. However, if the population size of FAS and PP is ≥ 95% of the size of randomized population, no additional summary table will be presented for FAS and PP populations.
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8.3 Disposition of Subjects

The number and percentage of subjects randomized and included in each analysis population will be summarized by treatment and overall. Reasons for excluding subjects from the analysis populations will be presented in a by-subject listing.

The number of randomized subjects who completed the study period for QD period, switched to TIW period, completed TIW period, switched dosing from TIW back to QD, completed study, discontinued early from study drug, completed or discontinued from the study, and reasons for discontinuation will be summarized by treatment group and overall. For dose changes including dose increase, decrease for different reasons and "dose not changed" will be described in section 8.9.

8.4 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major" in cooperation with Akebia. Major deviation will be categorized and summarized in table. A data listing of protocol deviations will be provided.

8.5 Demographics and Baseline Characteristics

Continuous demographic variables, such as age, weight, BMI, and height, will be summarized for the Randomized population, FAS, PP, and Safety using descriptive statistics (n, mean, median, SD, minimum, and maximum value). Categorical demographic variables, such as age category, race, ethnicity, and gender, will be summarized as a proportion of the Randomized population, FAS, PP, and Safety populations.

Ethnic group, race, gender, and age will be included in the demographics and baseline characteristics table. Age will be calculated as using function floor of (informed consent date – birth date + 1)/365.25.

8.6 Baseline Laboratory Data

Baseline laboratory including hematology, chemistry, folate, vitamin B12, iron indices (serum iron, ferritin, transferrin, TIBC, TSAT) and biomarkers (VEGF and hepcidin) will be summarized for each treatment group based on the safety population.

8.7 Medical History

Medical history terms including renal and cardiovascular History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23. and the number and percent of subjects with medical history will be summarized by (SOC) and Preferred Term (PT) for each treatment group based on the safety population.

Etiology of CKD, smoking status, and New York Heart Association Class (NYHA) of cardiovascular history will be summarized for each treatment group for safety population.

In addition, the history of dialysis, CKD diagnosis duration in years will be summarized for each treatment group based on the safety population.

8.8 Prior and Concomitant Medication

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO DD; Sep 2018) and summarized for each treatment group based on the safety population. Prior medication is defined as any medication taken prior to the first dose of the study medication in the initial treatment period. Any medication taken from the day of first dose of the study treatment up to the day of last date of the same study drug date + 4 weeks will be considered as concomitant medication for the treatment analysis.

8.9 Study Medication Exposure and Compliance

Study medication exposure and compliance will be summarized using descriptive statistics for the FAS and Safety Population. Study medication and subject dosing diary data will also be presented in data listings.

The calculated compliance rate for a given time period will be derived from exposure data as the number of days on dosing period collected on electronic case report forms (eCRFs) divided by the number of days in that time period.

Compliance will be summarized as follows:

- Descriptive statistics will be summarized by treatment group for entire treatment period.
- Percent compliance will be categorized according to the following categories for entire treatment period for safety population by treatment group:
    - less than 50% (significant drug noncompliance)
    - at least 50%, less than 80% (moderate drug noncompliance)
    - greater or equal 80% (drug compliance)
    - unknown

Study medication exposure and compliance will be summarized for the first 12 weeks, Weeks 12 – 20, and entire treatment period for each treatment group. In addition, for Weeks 12 – 20, patients who switched from daily vadadustat dose to TIW and patients who did not switch at Week 12 will be summarized separately.

For epoetin alfa group, increases in dose relative to last dose will be characterized in the following categories by percentage increase: <50%, ≥50% and <100%, and ≥100%. Subjects will be presented by their maximum category of increase for the first 12 weeks, Weeks 12 – 20, and entire treatment period.

Dose change information including the following categories will be summarized for the first 12 weeks and Weeks 12 – 20 treatment period for each treatment group:

- Dose not changed
- Protocol guided dose reduction
- Dose increased based on Hb assessment
- Dose decreased based on Hb assessment

- Dose interrupted based on Hb assessment
- Dose decreased due to adverse event
- Dose interrupted due to adverse event
- Dose restarted
- Transitioned from QD to TIW dosing
- Converted back from TIW to QD dosing

9 EFFICACY ANALYSIS

The primary efficacy endpoint as well as all other secondary endpoints will be summarized using descriptive statistics by treatment group, as well as by study visit and/or analysis period (the first 12 weeks and Weeks 12 – 20) as appropriate. The ESA hyporesponder parallel study will be analyzed separately from the main study. Mean values of Hb as well as selected other efficacy parameters will be plotted across study visits/periods by treatment group. No adjustment for multiplicity is being used in this exploratory study.

