CLINICAL PROTOCOL

PHASE 2, RANDOMIZED, OPEN-LABEL STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE TREATMENT OF ANEMIA IN SUBJECTS WITH DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (DD-CKD) WHO ARE HYPORESPONSIVE TO ERYTHROPOIESIS-STIMULATING AGENTS

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0018
US IND Number:	102,465
Phase:	Phase 2
Status; Date:	Amendment 1 (Version 2; 18 July 2017) Original protocol (Version 1; 30 November 2016)
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Cambridge, MA 02142 United States of America

1 SIGNATURE PAGES

1.1 Protocol Approval

[redacted] Date

[redacted]
Akebia Therapeutics, Inc.

1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, any amendments to the protocol (if applicable, a history of protocol changes are appended at the end of this document), the Investigator's Brochure, and other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonization Guideline for Good Clinical Practice E6 (R1).
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

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Signature of Investigator Date

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Investigator Name (print or type)

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Investigator's Title

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Phone Number

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Full Address

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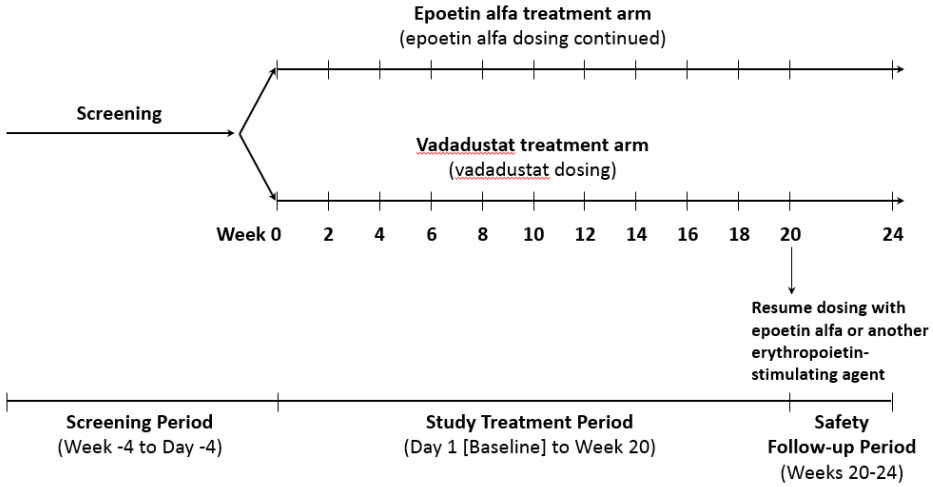
2 PROTOCOL SYNOPSIS

Study Title	Phase 2, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Treatment of Anemia in Subjects with Dialysis-Dependent Chronic Kidney Disease (DD-CKD) who are Hyporesponsive to Erythropoiesis-Stimulating Agents
Protocol Number	AKB-6548-CI-0018
Study Phase	Phase 2
Investigational Product	Vadadustat; 150 mg tablets
Reference Medicinal Product	Epoetin alfa solution for intravenous injection
Study Population	The study population will consist of subjects with DD-CKD who are ≥18 years of age, receiving chronic outpatient in-center hemodialysis (3 times per week), and are hyporesponsive to erythropoiesis-stimulating agents (ESAs) [redacted]
Investigative Sites	Approximately 35 investigative sites in the United States
Planned Number of Subjects	Approximately 50 subjects (n=25 per treatment arm)
Objectives	The primary objective of this study is to evaluate the ability of vadadustat to increase the Hb concentration in subjects with anemia secondary to DD-CKD who are hyporesponsive to ESAs. The secondary objectives of this study are to evaluate the safety and efficacy of vadadustat compared to epoetin alfa in subjects with anemia secondary to DD-CKD who are hyporesponsive to ESAs.
Study Design Overview	This is a Phase 2, randomized, open-label study to evaluate vadadustat for the treatment of anemia in subjects with DD-CKD who are hyporesponsive to ESAs. The study will include a screening period, a study treatment period, and a safety follow-up period as described below. **Screening Period (up to 28 days; Week-4 to Day-4):** The screening period starts at the time the informed consent is signed and will be a maximum of 28 days in duration. The baseline (Day 1) visit will be performed within 28 days of the start of screening and a minimum of 4 days must elapse between the last screening visit and the baseline visit (to allow for laboratory test results to be available prior to initiation of study drug administration). Subjects who meet all inclusion and none of the exclusion criteria will be randomly allocated (1:1 ratio) to participate in either the vadadustat treatment arm or the epoetin alfa treatment arm. **Study Treatment Period (Baseline [Day 1] to Week 20):** Study drug treatment will aim to maintain Hb level within target range of 10.0 to 11.0 g/dL. If possible, study visits should be scheduled on the day of the first hemodialysis session of the week to allow for the turnaround time for central lab Hb values (and dose adjustment as needed) before the end of the workweek. • **Vadadustat treatment arm:** Subjects who are randomized to the vadadustat treatment arm will discontinue epoetin alfa and will initiate vadadustat dosing at

	[redacted] on Day 1. Additional information on vadadustat dosing adjustments is provided in the study schematic figure and "Dosage and Regimens" below. • **Epoetin alfa treatment arm:** For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from baseline [Day 1] visit) will be the same dose that they were receiving during the screening period. Epoetin alfa will be administered based on the approved label for adult patients with CKD on dialysis. **Safety Follow-Up Period (Weeks 20 to 24):** The 4-week safety follow-up period starting at Week 20 will be followed by a post-treatment safety assessment conducted at Week 24. **Figure. Schematic of Study Design** 
Study Duration	Individual subjects will participate in the study for up to 28 weeks, including a screening period of up to 4 weeks, a 20-week treatment period, and a 4-week safety follow-up period.
Inclusion Criteria	Subjects must meet all the following inclusion criteria to be eligible for study participation: 1. ≥18 years of age 2. Receiving chronic maintenance in-center hemodialysis (3 times per week) for end-stage renal disease for at least 6 months prior to screening 3. Currently receiving epoetin alfa for anemia [redacted] 4. Two Hb measurements (by central lab analysis) between 8.5 and 10 g/dL during screening 5. Administered intravenous supplemental iron per investigative site's protocol to maintain serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% 6. Folate and vitamin B12 measurements ≥ lower limit of normal during screening 7. Having dialysis adequacy as indicated by K- dialyzer clearance of urea, t- dialysis time, V- volume of distribution of urea (Kt/V) >1.2 8. Understands the procedures and requirements of the study, willing and able to comply with all study procedures, and provides written informed consent and authorization for protected health information disclosure

Exclusion Criteria	Subjects who meet any of the following exclusion criteria will not qualify for entry into the study: 1. Anemia due to a cause other than CKD or subjects with active bleeding or recent blood loss 2. History of sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia 3. Red blood cell (RBC) transfusion within 4 weeks prior to or during screening. 4. Anticipated to recover adequate kidney function to no longer require dialysis 5. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2.0 x upper limit of normal (ULN) during screening. Subjects with a history of Gilbert's syndrome are not excluded 6. Uncontrolled hypertension (defined as confirmed pre-dialysis systolic blood pressure >190 mmHg or diastolic blood pressure >110 mmHg at rest) during screening 7. Severe heart failure during screening (New York Heart Association Class IV) 8. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure, or stroke within 12 weeks prior to or during screening 9. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 8 weeks prior to or during screening 10. History of active malignancy within 2 years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ 11. History of hemosiderosis or hemochromatosis 12. History of prior organ transplantation or scheduled organ transplant (subjects on the kidney transplant waiting list or with a history of failed kidney transplant are not excluded), or prior hematopoietic stem cell or bone marrow transplant; note that corneal transplants and stem cell therapy for knee arthritis are not excluded 13. History of an acute or chronic infection requiring intravenous antibiotics within 4 weeks prior to randomization 14. Hypersensitivity to vadadustat, epoetin alfa, or any of their excipients 15. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to screening 16. Previous participation in this study, previous participation in a Phase 3 study of vadadustat, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PH inhibitor) other than vadadustat 17. Females subjects who are pregnant or breastfeeding; or female subjects of childbearing potential who are unable or unwilling to use an acceptable method of contraception 18. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception 19. Any other reason, which in the opinion of the investigator, would make the subject not suitable for participation in the study
Retesting and Rescreening	**Retesting** Retesting is defined as repeating laboratory tests within the same Screening Period.

	Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 28-day screening period at the investigator's discretion. **Rescreening** Subjects who fail to meet the qualifying criteria for Hb during the initial 28-day screening period may be considered for rescreening at the discretion of the investigator if it is considered that the subject's status has changed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or vitamin B12 values may be considered for rescreening after receiving appropriate replacement therapy. Screening is limited to 3 attempts (initial screening and 2 additional rescreening attempts).
Efficacy Endpoints	The primary endpoint is to evaluate the change in Hb from baseline over time during the treatment period. Secondary endpoints: • Proportion of subjects demonstrating incremental increases in Hb from baseline over time during the treatment period • Proportion of subjects with Hb values within the target range of 10.0-11.0 g/dL during the treatment period • Proportion of subjects receiving epoetin alfa rescue • Proportion of subjects receiving RBC transfusion • Levels of various biomarkers, including C-reactive protein (CRP), hepcidin, and vascular endothelial growth factor (VEGF) • Mean weekly dose of intravenous elemental iron • Maintenance of iron sufficiency (defined as ferritin ≥100 ng/mL and TSAT ≥20%). • Resource utilization
Safety Endpoints	Safety endpoints include the following: • Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL • Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval • AEs and SAEs • Vital sign measurements and clinical laboratory values
Dosage and Regimens	Study drug treatment will aim to maintain Hb level within target range of 10.0 to 11.0 g/dL. Hemoglobin will be monitored throughout the study to determine the dose of study medication (vadadustat or epoetin alfa) that subjects should receive. Hb levels can be measured more frequently based on investigator's clinical judgment. On Day 1, subjects will withhold dosing until it is confirmed which treatment arm (vadadustat or epoetin alfa) they are assigned to. **<u>Dosing Regimen for the Epoetin Alfa Treatment Arm</u>** • For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from baseline/Day 1 visit) will be the same dose that they were receiving during the screening period.

- Epoetin alfa dose will be administered and titrated as clinically indicated based on an individual subject's central laboratory Hb value and the approved label for adult patients with CKD on dialysis.

Dosing Regimen for the Vadadustat Treatment Arm

- Vadadustat dosing (Day 1 to Week 20)
  - Starting dose of vadadustat: [redacted] once daily) starting at baseline (Day 1). The first dose of vadadustat will be administered at the investigative site after other baseline procedures have been completed.
  - Vadadustat dose will be adjustable from Day 1 to Week 20. The vadadustat dose can be up-titrated every 4 weeks or down-titrated more frequently based on the target Hb range of 10.0-11.0 g/dL. [redacted]
  - The vadadustat dose can be titrated (as presented in the "Guidelines for Vadadustat Dose Adjustments" below)
  - After the end of vadadustat treatment at Week 20 (or following early discontinuation of vadadustat), subjects will resume dosing with epoetin alfa (or another ESA), based on the approved label for adult patients with CKD on dialysis.

Guidelines for Vadadustat Dose Adjustments

Vadadustat dose adjustments will be guided by an interactive web response (IWR) system based on the Hb value and programmed Dose Adjustment Algorithms (as presented below).

When adjusting vadadustat dose, investigators should consider Hb rate of rise, rate of decline, and the subject's clinical condition (eg, recent illness, volume depletion, and volume overload). In cases of extenuating clinical circumstances, the investigator may elect to dose outside the IWR system dosing recommendation to maintain the Hb within the target range. In such cases, the clinical circumstances must be documented in the subject's record and IWR system.

- Do not increase the vadadustat dose more frequently than once every 4 weeks. Decreases in vadadustat dose can occur more frequently. Avoid frequent vadadustat dose adjustments.
- If a dose adjustment is required to maintain Hb within the target range (10.0-11.0 g/dL), then increase or decrease the vadadustat dose by 1 tablet.
- If the Hb decreases below 10.0 g/dL, increase the dose of vadadustat by 1 tablet.
- If the Hb exceeds 11.0 g/dL, interrupt vadadustat until Hb decreases to 11.0 g/dL or less, then resume dosing of vadadustat with 1 fewer tablet.

  NOTE: If subject was on 1 tablet prior to interruption, then resume dosing with 1 tablet.
- If the Hb increases rapidly (eg, >1.0 g/dL in any 2-week period or >2.0 g/dL in any 4-week period), decrease the dose of vadadustat by 1 tablet.