Primary efficacy endpoint will be analyzed and presented for Randomized population, FAS and PP Population. Key secondary efficacy endpoints will be analyzed for Randomized population and PP PopulationThe rest of efficacy endpoints will be analyzed for Randomized population. No inferential statistical modeling will be used for the efficacy analysis. All efficacy endpoints related to Hb, the observed data will be used for the analysis tables. In addition, a sensitivity analysis of LOCF to impute the missing Hb data will be performed for summary of change from baseline in Hb based on Randomized population.

9.1 Primary Endpoint

Mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 10 to 12). Baseline value is defined as the average of the final two Hb values prior to start of dosing on day 1.

Observed baseline, post-baseline values, and change from baseline values will be presented in descriptive statistics summary by treatment group, as well as by study visit and/or analysis period as appropriate. Mean values of Hb as well as selected other efficacy parameters will be plotted across study visits/periods by treatment group.

9.2 Secondary Endpoints

Similarly, all secondary endpoints will be summarized using descriptive statistics. For continuous variables, observed values at specified time points and changes between specified time points will be presented in descriptive statistics summary by treatment group, as well as by study visit and/or analysis period as appropriate. Counts of subjects satisfying stated criteria will be summarized analogously, using descriptive statistics for categorical variables.

- Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) for each treatment group
- For subjects who transitioned to TIW vadadustat dosing, mean change in Hb from primary evaluation period (average Hb from Weeks 10 to 12) to the secondary evaluation period (average Hb from Weeks 18 to 20) for each vadadustat dosing group

- Mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 18 to 20) for each treatment group
- Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) for each treatment group
- For subjects who transitioned to TIW vadadustat dosing, proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) for each vadadustat dosing group
- Proportion of subjects with a mean increase in Hb from Baseline to the primary evaluation period ≥0.5 g/dL (average Hb from Weeks 10 to 12) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) for each treatment group
- Proportion of subjects with a mean increase in Hb from Baseline to the secondary evaluation period ≥0.5 g/dL (average Hb from Weeks 18 to 20) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) for each treatment group

9.3 Other Secondary Endpoints

- Intravenous (IV) iron supplementation and oral iron

  The average weekly elemental iron use during the treatment period which is defined as first dose date to last dose date + 7 days will be calculated for weekly intervals from both oral and IV iron medications (Oral iron dose will be converted to elemental iron dose; the list will come from the medical team.). The treatment period will be divided in periods of 7 days and for each of these periods the weekly mean of IV iron will be used using the following formula:

  > Weekly iron use for each subject = Total iron in mg / [(last dose date + 7 – first dose date +1)/ 7]

  The average weekly iron use will be summarized by treatment group using descriptive statistics. The content of elemental iron for different kinds of IV iron is presented in Appendix 5.

  In addition, numbers and percentages of subjects with at least one administration of elemental iron will be summarized by treatment group.

- ESA administration and RBC transfusion

  ESA medication will be considered as rescue if the ESA medication was taken between the first dose date to the last dose date + 7 days and the reasons for the ESA medication use is checked as confirmed Hb <8.5 g/dL on the CRF and the ESA medication wasn't taken during the period of Eurofins ransomware attack (after Jun 20, 2019 and before July 9, 2019).

Epoetin alfa dose will be administered based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis. From Baseline/Day 1 to Week 20, dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 and 11.0 g/dL, inclusive. Because epoetin alfa is titratable, increase in dose is not considered rescue unless the investigator specifically designates it as such; however, increases in dose relative to last dose will be characterized in three categories by percentage increase: <50%, ≥50% and <100%, and ≥100%. In addition to the investigator's judgement of rescue, the increase in dose ≥50% or ≥100% will be considered as additional conditions for ESA rescue in EPO group.

RBC transfusion will be considered as rescue if the RBC transfusion was taken between the first dose date to the last dose date + 7 days and the reasons for the RBC transfusion is checked as Worsening Anemia due to CKD on the CRF.

The study will consider the following efficacy endpoints related to ESA administration and RBC transfusion.

- Receipt of any ESA administration
- Receipt of any ESA administration or dose with at least 50% increase for the EPO group
- Receipt of any ESA administration or dose with at least 100% increase for the EPO group
- Receipt of ESA administration as rescue
- Receipt of ESA administration as rescue or dose with at least 50% increase for the EPO group
- Receipt of ESA administration as rescue or dose with at least 100% increase for the EPO group
- Receipt of any RBC transfusion
- Receipt of RBC transfusion as recue

Number of subjects received ESA administration (any or rescue) and RBC transfusion (any or rescue) will be summarized by treatment group and time period. The following time periods will be summarizing:

- Baseline visit (inclusive) to week 12 (inclusive)
- Week 12 (exclusive) to week 20 (inclusive)
- Baseline visit (inclusive) to week 20 (inclusive)

9.4 Exploratory Endpoints

[redacted]

[redacted]

9.4.1 Health--related quality of life (HRQOL) measure 36-Item Short-Form General Health Survey (SF-36v2)

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36v2) is a multi-purpose, short-form health survey with 36 questions (see appendix 1). It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.

The SF-36 contains 36 items that measure eight dimensions: (1) physical functioning (PF); (2) role limitations due to physical health problems (RP); (3) bodily pain (BP); (4) social functioning (SF); (5) general health perceptions (GH); (6) role limitations due to emotional problems (RE); (7) vitality, energy or fatigue (VT); and (8) mental health (MH).

The SF-36v2 will be scored for the 8 domains according to the standard SF-36v2 scoring algorithms (0 to 100 scales) explained in the SF-36v2 Manual and Interpretation Guide (Ware et al., 1993). The PCS and MCS will be scored according to the standard SF-36v2 scoring algorithm (0 to 100 scales) explained in the SF-36v2 Physical and Mental Health Summary Scales Manual (Ware et al., 1994).

Each of these 8 domains is consisted of several questions. Table 1 and Appendix 1 describe the individual item for each domain**.**

Table 1: SF-36 8 Dimensions and Component Items

Domain	Individual Item
Physical Functioning (PF)	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
Role-Physical (RP)	4a, 4b, 4c, 4d
Body Pain (BP)	7, 8
General Health (GH)	1, 11a, 11b, 11c, 11d
Vitality (VT)	9a, 9c, 9g, 9i
Social Function (SF)	6, 10
Role-Emotional (RE)	5a, 5b, 5c
Mental Health (MH)	9b, 9c, 9d, 9f, 9g

Table 2 Transformation of SF-36 items to a scale from 0 to 100

Question # (Appendix 2)	Self-perceived health	
	0 (Poor)	100 (Better)
1, 2, 6, 8, 9a, 9d, 9e, 9h, 11b, 11d	5	1
3a to 3j	1	3
4a to 4d, 5a to 5c, 9b, 9c, 9f, 9g, 9i, 10, 11a, 11c	1	5
7	6	1
Programming note: Once transformed – the items should each span the range 0 to 100.		

Item scores for each dimension are coded, summed, and transformed to a scale from 0 to 100, with higher scores indicating better self-perceived health (See detail in Appendix 1 and Appendix 2). The calculation of the normalized domain scores relative to the original item response is presented in Appendix 3. The score for each domain ranges from 0 to 100.
In addition to the domain scores described above, standardized and norm-based scores are calculated for each domain. The formulae are given below.

Domain	Standardization (Z-score)	Norm-Based Score
Physical functioning	PF_Z = (PF-83.29094)/23.75883	50+10*PF_Z
Role-physical	RP_Z = (RP-82.50964)/25.52028	50+10*RP_Z
Bodily pain	BP_Z = (BP-71.32527)/23.66224	50+10*BP_Z
General health	GH_Z = (GH-70.84570/20.97821	50+10*GH_Z
Vitality	VT_Z = (VT-58.31411)/20.01923	50+10*VT_Z
Social functioning	SF_Z = (SF-84.30250)/22.91921	50+10*SF_Z
Role-emotional	RE_Z = (RE-87.39733)/21.43778	50+10*RE_Z
Mental heath	MH_Z = (MH-74.98685)/17.75604	50+10*MH_Z

Note: Standardization is based on the 1998 general United States population.

SF-36 physical and mental component transformed scores are calculated using the conventions described below.

Score	Calculation
Aggregate Standardized Score	
Physical component	AGG_PHYS = (PF_Z * 0.42402) + (RP_Z * 0.35119) + (BP_Z * 0.31754) + (GH_Z * 0.24954) + (VT_Z * 0.02877) + (SF_Z * -0.00753) + (RE_Z * -0.19206) + (MH_Z * -0.22069)

Score	Calculation
Aggregate Standardized Score	
Mental component	AGG_MENT = (PF_Z * -0.22999) + (RP_Z * -0.12329) + (BP_Z * -0.09731) + (GH_Z * -0.01571) + (VT_Z * 0.23534) + (SF_Z * 0.26876) + (RE_Z * 0.43407) + (MH_Z * 0.48581)
Transformed Summary	
Transformed physical	PCS = 50 + (AGG_PHYS * 10)
Transformed mental	MCS = 50 + (AGG_MENT * 10)

For each of the 8 dimensions, if less than 50% of the items which constitute that dimension are missing, the dimension score will be calculated by the mean of the available non-missing items. The physical health composite summary (PCS) and mental health composite summary (MCS) will only be calculated if a score has been calculated for all 4 dimensions that constitute the composite summary.