Dosing Instructions	**Vadadustat** Subjects assigned to the vadadustat arm will discontinue epoetin alfa and take vadadustat once daily for 20 weeks. All subjects will start with [redacted] administered once daily). [redacted] On Day 1, subjects will take their first dose of vadadustat at the investigative site after other baseline procedures have been completed. Thereafter, vadadustat will be taken once daily in the dialysis centers or on an outpatient basis. Subjects may take vadadustat with or without food. The full dose should be taken at approximately the same time each day. The subject should be instructed to take any oral iron supplements (including multivitamins containing iron), iron containing phosphate binders, or any medication containing iron at least 2 hours before or 2 hours after taking the vadadustat dose. **Epoetin alfa** Epoetin alfa will be administered based on the approved label for adult patients with CKD on dialysis.
Iron Supplementation	Investigators should prescribe iron supplementation (intravenous, oral, or intradialytic) as needed and maintain ferritin ≥100 ng/mL and TSAT ≥20%. **Important:** Because of the potential for oral iron to decrease the bioavailability of vadadustat, vadadustat should not be administered concurrently with an oral iron supplement (including multivitamins containing iron), iron containing phosphate binders, or any medications containing iron. The subject should be instructed to take any of these medications at least 2 hours before or 2 hours after taking the dose of vadadustat.
Rescue Therapy Guidelines	Hemoglobin levels will be monitored throughout the study at scheduled visits and can be measured more frequently based on investigator's clinical judgment. Rescue therapy with RBC transfusion or epoetin alfa are allowed, but not required during the treatment period. The following rescue therapy guidelines are provided to ensure the safety of study subjects and to standardize the use of rescue in the study. In cases of extenuating clinical circumstances, the investigator may elect to dose outside the rescue therapy guidelines to maintain the Hb within the target range. In such cases, the clinical circumstances should be documented in the subject's record. 1. **Red Blood Cell Transfusion:** Investigators should use their investigative site's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, RBC transfusion should be administered as clinically indicated. In less severe instances but where there may be worsening of anemia or moderate to severe symptoms of anemia, RBC transfusions are permitted based on investigator's clinical judgment. Study drug (vadadustat or epoetin alfa) may be continued during the transfusion period. 2. **Epoetin Alfa Rescue Therapy:** Starting at Week 6, subjects in both treatment arms will be allowed (although not required) to have their Hb rescued with epoetin alfa. When possible, a subject on vadadustat should be on maximum dose of vadadustat for 2 weeks prior to epoetin alfa rescue. Epoetin alfa rescue therapy should be administered based on the approved US product label for adult patients with CKD on dialysis. To qualify for epoetin alfa rescue therapy, each of the following conditions must be fulfilled. NOTE: Epoetin alfa rescue therapy should be stopped when Hb is ≥9.0 g/dL. – The subject has experienced a clinically significant worsening of their anemia or symptoms of anemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared to baseline

	– The subject's Hb is confirmed to be <9.0 g/dL – The Hb level decreased >0.5 g/dL from baseline – Reducing the risk of alloimmunization or transfusion-related risks or both is a goal • For the epoetin alfa treatment arm: In addition to meeting the rescue criteria noted above, dosing and administration of epoetin alfa rescue therapy should be based on the approved label for adult patients with CKD on dialysis. • For the vadadustat treatment arm: Epoetin alfa rescue may not be considered until the next study visit if a subject's current vadadustat dose can be increased (ie, if the subject's last vadadustat dose increase was at least 4 weeks earlier and the subject is currently receiving a vadadustat dose of 600 mg/day or less, then vadadustat dose can be increased by 1 tablet to maintain Hb within the target range of 10.0-11.0 g/dL). NOTE: Vadadustat must be temporarily interrupted during epoetin alfa rescue therapy. After epoetin alfa rescue therapy is completed, vadadustat should be resumed and adjusted per the dose adjustment guidelines (see "Dosage and Regimens"). A minimum interval must be observed prior to restarting vadadustat after the last dose of rescue medication, and treatment may be resumed 2 days after last dose of epoetin alfa rescue.
Therapeutic phlebotomy	If a subject's Hb exceeds 14.0 g/dL or the rate of rise of Hb raises concern to the investigator, the subject may be phlebotomized based on the investigator's clinical judgment. The method of phlebotomy will be in accordance with the investigative site's standard clinical practice.
Study Completion, Subject Completion, Discontinuation of Study Drug, or Withdrawal from the Study	NOTE: The need for rescue therapy does not constitute study completion and is not a criterion for subject withdrawal from the study or permanent discontinuation of study drug (vadadustat or epoetin alfa). NOTE: Subjects who permanently discontinue study drug or discontinue prematurely from the study will complete the end-of-treatment (EOT) (Week 20) visit assessments and should participate in the 4-week safety follow-up period and the Week 24 visit assessments. **Study Completion** The study will be considered completed after all enrolled subjects have completed study participation, and the adverse event reporting period has been completed for each enrolled subject. **Subject Completion** A subject will be considered as having completed the study after completing participation in the Week 24 visit (end of the 4-week follow-up period). **Discontinuation of Study Drug** During the study, it is anticipated that subjects may interrupt study drug (vadadustat or epoetin alfa) for any of the following reasons: • Unacceptable toxicity or drug intolerability • Adverse event • Missed dialysis visit • Investigator's discretion • Other reasons

	Unless contraindicated, treatment should be resumed wherever possible and routinely considered at every visit following study drug interruption. Subjects may permanently discontinue study drug (vadadustat or epoetin alfa) for any of the following reasons: • Unacceptable toxicity or drug intolerability • Investigator's discretion • Subject withdraws consent • Subject becomes pregnant • Receipt of kidney transplant • Other reasons
Study Termination/ Individual Study Site Termination	The entire study may be suspended or terminated by the sponsor for safety or other unanticipated reasons or upon request of regulatory agencies. If this occurs, prompt notification will be given to investigators, Institutional Review Boards (IRBs), and regulatory authorities in accordance with regulatory requirements. The investigator must notify the sponsor if the study is terminated by the investigator or the IRB at the site. If the investigator, IRB, or sponsor decides to terminate or suspend the study conduct at an investigative site for safety, non-enrollment, non-compliance with the protocol, or other unanticipated reasons, the above parties will be promptly notified.
Statistical Considerations	This study is exploratory in nature, designed to evaluate the change in Hb from baseline over time during the treatment period. No formal statistical testing will be performed. Summary statistics (mean, median, standard deviation [SD], range, proportion and 95% confidence intervals when appropriate) will be provided, by treatment groups for primary and secondary endpoints.
Sample Size Determination	About 50 subjects (n=25 per treatment arm) are planned for randomization in the study. Sample size has been determined to reflect the exploratory nature of this study.
Internal Safety Assessment	An internal Safety Monitoring Committee (SMC) will review safety data on a regular basis, throughout the course of the study. The details of the SMC will be outlined in a study-specific safety monitoring plan.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
CBC	complete blood count
CKD	chronic kidney disease
C_{max}	maximum concentration observed
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CV	cardiovascular
DD-CKD	dialysis-dependent chronic kidney disease
dL	deciliter
DVT	deep vein thrombosis
ECG	electrocardiogram; electrocardiography
EDC	electronic data capture
EOT	end-of-treatment
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
Hb	hemoglobin
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl hydroxylase
HPMC	hydroxypropyl methylcellulose
ICH	International Council for Harmonization
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IWR	interactive web response

kg	kilogram
Kt/V	k- dialyzer clearance of urea, t- dialysis time, V- volume of distribution of urea
MedDRA	Medical Dictionary for Regulatory Activities
µM	micromolar
MMC	microcrystalline cellulose
mg	milligram
mL	milliliter
NDD-CKD	non-dialysis dependent chronic kidney disease
ng	nanogram
PD	pharmacodynamics(s)
PE	pulmonary embolism
PHD	prolyl 4-hydroxylase domain
PRCA	pure red cell aplasia
PK	pharmacokinetic(s)
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SMC	Safety Monitoring Committee
SV1	screening visit 1
SV2	screening visit 2
TEAE	treatment-emergent AE
TIBC	total iron binding capacity
TSAT	transferrin saturation
ULN	upper limit of normal
US	United States
USA	United States of America
VEGF	vascular endothelial growth factor

4 BACKGROUND

4.1 Chronic Kidney Disease and Renal Anemia

Chronic kidney disease (CKD), defined as the presence of kidney damage or a decreased level of kidney function, is a major public health problem worldwide.

The prevalence and severity of renal anemia in CKD increases as renal function deteriorates. As CKD progresses, the combined effect of decreased red blood cell (RBC) production from lower erythropoietin (EPO) signaling, increased rate of RBC destruction, and reduced iron availability to the bone marrow results in the increased prevalence and severity of anemia. Anemia generally exists when hemoglobin (Hb) is less than 13.0 g/dL in men or less than 12.0 g/dL in women. Three principal factors contribute to the development of anemia as CKD progresses:

- Peritubular fibroblasts, a type of cell in the kidney, are designed to sense the amount of oxygen carried by the blood. These cells secrete EPO to adjust the production of RBCs by the bone marrow and maintain circulating oxygen levels at normal physiologic levels. As kidney disease progresses, the number of peritubular fibroblasts is reduced and EPO secretion is significantly decreased. This decline in EPO leads to a reduction in RBC production.
- On average, the RBCs in CKD patients have a shorter lifespan (approximate lifespan of 70 days) compared with the RBCs in healthy people (approximate lifespan of 90 to 120 days). Such a condition leads to increased RBC production in CKD patients to maintain normal physiologic levels.
- The availability of iron to the bone marrow is impaired. Iron is a required component in the formation of Hb, and is essential for the transport of oxygen to the tissues of the body.

The main impact of anemia on organ function is reduced oxygen delivery to tissues leading to a constellation of symptoms including fatigue, shortness of breath, and exercise intolerance (Stauffer 2014). In these patients, compensatory changes occur in cardiac structure and function including an increase in cardiac output and the development of left ventricular hypertrophy and eventually the development of heart failure (Metivier 2000). Other consequences from anemia in CKD patients include impaired cognitive function, sleep disorders, and depressed immune function which can impact the quality of life in patients (Iseki 2007; NICE 2011). Overall, anemia contributes to a poorer prognosis in patients with CKD (Iseki 2007; Nurko 2006).

4.2 Erythropoiesis-Stimulating Agents (ESAs) as Treatment for Renal Anemia and Associated Risks

Erythropoiesis-stimulating agents (ESAs), including epoetin alfa and darbepoetin alfa administered either intravenously or subcutaneously, along with iron therapy are currently the standard of care for treating anemia in patients with CKD. Treatment with exogenous recombinant ESAs can raise Hb, relieve symptoms, and reduce the complications of anemia including avoiding RBC transfusions which carry the risks of infection, iron overload, and impact candidacy for kidney transplantation.

Several large prospective randomized controlled studies in patients with CKD (glomerular filtration rate [GFR] categories G3a to G5) have suggested an increased risk of death and cardiovascular (CV) events when targeting higher Hb levels (Besarab 1998; Drueke 2006; Pfeffer 2009a; Pfeffer 2009b; Singh 2006). Additional analyses suggest that the ESAs

themselves may be causative of the increased frequency of adverse events and not the Hb level, and is supported by studies in CKD patients on dialysis with naturally occurring higher Hb levels and no increase in CV events (Solomon 2010; Szczech 2008; Goodkin 2011). The risks identified with ESAs from these studies have led to changes in prescribing information and clinical practice guidelines. In the US, the mortality and CV risks associated with ESAs are outlined in a black-box warning in the prescribing information of ESAs with a recommendation to use the lowest dose possible to avoid transfusions.

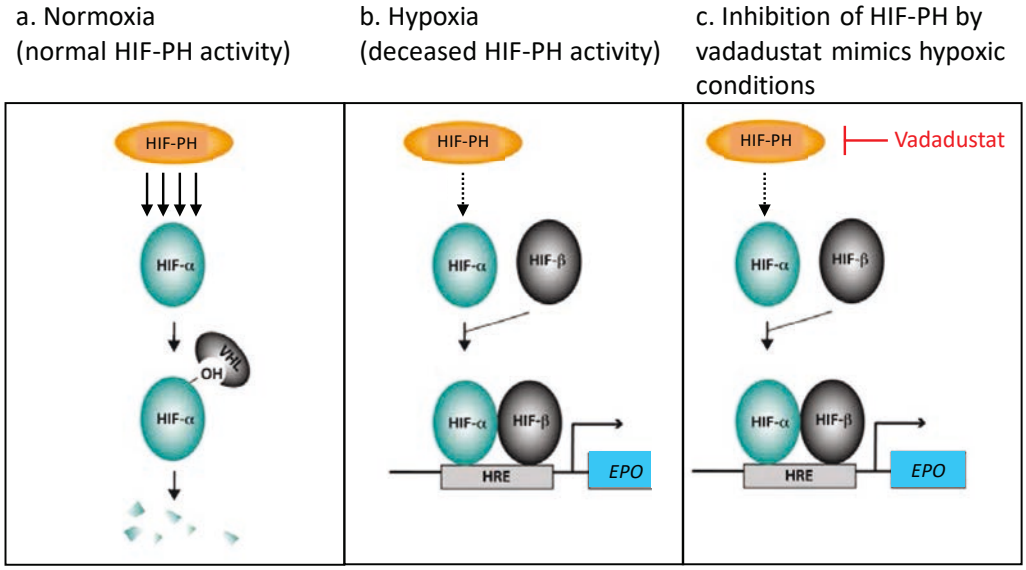
The risks associated with currently available recombinant ESAs highlight the need for novel therapies that may potentially minimize or avoid such risks and slow CKD progression.

4.3 Hypoxia-Inducible Factor and Hypoxia-Inducible Factor Prolyl-Hydroxylase Inhibitors

Hypoxia-inducible factor (HIF) is the primary regulator of the production of RBC and acts by simulating the body's physiologic response to hypoxia (Haase 2013). HIF proteins are consistently produced and their levels in cells are adjusted by the activity of the HIF-PH enzymes.

During hypoxic conditions, a controlled and coordinated adaptive erythropoietic response occurs whereby, HIF-PH enzyme activity decreases in the kidney and liver, leading to stabilization and increase in intracellular levels of HIF-α proteins. When HIF-α is stabilized, it travels to the nucleus of the cell, where it binds to the protein HIF-β (Figure 1). Dimerized HIF-α and HIF-β proteins bind to a promotor on the *EPO* gene to induce an increase in the production of EPO protein and other proteins. Therefore, stabilization of HIF proteins leads to an increased production of EPO and mobilization of iron to the bone marrow, increasing Hb and RBC production. Inhibitors of HIF-PH enzymes (such as vadadustat) decrease the degradation of HIFs thus mimicking physiological conditions at low oxygen levels.