The physical component score (PCS) includes 4 domains of the SF-36: (1) physical functioning (PF); (2) role limitations due to physical health problems (RP); (3) bodily pain (BP) and (4) general health perceptions (GH); while the mental component score (MCS) includes the other 4 domains. The mean change in these endpoints at weeks 12, 20, and 24 will be summarized by treatment group with descriptive statistics.

9.4.2 Patient Global Impression of Severity (PGI-S)

The patient global impression of severity (PGI-S) includes 2 questions with the patient response score of 0 (no impact at all) to 10 (as bad as it can be):

1. How would you rate the impact of your anemia and its treatment on how you feel?
2. How much does the treatment you currently take for anemia help you daily activities?

The change from baseline in PGI-S will be summarized by treatment group with descriptive statistics including the number of subjects, mean, median, standard deviation and range.

9.4.3 Patient Global Impression of Change (PGI-C)

The patient global impression of change (PGI-C) includes 1 question of "How would you compare the impact of your anemia and its treatment on how you feel now to when you were on the previous treatment (or the period your last visit)?" There are 7 patient responses for selection: very much worsened, much worsened, minimally worsened, no changed, minimally improved, much improved, and very much improved.

The PGI-C will be summarized with the number and percentage of subjects with response by treatment.

9.4.4 HRQOL measure EuroQol 5 Dimensions 5 Levels (EQ-5D-5L)

EQ-5D-5L includes 5 questions with "Under each heading, please check the ONE that best describes your health TODAY":

1. Mobility with 5 responses:
    a. I have no problems walking
    b. I have slight problems walking
    c. I have moderate problems walking
    d. I have severe problems walking
    e. I am unable to walk

2. Self-care with 5 responses:
    a. I have no problems washing or dressing myself
    b. I have slight problems washing or dressing myself
    c. I have moderate problems washing or dressing myself
    d. I have severe problems washing or dressing myself
    e. I am unable to wash or dress myself

3. Usual activities with 5 responses:

    a. I have no problems doing my usual activities
    b. I have slight problems doing my usual activities
    c. I have moderate problems doing my usual activities
    d. I have severe problems doing my usual activities
    e. I am unable to do my usual activities

4. Pain/Discomfort with 5 responses:

    a. I have no pain or discomfort
    b. I have slight pain or discomfort
    c. I have moderate pain or discomfort
    d. I have severe pain or discomfort
    e. I have extreme pain or discomfort

5. Anxiety / Depression with 5 responses:

    a. I am not anxious or depressed
    b. I am slightly anxious or depressed
    c. I am moderately anxious or depressed
    d. I am severely anxious or depressed

e. I am extremely anxious or depressed

EQ-5D-5L data will be summarized with the number and percentage of subjects with response by treatment.

In addition, the last question of EQ-5D-5L include “We would like to know how good or bad your health is TODAY.” A 0-100 scale will be marked by each patient using “X” and as a score of 0-100 will be recorded by the patient 0 indicates the worst health you can imagine and 100 indicates the best heath you can imagine. This health score of today will be summarized by treatment group with descriptive statistics including the number of subjects, mean, median, standard deviation and range.

9.5 Additional Sensitivity Analyses

Due to the Eurofins Ransomware Attack, the analysis of primary endpoint with excluding subjects who were randomized before July 23, 2019 for vadadustat group will be provided as sensitivity analyses.

For the above-mentioned efficacy endpoints, additional sensitivity analyses may be performed.

10 SAFETY ANALYSIS

The safety analysis will be performed using the Safety Population. Safety parameters include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations. For selected safety data, in additional, to the regular safety summary, for Weeks 12 – 20, patients who switched from daily vadadustat dose to TIW and patients who did not switch at Week 12 will be summarized separately.

10.1 Adverse Events

Safety analyses will be descriptive in nature.
All AEs will be coded using MedDRA version 23.0.

An AE (classified by preferred term) started during the treatment period will be considered a treatment-emergent adverse event (TEAE) if it was not present prior to the first dose of study medication, or it was present prior to the first dose of study medication but increased in severity during the treatment period An AE that occurs more than 28 days after the last dose of study medication will not be counted as a TEAE.

The number and percentage of subjects reporting TEAEs in each treatment group and each treatment period will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study medication. If more than one event occurs with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study medication.

The distribution of TEAEs by severity and relationship to study medication will be summarized by SOC and PT and treatment group. AEs will also be summarized by their maximum severity.

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

- SAEs
- Related TEAEs, as determined by the Investigator
- TEAEs leading to early discontinuation of study drug
- Adverse events of special interest (AESI); AESI is defined in Appendix 4.

10.2 Laboratory

Numbers and percentage of subjects with the following category will be summarized by treatment:

- Hb >12.0 g/dL,
- Hb>13.0 g/dL,
- Hb>14.0 g/dL

- Hb <8.0 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (Main Study);
- Hb <7.5 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (ESA hyporesponder parallel study)
- Hb increase >1.0 g/dL within any 2-week interval

All Hb related safety endpoints will be tabulated for each treatment group.

Descriptive statistics for laboratory values (in US conventional and SI units) and changes from baseline at each assessment time point will be presented by treatment group for the following laboratory parameters collected in the study including but are not limited to the following:

- Hematology: Hemoglobin, hematocrit, RBC count, RDW, MCV, MCH, MCHC, WBC count, WBC differential, platelet counts and Reticulocyte count;
- Chemistry: Alkaline phosphatase, ALT, AST, total bilirubin, LDH, total protein, albumin, glucose, phosphate, uric acid, BUN, creatinine, sodium, and potassium; HbA1C;

Shift tables will be presented using common terminology criteria for adverse events (CTCAE) grade.

A summary of liver function abnormalities by analysis period will be provided by treatment group. Any subject with at least 1 of the following liver function abnormalities will be summarized:

- Alanine aminotransferase (ALT) >2 × and ⩽3 × upper limit of normal (ULN); ALT >3 × and ⩽5 × ULN; ALT >5 × and ⩽10× ULN; ALT >10 × ULN
- Aspartate aminotransferase (AST) >2 × and ⩽3 × ULN; AST > 3× and ⩽ 5 × ULN; AST >5 × and ⩽10 × ULN; AST >10 × ULN
- Bilirubin >2× and ⩽3× ULN; Bilirubin >3× ULN

In addition, a table will summarize the occurrence of events that satisfy the following versions of Hy's Law:

- (ALT or AST >3× ULN and <= 5xULN) and total bilirubin >2× ULN;
- (ALT or AST >5× ULN and <= 10xULN) and total bilirubin >2× ULN;
- ALT or AST >10× ULN and total bilirubin >2× ULN

The following 3 data listings will be presented by subject:

- A listing of lab values for all lab tests at all collected time points.
- A listing of subjects with post-baseline (CTCAE) grade 3 or higher will be provided including the baseline and post-baseline values.

- A listing of all AEs for subjects with (CTCAE) grade 3 or higher including lipid profile, glucose, potassium, etc. will also be provided.

10.3 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, heart rate, respiratory rate and SO_2 (assessed in seated position after 5 minutes of rest and prior to blood draws), and dry weight and their changes from baseline at each visit and at the end of study will be presented by treatment group.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria listed in Table 2 below. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group. The percentages are to be calculated relative to the number of subjects with baseline and at least one post-baseline assessment. The numerator is the total number of subjects with at least one post-baseline PCS vital sign value. A supportive listing of subjects with post-baseline PCS values will be provided including the patient ID, study center, baseline, and post-baseline values. A listing of all AEs for subjects with PCS vital signs will also be provided.

Table 2. Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	Criteria*	
		Observed Value	Change from Baseline
Systolic Blood Pressure (mmHg)	High	≥ 160	Increase of ≥ 20, 10
	Low	≤ 90	Decrease of ≥ 20, 10
Diastolic Blood Pressure (mmHg)	High	≥ 110	Increase of ≥ 20, 10
	Low	≤ 50	Decrease of ≥ 20, 10
Pulse Rate (bpm)	High	≥ 120	Increase of ≥ 20
	Low	≤ 50	Decrease of ≥ 20

10.4 Electrocardiogram (ECG)

Baseline ECG data will be presented by subject listing.

10.5 Physical Examinations

Baseline physical examination data will be presented by subject listing.