Figure 1 Mechanism of Action of Vadadustat



a. Normoxia: HIF-PH hydroxylates HIF-α (high level of hydroxylation depicted by 4 arrows), targeting HIF-α for degradation in a VHL (von Hippel-Lindau)-dependent manner, and leading to low levels of HIF-α.
b. Hypoxia: HIF-PH activity is decreased (1 dashed arrow). Stabilized HIF-α travels to the cell nucleus, dimerizes with HIF-β, and binds to hypoxia response elements (HREs) that control various target genes, including activation of the *EPO* gene leading to increased production of EPO protein.
c. By inhibiting HIF-PH activity, vadadustat mimics the physiological effects of hypoxia, leading to increased production of EPO protein and mobilization of iron in the bone marrow, subsequently increasing the level of Hb and RBC production.

Adapted from Bigham 2014.

4.4 Description and Mechanism of Action of Vadadustat

Please see the vadadustat Investigator's Brochure for additional discussion and information for the following section.

Vadadustat is a synthetic, orally bioavailable, small molecule currently being developed for the treatment of anemia associated with CKD. Vadadustat works by inhibiting PHD enzymes (Figure 1), leading to stabilization and increased levels of HIF-α, and improved production of Hb and RBCs, while maintaining normal levels of EPO in patients.

Available clinical data suggests several potential safety and efficacy advantages over current injectable recombinant ESA therapy for the treatment of renal anemia:

- *Vadadustat increases and maintains Hb levels in CKD patients with anemia:* Two Phase 2 studies in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) demonstrated that vadadustat significantly increased Hb levels. In the first study (AKB-6548-CI-0005), vadadustat was shown to raise Hb in a dose-dependent manner compared to baseline and across all treatment arms ($p < 0.0001$). In the second study (AKB-6548-CI-0007), vadadustat effectively increased Hb while minimizing Hb excursions ≥13.0 g/dL with only 4.3% of patients who received vadadustat experiencing Hb excursion ≥13.0 g/dL. In addition, a third Phase 2 study (AKB-6548-CI-0011) demonstrated the desired outcome of maintaining stable Hb levels in hemodialysis patients who were converted from existing ESA therapy to vadadustat. Only one subject had a single Hb excursion of 13.1 g/dL.

- *Vadadustat restores the normal diurnal variation of EPO:* Instead of binding directly to and saturating the EPO receptor for prolonged periods, as is the case with current injectable ESA therapies, vadadustat acts by simulating the body's natural response to hypoxia by stabilizing HIF-α. Vadadustat allows for an enhancement in the normal diurnal variation in EPO concentration without continuous elevation of EPO levels.
- *Oral, once-daily dosing:* As demonstrated in NDD-CKD patients (Phase 2b Study AKB-6548-CI-0007), vadadustat offers flexible once-daily oral dosing that provides a more gradual and reliable means of Hb response and maintenance. This was also demonstrated in the Phase 2 study AKB-6548-CI-0011 in DD-CKD patients, where vadadustat maintained stable Hb levels in patients converting from ESA therapy. Vadadustat also offers improved convenience for patients as compared to injectable ESAs. This convenience may increase access to anemia therapy and improve patient compliance.
- *Improved mobilization of iron supply to the bone marrow for RBC production:* In clinical studies, vadadustat has demonstrated improved iron mobilization as reflected by a decrease in hepcidin and ferritin levels and an increase in total iron binding capacity (TIBC). Thus, unlike injectable recombinant ESAs which do not increase iron mobilization, vadadustat offers the added potential benefit of reducing the amount of supplemental iron required by anemic CKD patients. The potential for an intravenous iron sparing effect of vadadustat will be assessed in the global Phase 3 INNO$_2$VATE clinical studies in DD-CKD patients.
- *Differentiated safety profile:* Vadadustat's mechanism of action offers the potential opportunity to reduce the risk for CV and thrombotic events relative to injectable ESAs since CV risks have been associated with supraphysiological increases in EPO levels and excessive Hb fluctuations or excursions or both (McCullough 2013). The incidence of CV adverse events on vadadustat as compared with ESAs will be assessed in the global Phase 3 clinical studies. Furthermore, the risk of pure red cell aplasia (PRCA) observed with recombinant ESAs is not expected with vadadustat.

4.5 Summary of Clinical Experience

Please see the vadadustat Investigator's Brochure for additional information.

To date, the efficacy, safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of vadadustat have been characterized in 10 completed Phase 1 studies (9 studies in healthy volunteers and one study in subjects undergoing chronic hemodialysis), 3 completed Phase 2a studies in NDD-CKD subjects, one Phase 2b study in NDD-CKD, and one Phase 2 study in subjects with DD-CKD. In these studies, vadadustat was administered to 548 subjects, including 200 healthy subjects, 106 subjects with DD-CKD, and 242 subjects with NDD-CKD.

Key findings from two Phase 2 clinical studies of vadadustat in NDD-CKD and DD-CKD are presented below.

Study AKB-6548-CI-0007

This was a double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of vadadustat over 20 weeks of dosing in 210 subjects (n=138 received vadadustat and n=72 received placebo) with CKD GFR categories 3-5 (Pergola 2016). Subjects were enrolled into 1 of 3 groups and randomized (2:1) to once daily vadadustat or placebo:

- Group 1: ESA naïve with Hb ≤10.5 g/dL

- Group 2: Previously treated with ESA with hemoglobin ≤10.5 g/dL
- Group 3: Actively treated with ESA with Hb ≥9.5 and ≤12.0 g/dL

The primary endpoint was the percent of subjects with either a mean Hb of ≥11.0 g/dL or an increase in Hb by ≥1.2 g/dL from baseline.

At baseline, the mean age was 66 years, about 75% of subjects had diabetes mellitus, and the mean estimated GFR (eGFR) was 25 mL/min/1.73 m^2. The results from the study demonstrated that about 54.9% of vadadustat-treated subjects compared to 10.3% of placebo-treated subjects met the primary endpoint (p=0.0001). Only 4.4% of subjects in the vadadustat group had Hb excursion ≥13.0 g/dL. Group 3 placebo-treated subjects experienced a decline in the mean Hb within the first 2 weeks, whereas subjects randomized to vadadustat maintained a stable Hb throughout the study. Increases in Hb in the vadadustat group were associated with an increase in reticulocytes and TIBC, and a decrease in serum hepcidin and ferritin. There was no difference between the vadadustat and placebo groups in vascular endothelial growth factor (VEGF) levels during the study.

Vadadustat was generally well-tolerated, and the number of subjects who experienced at least one treatment-emergent AE (TEAE) in the vadadustat and placebo groups was comparable (74.6% versus 73.6%, respectively). More subjects experienced SAEs in the vadadustat group than in the placebo group (23.9% and 15.3%, respectively). This difference was primarily due to a greater incidence of renal-related SAEs in the vadadustat treatment group (vadadustat 9.4% versus placebo 2.8%), however, the number of subjects requiring dialysis (an objective measure of the severity of renal disease) was similar in the 2 treatment groups (vadadustat 8.0% versus placebo 9.7%). In addition, no trends in serum creatinine levels were observed between the vadadustat and placebo groups. Overall, the number of AEs for renal and urinary disorders was balanced (vadadustat 14.5% versus placebo 13.9%). Therefore, the disparity in renal SAEs was likely related to variability in reporting between investigators. Of the commonly reported events (reported in ≥5% of subjects in either treatment group), diarrhea, nausea, hyperkalemia, and hypertension were reported more frequently in the vadadustat than the placebo group. There were 3 deaths among the vadadustat-treated subjects (3/138; 2.2%).

Study AKB-6548-CI-0011

This was a multi-center, open-label, 16-week trial to assess the Hb response, safety, and tolerability of vadadustat in subjects with DD-CKD. The trial enrolled 94 subjects receiving hemodialysis (Hb level from 9 to 12 g/dL), who were maintained on ESAs prior to study entry. Subjects were converted from ESA to vadadustat, and assigned to 1 of 3 dose cohorts: 300 mg once daily; 450 mg once daily; or 450 mg three times weekly. For each dose cohort, the mean Hb level at study entry was compared to the average at Weeks 7 and 8, and to the average at Weeks 15 and 16. During the first 8 weeks of this study, subjects remained on the prescribed starting dose, or decreased if necessary to control Hb. Beginning at Week 8, the dose of vadadustat could be increased or decreased to maintain Hb levels as needed. Intravenous (IV) iron use was allowed.

The underlying demographics and profile of these CKD subjects were well-balanced across the 3 cohorts, and reflective of the DD-CKD population in the United States as reported in the literature. At baseline, the mean age was 58 years, average time on dialysis was 4.6 years, and the most common cause of end-stage renal disease was diabetes mellitus and/or hypertension.

Baseline Hb levels were similar (10.4 to 10.6 g/dL) in all 3 cohorts and the serum ferritin levels indicated that the subjects were iron replete at study entry and throughout the study.

The trial achieved its primary endpoint of maintaining stable Hb levels over 16 weeks, across all 3 cohorts converting from ESAs to vadadustat. Consistent with previous studies, all three starting dose regimens improved iron mobilization, as reflected by increases in TIBC and serum iron, and decreases in serum ferritin and hepcidin levels. Only one subject in the 300 mg once daily starting dose cohort had a single hemoglobin excursion to 13.1 g/dL.

Vadadustat was generally well-tolerated across the 3 treatment groups. There were no apparent differences in the type or frequency of the AEs that were reported across the 3 dosing groups. The type and frequency of SAEs were consistent with events that have been described in patients with DD-CKD with multiple comorbidities. No SAEs were reported by the investigators as related to vadadustat. No deaths, strokes, or transient ischemic attacks were reported.

Summary

Overall, oral administration of vadadustat has been well tolerated in clinical studies. The frequency and types of SAEs in Akebia-sponsored trials (Phase 1 and 2) have been consistent with those expected in a population with chronic renal failure. The most commonly reported AEs included nausea and diarrhea, and generally, these events have been mild to moderate in severity, non-serious, and resolved on vadadustat therapy. In some cases, these AEs lead to discontinuation of vadadustat therapy.

Vadadustat has also demonstrated a clear and consistent dose-response pattern in both PK and PD with sequential increases in EPO, reticulocytes, and Hb. The hematologic response has been accompanied by dose-responsive increase in iron mobilization (ie, decreases in hepcidin and ferritin, and an increase in TIBC). Together, these effects have stimulated an increase in reticulocytes and Hb, and such a combination of effects indicates that vadadustat increases erythropoiesis through a coordinated response. Furthermore, this is achieved with a modest increase in the daily peak level of EPO, which returns to baseline prior to the subsequent dose (in a manner that mimics the physiologic diurnal response in healthy individuals).

Vadadustat is eliminated from the body by dual routes (renal and fecal), elimination, both renal and fecal, which makes the compound appropriate for use in patients with CKD. Given the dual routes of elimination, it is unlikely that vadadustat will accumulate in patients with CKD.

Furthermore, in a clinical study conducted to evaluate the effect of hemodialysis on the exposures to vadadustat, the hemodialysis procedure did not impact the exposures of vadadustat or its metabolites, indicating that vadadustat can be administered irrespective of the dialysis session.

Collectively, these data support the ongoing clinical development of vadadustat as an orally bioavailable agent for the treatment of anemia secondary to CKD, and the safety and efficacy of vadadustat in subjects with DD-CKD and NDD-CKD are currently being evaluated in global Phase 3 studies (PRO_2TECT-Correction, PRO_2TECT-Conversion, $INNO_2$VATE-Correction, and $INNO_2$VATE-Conversion; ClinicalTrials.gov Identifier: NCT02648347, NCT02680574, NCT02865850, and NCT02892149, respectively).

4.6 Potential Benefits and Risks

Please see the vadadustat Investigator's Brochure for additional information.

Vadadustat offers the potential of flexible oral dosing that is easier to titrate than injectable hormone ESAs. The enhancement in the normal diurnal variation in EPO concentration without continuous elevation of EPO levels may avoid the overshoots and fluctuations in Hb levels seen with currently available injectable ESAs and provide for a controlled, steady rise in Hb concentration. This less aggressive approach to modifying the Hb concentration may be of benefit based on the suggestion from US Food and Drug Administration (US FDA) that fluctuations in Hb concentrations, rapidly increasing Hb levels, and overshoots of the target level are associated with an increased risk of CV events (Unger 2007; Unger 2010).

In addition, HIF activation is associated with increased expression of ferroportin and transferrin and decreased expression of hepcidin (Liu 2012; Peyssonnaux 2007; Tacchini 1999). These changes in iron biomarkers are consistent with enhanced iron mobilization and utilization to promote hemoglobin synthesis and erythropoiesis. In the Phase 1b multiple-ascending-dose study (AKB-6548-CI-0002), a prominent effect on iron metabolism was noted with the dosing of vadadustat, including a dose responsive increase in TIBC, and decreases in hepcidin and ferritin. A similar pattern was observed in the Phase 2a and Phase 2b studies AKB-6548-CI-0003, AKB-6548-CI-0004, AKB-6548-CI-0005, AKB-6548-CI-0007, and AKB-6548-CI-0011.

In preclinical safety studies, the main findings originated from an exaggerated pharmacological response, including increased erythropoiesis and hematocrit, and at high doses, blood hyperviscosity. These findings were reproducible across species and studies, were dose-dependent and showed reversibility.

In the completed clinical studies, vadadustat has been generally well-tolerated with no apparent differences among various dose groups and control groups, and consistent with the expected safety profile based on the evaluated patient populations. The AEs most frequently assessed by investigators as related to vadadustat and which occurred more frequently in subjects who received vadadustat versus placebo are nausea and diarrhea. Generally, these events have been mild to moderate in severity, non-serious, and resolved on vadadustat therapy, although these events led to discontinuation of vadadustat in some subjects.

4.7 DD-CKD Patients Hyporesponsive to ESAs

Although renal anemia in patients undergoing chronic hemodialysis treatment is generally treated with ESAs and iron supplements, there is a significant proportion of such patients who cannot achieve the target Hb range or they require persistently high doses of ESA to achieve the Hb target (Luo 2016). Such hyporesponsiveness to ESAs has been shown to be associated with poor patient outcomes, including higher mortality and a greater rate of missed hemodialysis treatments (Brookhart 2010; Inrig 2012; Kainz 2010; Kalantar–Zadeh 2009; Kilpatrick 2008; Luo 2016; McCullough 2013; Okazaki 2014; Weinhandl 2011). Moreover, because missed dialysis treatments frequently result in hospitalizations, it is likely that ESA hyporesponsiveness also has economic implications for health insurers and taxpayers beyond the management of a patient's anemia.

The mechanisms underlying ESA hyporesponsiveness have not been delineated, but various factors have been associated with a diminished response to ESAs including inflammatory response (eg, increased levels of the inflammatory biomarkers hepcidin and C-reactive protein [CRP]), iron deficiency (absolute or functional), inadequate vitamin D, an impaired nutritional

state, hyperthyroidism, low dialysis adequacy, and underlying illnesses or infections (Ganz 2016; Icardi 2013; Inrig 2011; Kalantar-Zadeh 2003; Lee 2003; Locatelli 2006; Lopez-Gomez 2008; Luo 2016; Movilli 2001).

Unlike ESAs, clinical studies of vadadustat have demonstrated correction and maintenance of Hb with improved iron mobilization following vadadustat administration as reflected by a decrease in hepcidin and ferritin levels and an increase in TIBC (Studies AKB–6548–CI–0003, AKB-6548-CI-0004, AKB-6548-CI-0005, AKB-6548-CI-0007, and AKB-6548-CI-0011; Haase 2015; Haase 2016b; Pergola 2016). In addition, post ad hoc analysis of results from Studies AKB-6548-CI-0007 and AKB-6548-CI-0011 demonstrated that the Hb response and vadadustat dose requirement for Hb maintenance were independent of the level of baseline markers of systemic inflammation (ie, CRP and hepcidin) and were not correlated with a patient's prior ESA dose (Haase 2016a; Haase 2016c). Thus, vadadustat may offer a new treatment option for this underserved patient population.

The ongoing, global, Phase 3 open-label, randomized trial evaluating vadadustat versus darbepoetin alfa in patients with DD-CKD ($INNO_2VATE$-Conversion; ClinicalTrials.gov Identifier: NCT02892149), allows the inclusion of subjects who could be characterized as ESA hyporesponsive, among a broader range of subjects who would not be characterized as ESA hyporesponsive.

The present study is designed to specifically assess the ability of vadadustat to increase the Hb concentration in subjects with anemia secondary to DD-CKD who are hyporesponsive to ESAs.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate the ability of vadadustat to increase the Hb concentration in subjects with anemia secondary to DD-CKD who are hyporesponsive to ESAs.

The primary endpoint is to evaluate the change in Hb from baseline over time during the treatment period.

5.2 Secondary Objectives and Endpoints

The secondary objectives of this study are to evaluate the safety and efficacy of vadadustat compared to epoetin alfa in subjects with anemia secondary to DD-CKD who are hyporesponsive to ESAs.

Secondary endpoints:

- Proportion of subjects demonstrating incremental increases in Hb from baseline over time during the treatment period
- Proportion of subjects with Hb values within the target range of 10.0-11.0 g/dL during the treatment period
- Proportion of subjects receiving epoetin alfa rescue
- Proportion of subjects receiving RBC transfusion
- Levels of various biomarkers, including CRP, hepcidin, and vascular endothelial growth factor (VEGF)
- Mean weekly dose of intravenous elemental iron
- Maintenance of iron sufficiency (defined as ferritin ≥100 ng/mL and transferrin saturation [TSAT] ≥20%).
- Resource utilization

Safety endpoints in this study include the following:

- Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
- Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
- AEs and SAEs
- Vital sign measurements and clinical laboratory values

6 STUDY DESIGN

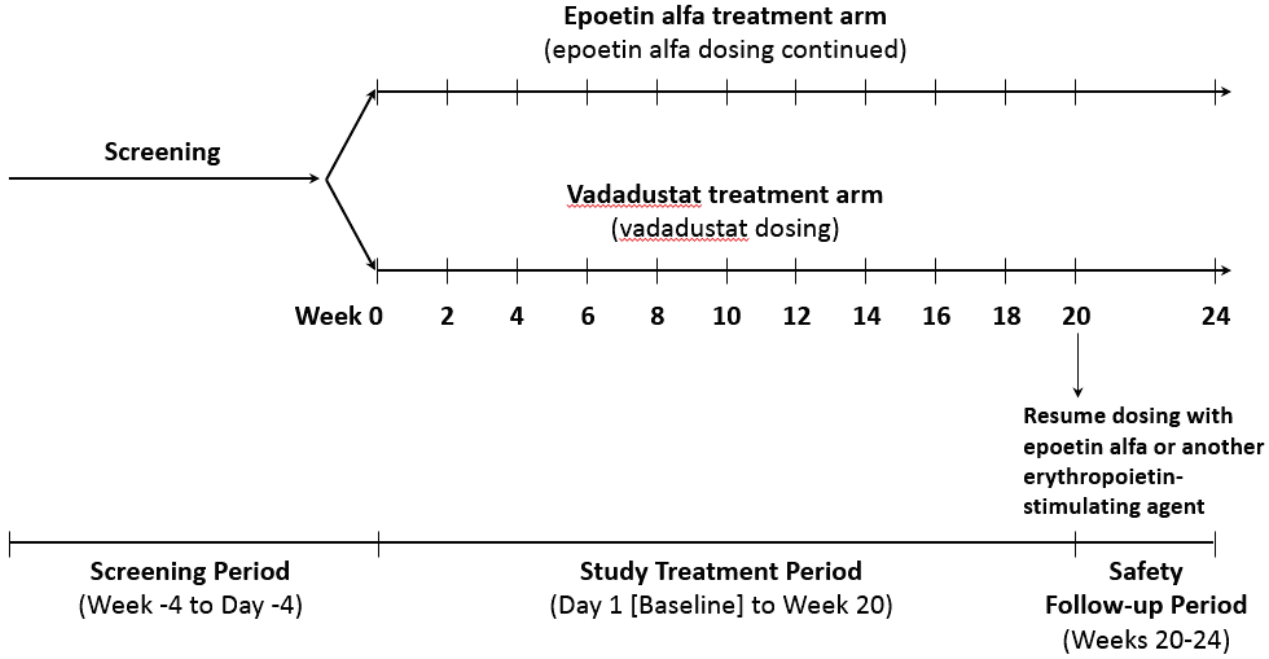
6.1 Study Design

This is a Phase 2, randomized, open-label study to evaluate vadadustat for the treatment of anemia in subjects with DD-CKD who are hyporesponsive to ESAs. Approximately 50 subjects (n=25 subjects per treatment arm) will be enrolled at approximately 35 investigative sites in the United States.

The study population will consist of subjects with DD-CKD who are ≥18 years of age, receiving chronic, maintenance, in-center hemodialysis on an outpatient basis (3 times per week) for end-stage renal disease and for at least 6 months prior to screening, and are hyporesponsive to ESAs [redacted]

As presented in Figure 2, the study includes a screening period (up to 28 days; Week-4 to Day-4), a study treatment period (from Day 1 to Week 20), and a safety follow-up period (Week 20-24). Therefore, individual eligible subjects will participate in the study for up to 28 weeks. Additional information about each of these study periods is provided below, and clinical and safety assessments will be performed as indicated in Appendix A.

Figure 2 Schematic of the Study Design



Screening Period (Week -4 to Day -4):

The screening period starts at the time the informed consent is signed and will be a maximum of 28 days in duration. The baseline visit on Day 1 will be performed within 28 days of the start of screening and a minimum of 4 days must elapse between the last screening visit and the baseline visit.

Subjects who meet all inclusion and none of the exclusion criteria will be randomly allocated (1:1 ratio) using the interactive web response (IWR) system to participate in either the vadadustat or epoetin alfa treatment arm. Permuted block randomization will be used to assign subjects to treatment.

Study Treatment Period (Baseline [Day 1] to Week 20):

Study drug treatment will aim to maintain Hb level within target range of 10.0 to 11.0 g/dL.

- **Vadadustat treatment arm**: Subjects who are randomized to the vadadustat treatment arm will discontinue epoetin and will initiate vadadustat dosing at [redacted] on Day 1. Additional information on vadadustat dosing adjustments is provided in Section 8.3.5.
- **Epoetin alfa treatment arm**: Subjects who are randomized to the epoetin alfa treatment arm will continue to receive epoetin alfa at the same dose that they were receiving during the screening period. Epoetin alfa dose can be titrated as clinically indicated; and additional information is provided in Section 8.3.4.

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

The 4-week safety follow-up period starting at Week 20 will be followed by a post-treatment safety assessment conducted at Week 24.

Internal Safety Assessment

An internal Safety Monitoring Committee (SMC) will review safety data on a regular basis, throughout the course of the study. The details of the SMC will be outlined in a study-specific safety monitoring plan.

6.2 Rationale for Study Design

The primary objective of this study is to evaluate the ability of vadadustat to increase the Hb concentration in subjects with anemia secondary to DD-CKD who are hyporesponsive to ESAs. In this study, epoetin alfa has been chosen as an active comparator as it is marketed and available globally, has an extensive safety profile, and has been the standard of care in many hemodialysis centers, including DaVita dialysis centers in the US. Since the study will be conducted mostly at DaVita dialysis centers in the US, a single active comparator epoetin alfa has been selected, thereby reducing variability and simplifying trial logistics.

In a previous study (AKB-6548-CI-0011), subjects with DD-CKD who were directly switched from ESA to vadadustat achieved stable levels of Hb over 16 weeks. This study also demonstrated improvement of iron mobilization, as reflected by increases in TIBC and serum iron, and decreases in serum ferritin and hepcidin levels.

The present study is to apply a similar design to switch subjects from their current dose of ESA to vadadustat. Subjects who are randomized to the direct switching arm will have an initial vadadustat dose of [redacted], with the flexibility of increasing or decreasing the dose level based on Hb response, which will be closely monitored throughout the study.

The study design also includes a comprehensive vadadustat dose adjustment guideline and epoetin alfa rescue algorithm to ensure Hb can be maintained within the target range of 10.0-11.0 g/dL (see Sections 8.3.5 and 8.3.10).

[redacted]

[redacted]

6.3 Dose Justification

To date, vadadustat has been evaluated in patients with DD-CKD and NDD-CKD. In the present Phase 2, open-label, study of ESA hyporesponsive subjects, an initial dose of [redacted] along with a dose range of [redacted], is planned.

[redacted]

In the ongoing, global, Phase 3 open-label, randomized trial evaluating vadadustat versus darbepoetin alfa in subjects with DD-CKD (INNO$_2$VATE-Conversion; ClinicalTrials.gov Identifier: NCT02892149), [redacted]

[redacted]

[redacted]

Vadadustat demonstrated dose-proportional PK and achieved serum EPO concentrations that are considered physiologic and below exposures achieved with injectable ESAs. A higher incidence of gastrointestinal AEs (e.g., nausea, diarrhea, abdominal pain) was observed in groups treated with [redacted] compared with lower vadadustat doses or placebo. Most AEs were mild, short-lived (1 or 2 days), and assessed as unrelated by investigators. No AEs led to study withdrawal, and no serious AEs were reported. In addition, there were no clinically meaningful changes or abnormalities in vital signs, safety laboratory studies, or ECG parameters.

In addition, the mean anticipated maximum concentration observed (C_{max})and area under the curve (AUC) at steady state for the 750 mg once daily dose are expected to be approximately 20% higher than those seen with the 600 mg once daily dose, previously tested in DD-CKD and NDD-CKD patient populations.

A vadadustat dosing algorithm designed to maintain Hb in a predictable and controlled manner while minimizing abrupt increases or excessive rises in Hb levels is being utilized in the global Phase 3 studies. In the present study, frequent Hb monitoring and use of the vadadustat dosing algorithm will be implemented to mitigate the potential risk of a rapid Hb rise. Furthermore, the protocol specifies that phlebotomy may be considered in the setting of high Hb levels (>14 g/dL) or a high Hb rate of rise, based on the Investigator's judgment. Lastly, the Phase 2b NDD-CKD study (CI-0007) demonstrated that cessation of treatment resulted in prompt reduction in mean Hb to baseline values.

Given that vadadustat only results in physiologic increases in erythropoietin—as opposed to pharmacologic increases following administration of recombinant ESAs—it is anticipated that the beneficial effect of HIF stabilization with vadadustat will be related to improvements in iron mobilization to the bone marrow and promotion of erythropoiesis, if observed in this ESA hyporesponsive patient population. Conversely, to minimize the possibility for sudden declines in Hb in the vadadustat treatment arm, frequent Hb monitoring, and guidance for rescue therapy (Epoetin Alfa Rescue Therapy and/or Red Blood cell transfusions) are provided.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 General Criteria

To be eligible for this study, a subject (or their legally acceptable representative) must provide valid informed consent and must meet the following criteria. Study procedures (including screening tests) may not be performed until after the informed consent has been legally signed.