11 PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) ANALYSIS

Pharmacokinetic (PK) parameters of Vadadustat, its O-glucuronide metabolite in Vadadustat treatment group and of EPO level in EPO treatment group and pharmacodynamics analyses of EPO level in Vadadustat treatment group will be evaluated. PK parameters will be calculated using SAS® program which will follow the same algorithm as that implemented in WinNonlin® Professional (Version 7.0, Pharsight Corporation, A Certara Company, St. Louis, MO). In addition, the SAS results will be validated using the parameters generated from WinNonlin 7.0. The baseline-adjusted and baseline-unadjusted PK parameters will be calculated for each subject for EPO. The baseline adjustment will use the concentration result at day 1 pre-dose timepoint. If any concentration is missing, the reason of the missing (e.g., lost sample; sample not collected) will be identified.

For pharmacokinetic analysis, all values below the limit of quantification (BLQ) will be presented as "BLQ" in the individual concentration data listing and treated as "0" in the descriptive summary statistics of concentration data. Leading BLQ values prior to the first measurable concentration will be treated as 0 when calculating the PK parameters; embedded and trailing BLQ values (post C_{max}) will be treated as "missing" when calculating PK parameters (e.g., AUC_{last} λ_z). All values above the upper limit of quantification (ULOQ) will be presented as "ULOQ" in the individual concentration data listing and treated as "missing" in the descriptive summary statistics of concentration data as well as calculating the PK parameters.

An exposure-response analysis of vadadustat and PD measures will be conducted as deemed appropriate.

The vadadustat and epoetin PK parameters will include (but not limited to) the following:

- AUC_{last}
- AUC_{inf}
- C_{max}
- Time to reach C_{max} (T_{max})
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (V_d/F)
- Terminal half-life ($t_{1/2}$)
- Elimination rate constant (λ_z)

The PD parameters will include (but are not limited to) the following:

- Hb
- EPO
- Reticulocytes
- Ferritin
- TIBC

- Hepcidin

PK and PD parameters will be summarized using descriptive statistics: number of subjects (N), mean, median, SD, minimum, maximum, and coefficient of variation, geometric mean and geometric mean SD. Mean plasma concentration over time profiles will be presented graphically.

For PK parameters, the following rules will be followed when presenting the summary statistics and data:

- C_{max} (µg/mL) and AUC (µg*hr/mL) values will be presented for both summary tables and individual listings of parameters.
- For summary tables, summary statistics including mean, median, min, max will be presented in 3 significant figures; while SD will have an additional figure.
- For individual PK parameters, 6 digits of the PK concentration will be used to calculate the summary statistics.
- Summary statistics for Tmax (median, min and max) will be presented using two decimal places.
- When dose interrupted at the time of PK sampling, the vadadustat concentration should be 0 and will be excluded from analysis.
- If PK concentration <BLQ at all the timepoints for a visit, those records will be excluded from analysis.
- If Cmax and AUC values are 0, those records will be excluded from analysis.
- PK parameter tables will be summarized with or without dose normalization.

The ESA hyporesponder parallel study will be analyzed separately from the main study.

Specific PD analyses for Hb and EPO will include the following:

- Hb response as defined by Hb increments of 1 g/dL and 2 g/dL by vadadustat dose
- EPO parameters (e.g. Cmax, AUC) by vadadustat dose, with any ESA usage, the PD records will be removed which happened within 5 days (IV) usage of Epo Alfa, 5 days (IV) or 9 days (SC) usage of Darbe , 30 days (IV) usage of Micera.

In addition, the following parameters may be summarized:

- Iron indices: serum Iron, ferritin, TSAT, Hepcidin
- Serum EPO levels:
    - 24-hour profile
    - C_{max} and AUC (correct/uncorrected)
- Glucose change from baseline
- Lipid profile;
    - Total chol
    - LDL chol

  - HDL Chol
  - HDL/Total ratio
- Inflammatory biomarkers
  - CRP
- Other biomarker: VEGF

12 SOFTWARE AND PROGRAMMING SPECIFICATIONS

Statistical analyses will be performed using SAS version 9.4 (or later versions).