7.2 Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for study participation:

1. ≥18 years of age
2. Receiving chronic maintenance in-center hemodialysis (3 times per week) for end-stage renal disease for at least 6 months prior to screening
3. Currently receiving epoetin alfa for anemia [redacted]
4. Two Hb measurements (by central lab analysis) between 8.5 and 10 g/dL during screening
5. Administered intravenous supplemental iron per investigative site's protocol to maintain serum ferritin ≥100 ng/mL and TSAT ≥20%
6. Folate and vitamin B12 measurements ≥ lower limit of normal during screening
7. Having dialysis adequacy as indicated by k- dialyzer clearance of urea, t- dialysis time, V- volume of distribution of urea (Kt/V) >1.2
8. Understands the procedures and requirements of the study, willing and able to comply with all study procedures, and provides written informed consent and authorization for protected health information disclosure

7.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not qualify for entry into the study:

1. Anemia due to a cause other than CKD or subjects with active bleeding or recent blood loss
2. History of sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia
3. Red blood cell (RBC) transfusion within 4 weeks prior to or during screening
4. Anticipated to recover adequate kidney function to no longer require dialysis
5. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2.0 x upper limit of normal (ULN) during screening. Subjects with a history of Gilbert's syndrome are not excluded
6. Uncontrolled hypertension (defined as confirmed pre-dialysis systolic blood pressure >190 mmHg or diastolic blood pressure >110 mmHg at rest) during screening
7. Severe heart failure during screening (New York Heart Association Class IV)

8. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure, or stroke within 12 weeks prior to or during screening
9. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 8 weeks prior to or during screening
10. History of active malignancy within 2 years prior to or during screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ
11. History of hemosiderosis or hemochromatosis
12. History of prior organ transplantation or scheduled organ transplant (subjects on the kidney transplant wait-list or with a history of failed kidney transplant are not excluded), or prior hematopoietic stem cell or bone marrow transplant; note that corneal transplants and stem cell therapy for knee arthritis are not excluded
13. History of an acute or chronic infection requiring intravenous antibiotics within 4 weeks prior to randomization
14. Hypersensitivity to vadadustat, epoetin alfa, or any of their excipients
15. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to screening
16. Previous participation in this study, previous participation in a Phase 3 study of vadadustat, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PH inhibitor) other than vadadustat
17. Females subjects who are pregnant or breastfeeding; or female subjects of childbearing potential who are unable or unwilling to use an acceptable method of contraception (see Section 9.2.4)
18. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception (see Section 9.2.4)
19. Any other reason, which in the opinion of the investigator, would make the subject not suitable for participation in the study

7.4 Retesting and Rescreening

7.4.1 Retesting

Retesting is defined as repeating laboratory tests within the same Screening Period.

All screening laboratory tests, including any repeat measurements, must be performed within the 28-day screening window with a minimum of 4 days between the last qualifying repeat measurement and the baseline visit on Day 1 (see Section 9.1).

Subjects who initially fail to qualify for the study based on laboratory test results may have their laboratory value retested once for each laboratory parameter within the 28-day screening period, at the investigator's discretion.

Retesting within the screening period does not constitute rescreening; however, if retesting falls outside of the screening period, it should be considered a rescreen (see Section 7.4.2).

For eligibility purposes, if Hb at screening visit 1 (SV1) is 10.0 to 10.5 g/dL, 1 retest complete blood count (CBC) should be performed prior to SV2. If the retest Hb is ≥10.0 g/dL, the subject should not proceed with SV2. If the Hb at SV1 is >10.5 g/dL, the subject should not proceed with any further screening procedures at that time.

7.4.2 Rescreening

Subjects who fail to meet the qualifying criteria for Hb may be considered for rescreening outside of the initial 28-day screening period at the discretion of the investigator, if it is considered that the subject's status has changed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low ferritin, TSAT, folate, or vitamin B12 values may be considered for rescreening after receiving appropriate replacement therapy.

Screening is limited to 3 attempts (the initial screening and 2 additional rescreening attempts). Subjects who fail to qualify for the study at the initial screening visit will receive a new subject number for each rescreening attempt. If rescreened, the subject will also sign a new informed consent form and will repeat all screening procedures for each rescreening attempt.

7.5 Study Completion, Study Termination, and Individual Study Site Termination

7.5.1 Study Completion

The study will be considered completed after all enrolled subjects have completed study participation, and the AE reporting period has been completed for each enrolled subject (see Section 10.3.1 for information regarding the AE reporting period).

7.5.2 Study Termination

The entire study may be suspended or terminated by the sponsor for safety or other unanticipated reasons or upon request of regulatory agencies. If this occurs, prompt notification will be given to investigators, Institutional Review Boards (IRBs), and regulatory authorities in accordance with regulatory requirements.

Criteria for premature study termination or suspension are detailed in Section 14.1.

7.5.3 Individual Study Site Termination

Study participation may be suspended or terminated at an individual investigational site for various reasons.

The investigator must notify the sponsor if the study is terminated by the investigator or the IRB at the site. If the investigator, IRB, or sponsor decides to terminate or suspend the study conduct at an investigative site for safety, non-enrollment, non-compliance with the protocol, or other unanticipated reasons, the above parties will be promptly notified.

Criteria and procedures for premature termination or suspension of an investigational site are detailed in Section 14.2 and Section 14.3.

7.6 Subject Completion and Individual Subject Discontinuation

NOTE: The need for rescue therapy does not constitute study completion and are not criteria for subject withdrawal from the study or permanent discontinuation of study drug (vadadustat or epoetin alfa).

7.6.1 Subject Completion

A subject will be considered as having completed the study after completing participation in the Week 24 visit (end of the 4-week safety follow-up period).

7.6.2 Individual Subject Study Drug Discontinuation or Individual Subject Discontinuation

The investigator must document the primary reason for temporary or permanent study drug discontinuation on the case report form (CRF). For subjects who discontinue study drug, the investigator should resume treatment based on standard of care and clinical judgment.

7.6.2.1 Interruption of Study Drug by Individual Subjects

Subjects who interrupt their study drug (vadadustat or epoetin alfa) after receiving the first dose on Day 1 and prior to completion of the study, should continue with the Schedule of Activities and safety assessments through Week 20, and should complete the 4-week safety follow-up period and the Week 24 visit assessments (see Appendix A).

During the study, it is anticipated that subjects may interrupt their study drug for any of the following reasons:

- Unacceptable toxicity or drug intolerability
- Investigator's discretion
- Adverse event
- Missed dialysis visit
- Other reasons

7.6.2.2 Permanent Discontinuation of Study Drug by Individual Subjects

NOTE: Subjects who permanently discontinue study drug (after randomization and prior to completion of the study drug treatment period) will complete the end-of-treatment (EOT) (Week 20) visit assessments within 1 day of stopping study drug (if possible), and should complete the 4-week safety follow-up period and the Week 24 visit assessments.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

During the study, it is anticipated that subjects may permanently discontinue their study drug (vadadustat or epoetin alfa) for any of the following reasons:

- Unacceptable toxicity or drug intolerability
- Investigator's discretion
- Subject withdraws consent
- Subject becomes pregnant
- Receipt of kidney transplant
- Other reasons

8 STUDY DRUGS AND TREATMENT OF SUBJECTS

8.1 Epoetin Alfa

See the approved epoetin alfa US package insert for information on administration and storage.

Epoetin alfa solution for intravenous injection in single-dose or multi-dose vials (ie, 2000, 3000, 4000, 10000, and 20000 units/mL) will be provided by the sites in commercially-approved primary packaging and stored per the approved label.

Epoetin alfa will be administered to subjects by site staff in accordance with the approved label. The prescribed and actual dose of epoetin alfa administered will be documented in the subject's medical records.

8.2 Vadadustat

8.2.1 Study Drugs, Supplies, and Storage

The starting dose of vadadustat is [redacted] once daily) and allowed doses include [redacted]

Vadadustat is formulated for oral dosing. The tablets are white to off-white, round, bi-convex film-coated tablets (8 mm diameter) containing 150 mg vadadustat and the following inactive ingredients: microcrystalline cellulose (MCC), sodium starch glycolate, hydroxypropyl methylcellulose (HPMC), colloidal silicon dioxide, and magnesium stearate, and a film coating.

Vadadustat tablets will be provided to sites by the sponsor or its designee.

Vadadustat should be stored per the product label. A min-max thermometer is preferred for this study. A temperature log should be maintained with drug storage temperatures recorded in accordance with the pharmacy manual.

All study drug supplies must be kept in a locked facility and accessible only to authorized study personnel.

Packaging and labeling will be in accordance with current Good Manufacturing Practice and local regulatory requirements.

8.2.2 Dispensing Procedures for Vadadustat

The site pharmacist or designated study personnel will be responsible for preparing study drugs for dispensation, and will maintain an investigational medication distribution form itemizing all study drugs dispensed to and returned from each subject during the study.

At the baseline (Day 1) visit, subjects who are randomized to the vadadustat treatment arm will be provided with 1 bottle of vadadustat. Each bottle of vadadustat will contain 100 tablets of vadadustat (150 mg/tablet).

Subjects should be instructed to bring unused vadadustat and empty bottles to each study visit for product accountability. Subjects will be instructed to finish 1 bottle before opening a new bottle.

Empty bottles will be collected at the study visits. Previously dispensed bottles (whether opened or unopened) with remaining tablets may be re-dispensed to the subject during the dosing phase of the study.

Resupply of additional vadadustat at subsequent visits will be managed via the IWR system and will be dependent on the current dose level of vadadustat and the number of tablets remaining in the subject's current vadadustat supply at a given study visit.

8.2.3 Product Accountability and Destruction

Vadadustat accountability should be an ongoing process throughout the study. Vadadustat must be accounted for and any discrepancies explained. The designated study personnel are responsible for keeping accurate records of the clinical supplies, all supplies retained in inventory at the investigative site, and study drug dispensed to or returned from each subject. Records should be maintained that accurately reflect the drug accountability throughout the study.

Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates, if expiry date or retest date is provided to the site
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the log is completed for all drug received and that all required fields are complete, accurate, and legible.

If any dispensing errors or discrepancies are discovered, the sponsor or designee must be notified immediately.

During the study, the investigator will be notified of any expiry dates or retest date extensions of clinical study material. If an expiry date notification is received during the study, the investigative site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

Prior to investigative site closure and at appropriate intervals during the study, a representative from the sponsor will perform clinical study material accountability and reconciliation.

At the end of the study, the investigator will retain all original documentation regarding clinical study material accountability, return, or destruction, and copies will be sent to the sponsor or designee.

All unused or partially used study drug should be returned to the sponsor or destroyed at the investigational site, as specified by the sponsor. Appropriate records of the disposal will be documented and maintained. No unused study drug may be disposed of until fully accounted for by the sponsor's monitor or designee. Empty containers may be disposed of in accordance with local procedures.

8.3 Treatment of Subjects

Study drug treatment will aim to maintain Hb level within target range of 10.0 to 11.0 g/dL.

8.3.1 Randomized Treatment Group Assignments

Subjects will be randomly allocated (1:1 ratio) via the IWR system to participate in either the vadadustat treatment arm or the epoetin alfa treatment arm. On Day 1, subjects will withhold dosing until it is confirmed which treatment arm (vadadustat or epoetin alfa) they are assigned to.

8.3.2 Blinding During the Study

This is an open-label study and will not involve any blinding procedures.

8.3.3 Measurement of Hemoglobin Levels for Dose Adjustment Consideration

Hemoglobin values will be measured by a central laboratory. Study drug treatment will aim to maintain Hb level within target range of 10.0 to 11.0 g/dL. Hemoglobin will be monitored throughout the study to determine the dose of study medication (vadadustat or epoetin alfa) that subjects should receive. Refer to Section 8.3.5. Hb levels can be measured more frequently based on investigator's clinical judgment.

If dose adjustment is recommended based on Hb value and protocol-specified guidelines, dosing instructions can be provided to the subject during the next dialysis session at the investigative site (or dialysis center) or during an unscheduled site visit within 3 business days after receiving the Hb result from the central laboratory. If scheduling the subject within this time frame is not possible, dosing instructions will be provided to the subject over the telephone.

8.3.4 Dosing Regimen for the Epoetin Alfa Treatment Arm

For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from baseline [Day 1] visit) will be the same dose that they were receiving during the screening period.

Epoetin alfa dose will be administered and titrated as clinically indicated based on an individual subject's central lab Hb value and the approved label for adult patients with CKD on dialysis.

8.3.5 Dosing Regimen for the Vadadustat Treatment Arm and Guidelines for Vadadustat Dose Adjustment

Subjects assigned to the vadadustat arm will discontinue epoetin alfa and take vadadustat once daily for 20 weeks.

The following dosing regimen are for subjects who are randomized to the vadadustat treatment arm:

- Vadadustat dosing (Day 1 to Week 20)
  - Starting dose of vadadustat: [redacted] once daily) starting at baseline/Day 1. The first dose of vadadustat will be administered at the investigative site after other baseline procedures have been completed. Thereafter, vadadustat will be taken once daily in the dialysis centers or on an outpatient basis.
  - The vadadustat dose can be up-titrated every 4 weeks or down-titrated more frequently based on the target Hb range of 10.0-11.0 g/dL.
  - [redacted]
  - Dosing instructions: Subjects should be instructed to swallow intact tablet(s) of vadadustat with water or another beverage. Subjects may take vadadustat with or without food. The full dose should be taken at approximately the same time each day. The subject should be instructed to take any oral iron supplements (including multivitamins containing iron), iron containing phosphate binders, or any medication containing iron at least 2 hours before or 2 hours after taking the vadadustat dose.
  - After the end of vadadustat treatment at Week 20 (or following early discontinuation of vadadustat), subjects will resume dosing with epoetin alfa (or another ESA), based on the approved label for adult patients with CKD on dialysis.

Guidelines for Vadadustat Dose Adjustments

Vadadustat dose adjustments will be guided by an IWR system based on the Hb value and programmed Dose Adjustment Algorithms (as presented below).

When adjusting vadadustat dose, investigators should consider Hb rate of rise, rate of decline, and the subject's clinical condition (eg, recent illness, volume depletion, and volume overload). In cases of extenuating clinical circumstances, the investigator may elect to dose outside the IWR system dosing recommendation to maintain the Hb within the target range. In such cases, the clinical circumstances must be documented in the subject's record and IWR system.