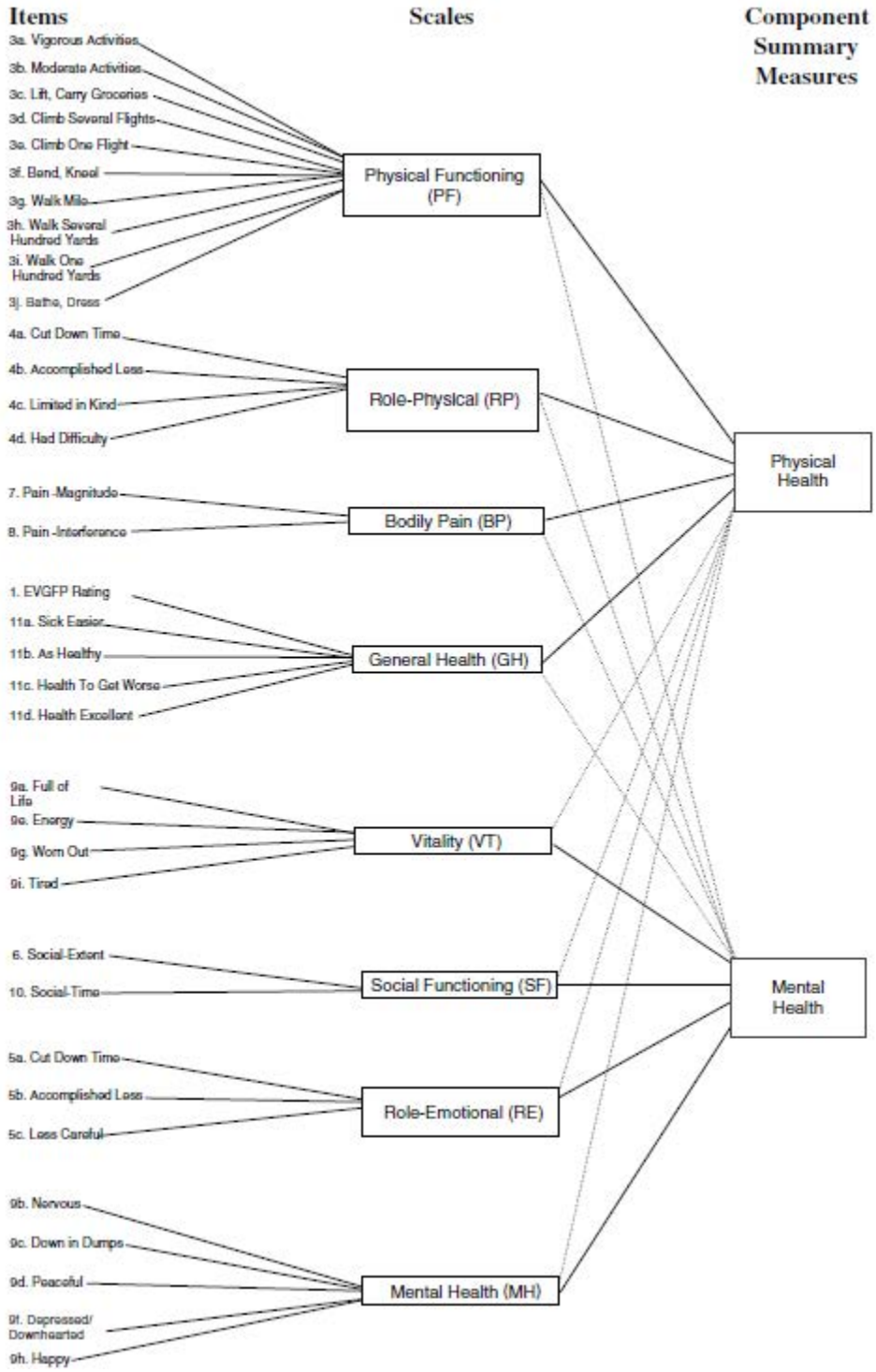
13 REFERENCES

Ware, J.E., Snow, K.K., Kosinski, M., & Gandek, B. (1993). SF-36® Health Survey Manual and Interpretation Guide. Boston, MA: New England Medical Center, The Health Institute

Ware, J.E., Kosinski, M., & Keller, S.K. (1994). SF-36® Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: The Health Institute

APPENDIX 1

Figure 1. SF-36 Model V2



APPENDIX 2: SF-36 V2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 v2

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

SF-36 v2

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

SF-36 v2

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-36 v2

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and low?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

SF-36 v2

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

APPENDIX 3. SF-36 V2 SCORING ASSIGMENT

Scale	Item	Coding	Range of Raw Score	Normalized Score*
Physical functioning	*Items 3a to 3j*	Yes, limited a lot = 1 Yes, limited a little = 2 No, not limited = 3	10-30	(S-10)/20 × 100
Role-physical	*Items 4a to 4d*	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5	4-20	(S-4)/16 × 100
Bodily pain	*Item 7*	None = 6 Very mild = 5.4 Mild = 4.2 Moderate = 3.1 Severe = 2.2 Very severe=1	2-12	(S-2)/10 × 100
	Item 8 if both items 7 and 8 are answered	Not at all and item7 equals 'None' = 6 Not at all and item7 not equal 'None' = 5 A little bit = 4 Moderately = 3 Quite a bit = 2 Extremely = 1		