- Do not increase the vadadustat dose more frequently than once every 4 weeks. Decreases in vadadustat dose can occur more frequently. Avoid frequent vadadustat dose adjustments.
- If a dose adjustment is required to maintain Hb within the target range (10.0-11.0 g/dL), then increase or decrease the vadadustat dose by 1 tablet.
- If the Hb decreases below 10.0 g/dL, increase the dose of vadadustat by 1 tablet.
- If the Hb exceeds 11.0 g/dL, interrupt vadadustat until Hb decreases to 11.0 g/dL or less, then resume dosing of vadadustat with 1 fewer tablet.

NOTE: If subject was on 1 tablet prior to interruption, then resume dosing with 1 tablet.

- If the Hb increases rapidly (eg, >1.0 g/dL in any 2-week period or >2.0 g/dL in any 4-week period), and a subject is not receiving epoetin alfa, decrease the dose of vadadustat by 1 tablet.

8.3.6 Late or Missed Doses of Study Drug Treatment

Subjects on vadadustat should be instructed to take the study drug at approximately the same time each day. If a dose is forgotten, subjects should be instructed to take the dose as soon as they remember during the same day. If a forgotten dose is not remembered on the same day, the subject should skip the dose and resume the normal dosing schedule the following day. Subjects should not double-up on missed doses.

Epoetin alfa dose (including handling of late or missed dose) should be administered as clinically indicated based on an individual subject's Hb value and the approved label for adult patients with CKD on dialysis.

8.3.7 Compliance with Vadadustat Treatment

Subjects will be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to vadadustat dosing. The investigator will also maintain drug accountability logs itemizing vadadustat dispensed to and returned from each subject during the study. Treatment compliance will be determined from these forms along with the subject questioning.

Subjects who miss doses will be counseled on the importance of compliance.

NOTE: At the Week 2 and Week 18 visits, subjects in the vadadustat treatment arm should be reminded and instructed to hold their vadadustat dose on the day of the Week 4 and Week 20 visits (respectively). This is because a blood sample for PK analysis will be collected on the day of the Week 4 and Week 20 visits before the vadadustat dose is administered at the investigative site.

Subjects will also be questioned regarding the timing of their last dose of vadadustat during PK sample collection at the Day 1 visit and Week 4 and Week 20 visits. The date and time of these doses should be recorded.

8.3.8 Continuation of Study Drug Treatment

Subjects in the vadadustat treatment arm will not receive vadadustat past the treatment period of approximately 20 weeks. Subjects in the vadadustat treatment arm who complete Week 20, or discontinue early, will resume dosing with epoetin alfa (or another ESA) at Week 20 after all EOT procedures are completed.

8.3.9 Iron Supplementation (Information on Allowed Use)

Investigators should prescribe iron supplementation (intravenous, oral, or intradialytic) as needed and maintain ferritin ≥100 ng/mL and TSAT ≥20%. The duration, dosage, and frequency of use of supplemental iron should be recorded.

Important: Because of the potential for oral iron to decrease the bioavailability of vadadustat, vadadustat should not be administered concurrently with an oral iron supplements (including

multivitamins containing iron), iron containing phosphate binders, or any medications containing iron. Subjects should be instructed to take any of these medications at least 2 hours before or 2 hours after taking the dose of vadadustat.

8.3.10 Rescue Therapy Guidelines

Hemoglobin levels will be monitored throughout the study at scheduled visits and can be measured more frequently based on investigator's clinical judgment.

Rescue therapy with RBC transfusion or epoetin alfa are allowed, but not required during the treatment period. The following rescue therapy guidelines are provided to ensure the safety of study subjects and to standardize the use of rescue in the study. In cases of extenuating clinical circumstances, the investigator may elect to dose outside the rescue therapy guidelines to maintain the Hb within the target range. In such cases, the clinical circumstances should be documented in the subject's record.

- **RBC transfusion**: Investigators should use their investigative site's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, RBC transfusion should be administered as clinically indicated. In less severe instances but where there may be worsening of anemia or moderate to severe symptoms of anemia, RBC transfusions are permitted based on the investigator's clinical judgment. Study drug (vadadustat or epoetin alfa) may be continued during the RBC transfusion period.
  - **Epoetin alfa rescue therapy**: Starting at Week 6, subjects in both treatment arms will be allowed (although not required) to have their Hb rescued with epoetin alfa. When possible, a subject on vadadustat should be on maximum dose of vadadustat for 2 weeks prior to epoetin alfa rescue. Epoetin alfa rescue therapy should be administered based on the approved US product label for adult patients with CKD on dialysis.
    - To qualify for epoetin alfa rescue therapy, each of the following conditions must be fulfilled.

      NOTE: Epoetin alfa rescue therapy should be stopped when Hb is ≥9.0 g/dL.

      - The subject has experienced a clinically significant worsening of their anemia or symptoms of anemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared to baseline
      - The subject's Hb is confirmed to be <9.0 g/dL
      - The Hb level decreased >0.5 g/dL from baseline
      - Reducing the risk of alloimmunization or transfusion-related risks or both is a goal
    - For the epoetin alfa treatment arm:
      - In addition to meeting the rescue criteria noted above, dosing and administration of epoetin alfa rescue therapy should be based on the approved label for adult patients with CKD on dialysis.

- For the vadadustat treatment arm:
  - Epoetin alfa rescue may not be considered until the next study visit if a subject's current vadadustat dose can be increased (ie, if the subject's last vadadustat dose increase was at least 4 weeks earlier and the subject is currently receiving a vadadustat dose of 600 mg/day or less, then vadadustat dose can be increased by 1 tablet to maintain Hb within the target range of 10.0-11.0 g/dL).

    NOTE: vadadustat must be temporarily interrupted during epoetin alfa rescue therapy. After epoetin alfa rescue therapy is completed, vadadustat should be resumed and adjusted per the dose adjustment guidelines (Section 8.3.5).

    A minimum interval must be observed prior to restarting vadadustat after the last dose of rescue medication, and treatment may be resumed 2 days after last dose of epoetin alfa rescue.

8.3.11 Therapeutic Phlebotomy

If a subject's Hb exceeds 14.0 g/dL or the rate of rise of Hb raises concern to the investigator, the subject may be phlebotomized based on the investigator's clinical judgment. The method of phlebotomy will be in accordance with the investigative site's guidelines and standard clinical practice.

8.4 Prior and Concomitant Therapy

8.4.1 General

All medications (except those routinely administered as part of the dialysis procedure or flushes used for routine catheter maintenance) taken within 30 days prior to Day 1 and through the final study visit should be recorded on the appropriate CRF. In addition, ESA history will be recorded in the CRF.

At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit.

This includes single use or as needed medication use. All medications and treatments, including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded on the appropriate CRF.

8.4.2 Erythropoiesis-Stimulating Agents

Subjects are prohibited from taking non-protocol ESAs starting from the screening period and through Week 20, unless the subject permanently discontinues study treatment.

Epoetin alfa rescue therapy is allowed as presented in Section 8.3.10.

8.4.3 RBC Transfusion, Epoetin Alfa Rescue Therapy, Iron Supplementation, and Therapeutic Phlebotomy

Use of epoetin alfa rescue therapy, iron supplementation, and therapeutic phlebotomy within 30 days prior to Day 1 will be recorded.

Receipt of RBC transfusion, epoetin alfa rescue therapy, iron supplementation, and therapeutic phlebotomy during the study will be recorded.

NOTE: RBC transfusion within 4 weeks prior to or during screening is a study exclusion criterion.

8.4.4 Dialysis Treatment and Renal Replacement Therapy

Information on dialysis treatment, including dialysis vascular access type, dialysis adequacy, and history of and changes in renal replacement therapies, will be recorded.

8.4.5 Investigational Medications

Study subjects should not have received any investigational medication or participated in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to screening. In addition, subjects should not have participated in a study with another HIF-PH inhibitor other than vadadustat.

Subjects should not take another investigational medication while participating in this study.

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

9.1 Schedule of Visits

If possible, study visits should be scheduled on the day of the first hemodialysis session of the week to allow for the turnaround time for central lab Hb values (and dose adjustment as needed) before the end of the workweek.

As presented in Appendix A, this study includes the following visits:

- Eligibility screening period (from Day -28 to Day -4; screening must be performed within 4 weeks prior to dosing on Day 1 and the last screening visit must be completed at least 4 days before dosing starts on Day 1 to allow for laboratory test results to be available prior to initiation of study drug)
  - Screening visit 1
  - Screening visit 2
- Study treatment period (from Day 1 to Week 20 visit)
  - Baseline visit (Day 1)
  - Week 2 visit ± 3 days
  - Week 4 visit ± 3 days
  - Week 6 visit ± 3 days
  - Week 8 visit ± 3 days
  - Week 10 visit ± 3 days
  - Week 12 visit ± 3 days
  - Week 14 visit ± 3 days
  - Week 16 visit ± 3 days
  - Week 18 visit ± 3 days
  - Week 20 visit ± 3 days (end-of-treatment visit)
- Safety follow-up period
  - Week 24 visit ± 5 days

9.2 Administrative Procedures

9.2.1 Screening Documentation

Investigators will maintain documentation of all study candidates evaluated and reasons that subjects who were considered for the study did not qualify.

Investigators must account for all subjects who sign informed consent and will maintain a log of subjects screened and indicate who was randomized or excluded. If the subject is found to be ineligible for randomization, the reason(s) for ineligibility and not proceeding to screening or study enrollment, must be documented by the investigator.

Screening numbers assigned to subjects who fail screening will not be re-used.

The investigator will maintain a log of subjects and indicate who was enrolled or excluded and the reason for exclusion (see Section 9.2).

9.2.2 Informed Consent

Informed consent must be obtained and legally signed prior to a subject's entry into the study and before any protocol-directed procedures (including screening tests) are performed (see Section 15.3). After providing informed consent and receiving a unique subject identification number, subjects will undergo various screening activities. Additionally, subjects will be asked to provide separate written informed consent for the collection and storage of a blood sample for future genetic analyses.

9.2.3 Review of Inclusion and Exclusion Criteria

A subject must meet all inclusion criteria listed in Section 7.2 to be eligible for study participation.

A subject who meets any of the exclusion criteria listed in Section 7.3 will not qualify for study participation.

9.2.4 Acceptable Methods of Contraception

In nonclinical animal embryo-fetal development and fertility studies, there was no evidence of teratogenicity, no skeletal or visceral malformations, and no changes in male or female reproductive and fertility indices, or in sperm parameters. In rats, decreased fetal body weight and reduced skeletal ossification were noted at the highest dose tested of 160 mg/kg/day. Peri-postnatal development studies of vadadustat in the rat are ongoing, and there are no data on the transmission of vadadustat in breast milk or the effect of vadadustat on infants.

The potential risk of vadadustat on the developing fetus is limited based on available study results. However, this protocol requires that all subjects must agree to use acceptable methods of contraception throughout the study and for 30 days after the last dose of study drug. In addition, men must not donate sperm during the study and for at least 90 days after the last dose of study drug.

Acceptable methods of contraception are defined as follows:

- Female subjects must be surgically sterile or postmenopausal (no menses for at least 1 year)
- Female subjects of childbearing potential (ie, are not surgically sterile or postmenopausal) must have negative pregnancy test results (see Section 9.3.2 for information on pregnancy tests)
- Female subjects of childbearing potential (ie, are not surgically sterile or postmenopausal) and male subjects who are not vasectomized must practice at least one of the following acceptable methods of contraception:
    - Total abstinence from sexual intercourse, with a minimum of one complete menstrual cycle prior to screening visit, throughout the study, and for 30 days after the last dose of study drug
    - A vasectomized partner
    - Hormonal contraceptives (oral, parenteral, or transdermal) for at least 3 months prior to study drug administration, throughout the study, and for 30 days after the last dose of study drug
    - Intrauterine contraceptive device starting at the screening visit, throughout the study, and for 30 days after the last dose of study drug

- Double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap together with spermicidal foam, gel, film, or suppository) starting at the screening visit, throughout the study, and for 30 days after the last dose of study drug.

9.2.5 Randomization

Subjects who meet all inclusion and none of the exclusion criteria will be randomly allocated (1:1 ratio) using the IWR system to participate in either the vadadustat or epoetin alfa treatment arm. Permuted block randomization will be used to assign subjects to treatment.

9.3 Study Procedures and Evaluations

9.3.1 Clinical and Safety Assessments

The following clinical evaluations will be conducted during the study. Detailed information regarding the timing of the assessments is presented in Section 9.4 and summarized in Appendix A. Clinical evaluations should be completed prior to dialysis on the day of the visit, if applicable.

- Demographics and medical history: Relevant medical history (with emphasis on previous medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases should be documented.
- Physical examination: Physical examination, including height measurement. After the screening period, an abbreviated, symptom-directed physical examination may be performed based on investigator's clinical judgment.
- Dry weight, dialysis adequacy, and dialysis treatment review: Dry weight will be recorded. Dialysis adequacy (measured as Kt/V), as available from local collection, will be recorded. Dialysis treatment will be reviewed including frequency of dialysis and vascular access type (eg, arteriovenous fistula, arteriovenous graft, and venous catheter).
- Vital signs: Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure and heart rate will be collected in the seated position after 5 minutes of rest. Vital signs should be collected prior to blood draws, when possible.
- 12-lead electrocardiography (ECG): A standard 12-lead ECG should be obtained after the subject has been resting comfortably in a supine position for approximately 10 minutes. ECGs should be taken prior to blood draws when possible. The subject should consume no more than a light meal or snack during the 1-hour period prior to the ECG. With the subject in a supine position obtain the 12-lead tracing. Each 12-lead ECG must be recorded with a paper speed of 25 mm/sec and printed as a paper copy. The investigator (or a qualified observer at the investigational site) will interpret the ECG and record the results including the following parameters: Heart rate, PR interval, QT interval, QRS interval, and QTc (corrected). All abnormal rhythms will be reviewed by the study physician for the presence of rhythms of potential clinical concern. A printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.
- Adverse event review: Beginning with the first dose of study medication and through the follow-up visit, the investigator and study personnel will review each subject's laboratory and clinical evaluation findings and query the subject directly regarding AEs. Additional

information is provided in Section 10 and follow-up of unresolved AEs, SAEs, and non-serious events is described in Section 10.3.6.