Scale	Item	Coding	Range of Raw Score	Normalized Score*
	Item 8 if item 7 is not answered	Not at all = 6 A little bit = 4.75 Moderately =3.5 Quite a bit = 2.25 Extremely = 1		
General health	*Item 1*	Excellent = 5 Very good = 4.4 Good = 3.4 Fair = 2 Poor = 1	5-25	(S-5)/20 × 100
	Items 11a and 11c	Definitely true = 1 Mostly true = 2 Don't know = 3 Mostly false = 4 Definitely false = 5		
	Items 11b and 11d	Definitely true = 5 Mostly true = 4 Don't know = 3 Mostly false = 2 Definitely false = 1		

Scale	Item	Coding	Range of Raw Score	Normalized Score*
Vitality	*Items 9a and 9e*	All of the time = 5 Most of the time = 4 Some of the time = 3 A little of the time = 2 None of the time = 1	4-20	(S-4)/16×100
	Items 9g and 9i	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5		
Social functioning	*Item 6*	Not at all = 5 Slightly = 4 Moderately = 3 Quite a bit = 2 Extremely = 1	2-10	(S-2)/8 × 100
	Item 10	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5		

Scale	Item	Coding	Range of Raw Score	Normalized Score*
Role-emotional	*Items 5a to 5c*	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5	3-15	(S-3)/12 × 100
Mental health	*Items 9b, 9c and 9f*	All of the time = 1 Most of the time = 2 Some of the time = 3 A little of the time = 4 None of the time = 5	5-25	(S-5)/20 × 100
	Items 9d and 9h	All of the time = 5 Most of the time = 4 Some of the time = 3 A little of the time = 2 None of the time = 1		

*S = raw score = sum of item scores after coding

APPENDIX 4. ADVERSE EVENTS OF SPECIAL INTEREST

F.1. Potential risks

The following potential risks associated with vadadustat will be presented as adverse events of special interest (AESI).

- Hypersensitivity: Hypersensitivity MedDRA SMQ Narrow
- Hyperkalemia: Hyperkaliemia MedDRA PT, Blood potassium abnormal MedDRA PT, Blood potassium increased MedDRA PT
- Hypertension: Hypertension MedDRA SMQ Narrow

F.2. Events of special interest

The following will be presented as AESI.

- Hepatotoxicity: Drug related hepatic disorders Comprehensive SMQ Broad
- Pulmonary Hypertension: Pulmonary Hypertension SMQ Narrow
- Cardiac Valve disorders: Cardiac Valve disorders HGLT
- Adrenal disorder: HLT Adrenal gland disorders NEC, HLT Adrenal cortex tests

F.3. Events under monitoring

The following will be presented as AESI.

- Malignancies: Malignancies MedDRA SMQ Narrow
- Congestive heart failure: Cardiac failure MedDRA SMQ Narrow
- Retinal effects due to Vascular Endothelial Growth Factor (VEGF) expression: Retinal disorders SMQ Narrow

APPENDIX 5: ELEMENTAL IRON CONTENT IN IV IRON

Commercial Name	Active ingredient	Amount of elemental iron
COSMOFER	Iron dextran	50 mg Iron (ferric) /ml
DIAFER	Iron isomaltoside	50 mg Iron (ferric) /ml
FER MYLAN	iron sucrose	100 mg iron/5 ml
FERAHEME	ferumoxytol	30 mg iron / ml
FERINGEKT	Ferric carboxymaltose	50 mg iron / ml
FERRIC HYDROXIDE SACCARATE	FERRIC HYDROXIDE SACCHARATE	20 mg iron/ml
FERRIC PYROPHOSPHATE (triferic)	FERRIC PYROPHOSPHATE	(5.44 mg of iron (III) per mL
FERRIECIT	Sodium ferric gluconate	62.5mg iron /5ml
FERROVIN	Ferric hydroxide sucrose complex	20mg/mL
INFED / IRON DEXTRAN	iron dextran complex	50 mg iron/ml
IRON POLYMALTOSE	Iron(III)hydroxide-polymaltose	100 mg iron/2ml
MONOVER	Iron(III) isomaltoside 1000	100 mg iron/ml
Venofer	iron sucrose	20 mg/mL