- Concomitant medication review: All medications taken within 30 days prior to the start of study medication and through the final study visit should be recorded on the appropriate CRF. See Section 8.4 for additional information.

9.3.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis (unless noted otherwise). Detailed instructions for the collection, processing, and shipment of laboratory samples will be provided by the sponsor and the central laboratory. The investigator is responsible for reviewing laboratory results for clinical significance.

The following laboratory evaluations will be conducted during the study:

- Pregnancy test(s): Female subjects of childbearing potential (ie, are not surgically sterile or postmenopausal) must participate in pregnancy test(s).
  - A serum pregnancy test should be performed within 4 to 8 days prior to the baseline (Day 1) visit to allow sufficient time to obtain the pregnancy test results prior to randomization on Day 1. The results must be available and negative before the subject initiates study drug.
  - If the serum pregnancy test takes place more than 8 days prior to Day 1, then one of the following tests should be conducted:
    - Subjects who produce urine will participate in a urine pregnancy test on Day 1. The results must be available and negative before the subject initiates study drug.
    - Subjects who cannot produce urine will be asked to return to the study site within 4 to 8 days prior to Day 1 for an unscheduled serum pregnancy test. The results must be available and negative before the subject initiates study drug.
  - Serum pregnancy test samples will be analyzed by the central lab and urine pregnancy test samples will be analyzed by the local lab.
  - Additional pregnancy tests may be conducted during the study to establish the absence of pregnancy based on the investigator's clinical judgment or as required by local regulations.
- CBC: A CBC with differential will be performed at the baseline (Day 1) visit and at the Week 20 (or EOT) visit. At the other visits including the screening visits, a CBC without differential will be performed. CBC with differential will include: Hb, hematocrit, RBC count, mean corpuscular volume, mean corpuscular Hb, mean corpuscular Hb concentration, red cell distribution width, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelets.

  Hemoglobin will be monitored throughout the study to determine the dose of study medication (vadadustat or epoetin alfa) that subjects should receive. Refer to Section 8.3.5 Hb levels can be measured more frequently based on investigator's clinical judgment.
- Reticulocyte count: An automated reticulocyte count (both absolute and percent) will be performed.

- Coagulation tests: Blood sample will be collected to assess the prothrombin time, partial thromboplastin time, and international normalized ratio (INR).
- Folate and vitamin B12: Blood sample will be collected to assess folate and vitamin B12 levels.
- C-reactive protein: Blood sample will be collected to assess CRP.
- Serum chemistry: Blood sample will be collected to assess sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen, creatine phosphokinase, uric acid, albumin, and total protein.
- Liver function tests: Blood sample will be collected to assess total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, and lactate dehydrogenase.
- Iron indices: Blood samples will be collected to assess the following indices: ferritin, iron, TIBC, and TSAT.
- Lipid panel: Blood sample will be collected to assess total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides.
- PK evaluations (for subjects in the vadadustat treatment arm): Plasma samples will be analyzed for vadadustat and its metabolites. Detailed instructions for collection, processing, storage, and shipment of the samples for PK and metabolite analyses will be provided by the sponsor or a designated laboratory.
- Additional biomarkers: Blood samples for additional biomarker analysis (eg, hepcidin and VEGF) will be collected.
- Erythropoietin: Blood samples for analysis of EPO levels will be collected.
- Exploratory analyses: Additional blood samples may be collected for exploratory analyses of biomarkers (eg, factors relating to the activation of the HIF pathway). Subjects will also be asked to provide optional written informed consent to obtain and store a blood sample for future genetic analyses.

9.3.3 Procedures Related to Study Drug Treatments

- Epoetin alfa dosing (for epoetin alfa treatment arm only): See Section 8.3.4 for additional information.
- Epoetin alfa dose reduction (for vadadustat treatment arm only): See Section 8.3.5 for additional information.
- Vadadustat dosing (for vadadustat treatment arm only): See Section 8.3.5 for additional information.
- Vadadustat drug dispensation (for vadadustat treatment arm only): See Section 8.2.2 for additional information.
- Review vadadustat dosing instructions (for vadadustat treatment arm only): See Section 8.3.5 for additional information.
- Vadadustat drug reconciliation (for vadadustat treatment arm only): See Section 8.2.2 for additional information.

- Review vadadustat dosing compliance (for vadadustat treatment arm only): Subjects will be questioned regarding dosing compliance. See Section 8.3.7 for additional information.
- Resuming dosing with epoetin alfa (or another ESA) (for vadadustat treatment arm only): See Section 8.3.5 for additional information.
- Recording of use of rescue therapy (RBC transfusions and epoetin alfa rescue therapy): See Section 8.3.10 for additional information.
- Recording of use of supplemental iron: See Section 8.3.9 for additional information.
- Recording of use of therapeutic phlebotomy: See Section 8.3.11 for additional information.

9.4 Schedule of Activities

The Schedule of Events in Appendix A shows the timing of planned study procedures.

Subjects will take study drug per their treatment randomization.

Every effort should be made to adhere to this procedure schedule and the planned assessments should be completed at each study visit.

NOTE: If possible, study visits should be scheduled on the day of the first hemodialysis session of the week to allow for the turnaround time for central lab Hb values (and dose adjustment as needed) before the end of the workweek.

9.4.1 Screening Visits

Screening visits must be performed within 4 weeks prior to dosing on Day 1 and the last screening visit must be completed at least 4 days before dosing starts on Day 1 to allow for laboratory test results to be available prior to initiation of study drug.

For eligibility purposes, if Hb at SV1 is 10.0 to 10.5 g/dL, 1 retest CBC should be performed prior to SV2. If the retest Hb is ≥10.0 g/dL, the subject should not proceed with SV2. If the Hb at SV1 is >10.5 g/dL, the subject should not proceed with any further screening procedures at that time.

Subjects will continue their epoetin alfa dosing regimen during the screening period.

At SV1, the following activities/procedures will be performed:

- Signing of informed consent
- In addition, subjects may be asked during screening or at any study visit thereafter to provide optional written informed consent to obtain and store a blood sample for future genetic analyses.
- Review of study inclusion and exclusion criteria
- Review acceptable methods of contraception
- Vital signs
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws should be done prior to dialysis, if applicable):
  - CBC
  - Iron indices
- Epoetin alfa dosing will continue

At SV2, the following activities/procedures will be performed:

- Review of study inclusion and exclusion criteria
- Review acceptable methods of contraception
- Demographics, medical history, and physical examination
- Vital signs
- Review of concomitant medications
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws should be done prior to dialysis, if applicable):
    - Serum pregnancy test (see Section 9.3.2 for additional information)
    - CBC
    - Folate and vitamin B12 levels
    - Serum chemistry
    - Liver function tests
- Epoetin alfa dosing will continue

9.4.2 Baseline Visit (Day 1)

There must be a minimum of 4 days between the last screening visit and the baseline visit.

On Day 1, blood sample collection and other baseline procedures should be completed prior to dosing with study drug (vadadustat or epoetin alfa). On Day 1, study drug will be administered at the investigative site, and may be administered prior to or during the dialysis session.

At the baseline visit, the following activities/procedures will be performed:

- Review of study inclusion and exclusion criteria
- Review acceptable methods of contraception
- Subject randomization
- Dry weight and dialysis treatment review
- Dialysis adequacy (from dialysis performed during screening)
- Vital signs
- 12-lead ECG (ECGs should be completed prior to blood draws when possible and should be obtained after the subject has been resting supine comfortably for approximately 10 minutes; ECG may be completed and reviewed by the investigator on Day 1 or if needed for scheduling reasons [eg, dialysis treatment is scheduled for early morning of Day 1], the ECG can be completed and reviewed up to 1-3 days prior to Day 1)
- AE review
- Recording of any concomitant medication use since screening visit
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws should be done prior to dialysis, if applicable):
    - Urine pregnancy test (see Section 9.3.2 for additional information)
    - CBC with differential
    - Reticulocyte count
    - Coagulation tests
    - C-reactive protein
    - Serum chemistry
    - Liver function tests

  - Iron indices
  - Lipid panel
  - Sample for PK analysis (vadadustat treatment arm only; the sample will be collected between 30 minutes to 1 hour after vadadustat administration either prior to or during dialysis; the time of the vadadustat dose, the PK sample collection time, and the start and stop times of the dialysis session will be documented)
  - Biomarkers
  - Sample for erythropoietin measurement
  - Sample for exploratory analyses
- Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa
- For subjects in the vadadustat treatment arm only:
  - Initiate vadadustat dosing
  - Vadadustat drug dispensation
  - Review vadadustat dosing instructions
- Review use of rescue therapy (RBC transfusions and epoetin alfa rescue therapy)
- Review use of iron supplementation

9.4.3 Week 2, 4, 6, 8, 10, 12, 14, 16, and 18 Visits

At the Week 2 and Week 18 visits, subjects in the vadadustat treatment arm should be reminded and instructed to hold their vadadustat dose on the day of the Week 4 and Week 20 visits (respectively), as blood sample for PK analysis will be collected on the day of the Week 4 and Week 20 visits prior to vadadustat administration at the investigative site.

The following activities/procedures will be performed at the visits on Week 2, 4, 6, 8, 10, 12, 14, 16, and 18, unless noted otherwise:

- Review acceptable methods of contraception
- Dry weight and dialysis treatment review
- Dialysis adequacy (Week 8 only)
- Vital signs
- AE review
- Concomitant medication review
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws should be done prior to dialysis, if applicable):
  - CBC
  - Reticulocyte count (Weeks 4, 8, 12, and 16 only)
  - C-reactive protein (Week 8 only)
  - Serum chemistry (Weeks 4, 8, and 16 only)
  - Liver function tests (Weeks 4, 8, and 16 only)
  - Iron indices (Weeks 8 and 16 only)
  - 2 samples for PK analyses (Week 4 only; vadadustat treatment arm only; the first sample will be collected prior to vadadustat administration and the second sample will be collected at least 15 minutes post dialysis. If post dialysis collection is not possible, the second PK sample will be collected at least 3 hours after vadadustat administration. The time of the last dose of vadadustat taken prior to the PK sampling, as well as the timing of the PK sample collection, will be documented)

- Biomarkers (Week 8 only)
- Sample for erythropoietin measurement (Weeks 8 and 16 only)
- Sample for exploratory analyses (Week 8 only)

- Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa
- For subjects in the vadadustat treatment arm only:
  - Vadadustat dosing
  - Vadadustat drug dispensation (Weeks 4, 8, 12, 16, and other visits as applicable)
  - Review vadadustat dosing instructions
  - Vadadustat drug reconciliation (Weeks 4, 8, 12, 16, and other visits as applicable)
  - Review vadadustat dosing compliance
- Review use of rescue therapy (RBC transfusions and epoetin alfa rescue therapy)
- Review use of iron supplementation
- Review use of therapeutic phlebotomy

9.4.4 Week 20 Visit (End-of-Treatment)

On the day of the Week 20 visit, the vadadustat dose will be taken at the investigative site after a blood sample for PK analysis has been collected.

At the Week 20 visit, the following activities/procedures will be performed:

- Review acceptable methods of contraception
- Dry weight and dialysis treatment review
- Dialysis adequacy
- Vital signs
- AE review
- Concomitant medication review
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws should be done prior to dialysis, if applicable):
  - CBC with differential
  - Reticulocyte count
  - C-reactive protein
  - Serum chemistry
  - Liver function tests
  - Iron indices
  - Lipid panel
  - 2 samples for PK analyses (vadadustat treatment arm only; the first sample will be collected prior to vadadustat administration and the second sample will be collected at least 15 minutes post dialysis. If post dialysis collection is not possible, the second sample will be collected at least 3 hours after vadadustat administration. The time of the last dose of vadadustat taken prior to the PK sampling, as well as the timing of the PK sample collection, will be documented)
  - Biomarkers
  - Sample for erythropoietin measurement
  - Sample for exploratory analyses
- Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa

- For subjects in the vadadustat treatment arm only:
  - Vadadustat drug reconciliation
  - Review vadadustat dosing compliance
  - Resume dosing with epoetin alfa (or another ESA): After the end of vadadustat treatment at Week 20 (or following early discontinuation of vadadustat), subjects may resume dosing with epoetin alfa (or another ESA), based on the approved label for adult patients with CKD on dialysis
- Review use of rescue therapy (RBC transfusions and epoetin alfa rescue therapy)
- Review use of iron supplementation
- Review use of therapeutic phlebotomy

9.4.5 Week 24 Visit

At the Week 24 visit, the following activities/procedures will be performed:

- AE review
- Concomitant medication review
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws should be done prior to dialysis, if applicable):
  - CBC
  - C-reactive protein
  - Serum chemistry
  - Liver function tests
  - Iron indices
  - Biomarkers
- All subjects will continue to receive epoetin alfa (or another ESA), based on the approved label for adult patients with CKD on dialysis
- Review use of rescue therapy (RBC transfusions and epoetin alfa rescue therapy)
- Review use of therapeutic phlebotomy

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events (AEs)

For the purposes of this study, an AE is any untoward medical occurrence (including a clinically significant abnormal laboratory finding) that occurs in the protocol-specified AE reporting period; the event does not necessarily have a causal relationship with that treatment or usage.

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

Adverse events therefore include the following:

- All AEs, whether suspected to be causally related to study drug or otherwise

- All AEs secondary to any medication overdose, medication error, abuse, withdrawal, sensitivity, or toxicity
- Illnesses apparently unrelated to study drug, including the worsening of a pre-existing illness (see paragraph below on Pre-Existing Conditions).
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (eg, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event reported as an AE (eg, elevated liver enzymes in a subject with jaundice) should be described under 'Comments' on the report of the clinical event rather than reported as separate AEs.

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

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

Procedures – Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy noted under "Comments."

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

Kidney Transplantation – A kidney transplant will not be recorded as an AE. Subjects who discontinue study drug because of receipt of a kidney transplant should continue with the Schedule of Activities (Appendix A).

Pre-Existing Conditions – In this study, a pre-existing condition (ie, a disorder present before the AE reporting period started and noted on the pre-treatment medical history/physical examination form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

Abnormal Test Findings – All laboratory test results will be reviewed by the investigator. Investigators will utilize their judgment in determining if out of range laboratory values are clinically significant and should denote this using the abbreviation "CS" on the laboratory report for source documentation. Laboratory tests that are labeled as clinically significant should be reported as AEs, either separately or as part of a description of a symptomatic AE. If there are significant changes in a laboratory report from a previous visit that are determined to be clinically significant, these should also be reported as AEs. Any abnormal laboratory value

which requires treatment or further diagnostic testing or results in discontinuation from study should be reported as AEs. An expected laboratory abnormality from a condition that is part of the medical history is not considered clinically significant for the purposes of the study unless it represents a worsening of the condition.

Abnormalities in ALT, AST and Total Bilirubin – Abnormalities in ALT, AST and total bilirubin should be reported to the sponsor's medical monitor (or medical director) or contract research organization (CRO) designee within 24 hours of awareness as a serious adverse event (SAE) with 'other medically important event' criterion selected, if the following conditions are met:

- New elevation in ALT or AST >3 times ULN, with or without an elevation of total serum bilirubin >2 times ULN, AND
- No other reason was identified that explains the increased ALT/AST with or without an increased bilirubin (eg, viral hepatitis, acute liver disease).

If new elevations in ALT or AST >3 times ULN, with or without an elevation of total serum bilirubin >2 times ULN are identified, the following steps are to be taken:

- Temporary discontinuation of study medication
- Repeat testing of ALT, AST, ALP, and total bilirubin, to be completed within 48 to 72 hours to confirm the abnormalities and to determine trend
- Study medication should not be resumed until monitoring indicates abnormalities have resolved, are stable, or are not rapidly increasing

Worsening of Anemia – In this study, it is possible that some subjects may experience a worsening of anemia. Worsening of anemia should not be considered an AE unless the worsening of anemia is associated with a cause other than the subject's CKD.

10.1.2 Serious Adverse Events (SAEs)

Each AE must be classified by the investigator as SERIOUS or NONSERIOUS. An AE that meets 1 or more of the following criteria (or outcomes) is classified as serious:

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

Serious also includes any other event that the investigator or sponsor judges to be serious. If there is any doubt whether the information constitutes an AE or SAE, the information is to be treated as an SAE.

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

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

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

10.2 Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs at each visit following the initiation of treatment.

10.3 Reporting

Each AE is to be classified by the investigator as SERIOUS or NONSERIOUS.

All AEs that occur in study subjects during the AE reporting period specified in the protocol must be reported whether or not the event is considered related to study medication.

10.3.1 Reporting Period

The AE reporting period for a subject begins upon receiving the first dose of study medication and ends at the final protocol-required visit.

In addition, SAEs that occur after the protocol-defined AE reporting period that are considered to be related to the study medication should be recorded and reported to the sponsor's medical monitor or CRO designee.

10.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the AE CRF.

10.3.3 Reporting SAEs

Any SAE, regardless of causal relationship, must be reported to the sponsor's medical monitor (or medical director) or CRO designee **within 24 hours** after the investigator becomes aware of the SAE. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

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

- Subject identification number, sex, age, and date of birth
- Date of report

- Name of the reporter
- Name of the suspected medicinal product
- Description of the event, including event term(s), seriousness criteria, and a clinical summary of the event
- Causality assessment

Information about all SAEs (either initial or follow-up information) should be collected and recorded in English on the electronic SAE Report Form within the electronic data capture (EDC) system. The investigator must assess the relationship to each specific component of the study treatment. If the event meets serious criteria and it is not possible to access the EDC system, a paper SAE Report Form should be sent to the CRO via email or fax within 24 hours of being made aware of the SAE (reference the site manual for contact information). When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

The investigator must report follow-up information relating to an SAE to the sponsor's medical monitor (or medical director) or CRO designee within 24 hours of awareness by updating the electronic CRF with the new information or by submitting a paper SAE Report Form (only if the EDC is not available). When the EDC system becomes available, the SAE information must be entered within 24 hours. The subject should be observed and monitored carefully until the condition resolves or stabilizes.

All deaths are to be thoroughly investigated and reported. Autopsy reports are to be obtained, if possible, and sent to the CRO via email or fax.

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

The investigators are responsible for submitting required safety information to their local IRB per local regulations. This information includes but is not limited to, any safety alert letter received from the sponsor and any SAEs occurring at their investigative site.

10.3.4 Relationship to Study Medication

The causal relationship of the AE to study medication will be assessed by both the investigator and the sponsor. The investigator should provide causality assessment with the initial SAE report within 24 hours of becoming aware of the event.

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

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

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

Related: There is 'reasonable possibility' that the drug caused the AE. The AE follows a reasonable temporal sequence from the time of drug administration. There is supportive evidence

(facts) to suggest a possible causal relationship, irrespective of the degree of certainty between the observed AE and the drug.

Unrelated: An AE does not follow a reasonable temporal sequence from administration of the product and/or there is no reasonable possibility that the drug caused the AE. This assessment includes situations where the AE is related to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

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

Investigators are encouraged to choose the most plausible cause for the event(s) from the following list: medical history, lack of efficacy or worsening of treated condition, study treatment, other treatment (concomitant, or previous), withdrawal of study treatment, administration error, protocol-related procedure, others (specify).

10.3.5 Severity

The investigator will assess each AE as either MILD, MODERATE, or SEVERE using the following guidelines to describe the maximum severity of the AE:

- MILD: Does not interfere with subject's usual function.
- MODERATE: Interferes to some extent with subject's usual function
- SEVERE: Interferes significantly with subject's usual function.

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

10.3.6 Follow-Up of Unresolved Events

All AEs should be followed until they are resolved or the investigator assesses them as chronic or stable or the subject's participation in the study ends (ie, until a final report is completed for that subject).

In addition, all SAEs and those non-serious events assessed by the investigator as related to the study medication should continue to be followed even after the subject's participation in the study is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the appropriate CRF.

10.4 Exposure In Utero

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

The study medication should be immediately discontinued once the pregnancy of a female subject has been confirmed.

If any study participant becomes or is found to be pregnant while receiving a study medication or within 30 days of discontinuing the study medication, the pregnancy must be recorded on the Pregnancy Reporting Form/Exposure In Utero Form within 24 hours of awareness of the

pregnancy and sent to the CRO via email or fax (reference the site manual for contact information).

Pregnancy during this time frame of the female partner of a male subject should also be reported.

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

The investigator will follow the subject (or female partner of a male subject) until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death within 1 month of birth, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting an SAE within 24 hours of awareness. A pregnancy in and of itself is not considered an AE; however, unexpected complications are considered AEs.

Additional information about pregnancy outcomes follows:

- Note that "spontaneous abortion" includes miscarriage and missed abortion.
- Neonates should be followed through gestational age of 46 weeks.
- Follow-up information includes the course, duration, and the outcome of the pregnancy and the neonate's health.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as related or unrelated to the in utero exposure to the study medication should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

10.5 Special Situations

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

- Overdose of the study drug
- Suspected abuse or misuse of the study drug
- Inadvertent or accidental exposure to the study drug
- Medication error involving the study drug (with or without subject exposure to the sponsor's study drug, eg, name confusion)
- Drug-drug interaction involving the study drug

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

11 DATA ANALYSIS

Data collected throughout the study will be summarized using descriptive statistics and listed in by-subject listings. Continuous variables will be summarized using number of subjects with data, mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated.

For continuous endpoints (eg, Hb) where change from baseline will be analyzed and multiple pretreatment values are recorded, baseline will be defined as the mean of all qualifying values collected prior to the first dose of study drug. For other continuous endpoints baseline will be defined as the last available value prior to the first dose of study drug.

11.1 Sample Size Determination

About 50 subjects (n=25 per treatment arm) are planned for randomization in the study.

Sample size has been determined to reflect the exploratory nature of this study.

11.2 Study Analysis Populations

The following analysis populations will be used in this study:

- Modified-intent-to-treat (MITT) population: All randomized subjects who receive at least 1 dose of study drug starting from baseline (Day 1) visit, have at least one pre-treatment Hb measurement, and at least one post-treatment Hb measurement. Subjects in the MITT population will be analyzed based on their randomized treatment assignment.
- Per-protocol population: All randomized subjects who receive at least 1 dose of study drug starting from baseline (Day 1) visit, have at least one pre-treatment Hb measurement, have at least one post-treatment Hb measurement, have epoetin alfa dose recorded during Week 18 to 20, and did not receive any rescue therapy from Weeks 12 to 20. Subjects in the per-protocol population will be analyzed based on their randomized treatment assignment.
- Safety population will include subjects who received at least 1 dose of study drug. Subjects in the safety population will be analyzed based on the study drug treatment that they received.

Efficacy analyses will utilize the MITT and per-protocol populations. Safety analyses will utilize the safety population.

11.3 Analysis of Demographics and Pretreatment Variables

Descriptive statistics will be generated for demographic and pretreatment variables for each analysis population.

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class and Preferred Term for each treatment group based on the safety population.

11.4 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, discontinued early from study drug, completed or discontinued from the study, and reasons for discontinuation will be summarized by treatment group and overall.

11.5 Missing Data

It is expected that few subjects will discontinue follow-up for epoetin alfa use. The reasons for any missing data will be summarized by treatment arm. The primary analysis will be based upon observed data without imputation.

11.6 Efficacy Analyses

This study is exploratory in nature, designed to evaluate the change in Hb from baseline over time during the treatment period. No formal statistical testing will be performed.

Summary statistics (mean, median, standard deviation [SD], range, proportion and 95% confidence intervals when appropriate) will be provided, by treatment groups for primary and secondary endpoints.

11.7 Safety Analyses

Adverse events will be summarized using the number and percentage of subjects with AEs for all subjects in the safety population.

All AEs will be coded using MedDRA. Treatment-emergent and post-treatment AEs will be summarized by System Organ Class and Preferred Term for each treatment group. Adverse events will also be summarized by their maximum severity.

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

- SAEs
- Related AEs, as determined by the investigator
- AEs leading to early discontinuation of study drug

The safety endpoint of Hb changes will be summarized using descriptive statistics with 2-sided confidence intervals calculated using the methods used for the secondary efficacy endpoints.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms and Electronic Data Capture

This study will utilize an EDC system to manage data collection during this study. The system is fully Code of Federal Regulations 21 part 11 compliant. An EDC system contains certain functionality including, but not limited to, a graphical user interface to help facilitate data entry, a data validation element to check user data, and a reporting function to assist with the review and analysis of data. CRFs available through this system are required and should be completed for each randomized subject.

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

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered in the EDC or any other data collection forms. The CRFs must be signed electronically by the investigator to attest that the data contained on the CRFs is true.

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

12.2 Record Retention

To enable evaluations or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the International Council for Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

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

13 QUALITY CONTROL (QC) AND QUALITY ASSURANCE (QA)

13.1 Study Site Monitoring Visits

During study conduct, the sponsor or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow the sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject one or more of the following activities:

- Quality assurance audits performed by the sponsor or its designees

- Review by the IRB
- Inspection by appropriate regulatory authorities

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

13.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action.

The site should document all protocol deviations in the subject's source documents. In the event of a major protocol deviation, the site should notify the sponsor or its designee (and IRB, as required). Major protocol deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments.

14 STUDY DISCONTINUATION AND INVESTIGATIVE SITE TERMINATION

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

14.1 Criteria for Premature Termination or Suspension of the Study

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

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

Temporary suspension or early termination may also be initiated by a regulatory authority decision, change in opinion of the IRB, or at the discretion of the sponsor.

14.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

14.3 Procedures for Premature Termination or Suspension of the Study or Investigational Site(s)

In the event that the sponsor elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be

provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

15 ETHICS

15.1 Ethical Conduct of the Study

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

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP (1996), and applicable local regulatory requirements and laws.

15.2 Institutional Review Board (IRB)

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

In case of substantial protocol amendment, the sponsor will obtain approval from responsible Regulatory Authorities before implementation.

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

15.3 Subject Information and Consent

Prior to inclusion in the study, it is the responsibility of the investigator to give each subject (or the subject's acceptable representative) full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The subjects must be informed about their right to withdraw from the study at any time.

Furthermore, it is the responsibility of the investigator, or a person designated by the investigator, to obtain signed informed consent from each subject or the subject's legally acceptable representative prior to inclusion in the study. The investigator will retain the original of each subject's signed consent form.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and sponsor before use.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the sponsor should be informed immediately.

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

15.5 Subject Confidentiality

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

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

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

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

16 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between sponsor and the investigator (or the investigator's institution). The sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication or presentation. Any information identified by the sponsor as confidential must be deleted prior to submission.

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

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18 APPENDIX A: SCHEDULE OF ACTIVITIES

Please refer to Section 9.1 for information regarding the visit schedule (including duration of the screening period), Section 9.3 for detailed information regarding the study procedures and evaluations, and Section 9.4 for detailed information regarding the activities to be performed at each study visit.

Study Period	**Screening**		**Study Treatment Period**										**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Week	**Week -4 to Day -4**		**Baseline/ Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**Week 20 (EOT) [8]**	**Week 24 (follow-up)**
Visit Window (Days)	—		—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±5
Administrative Procedures														
Informed consent [1]	X													
Inclusion and exclusion criteria	X	X	X											
Review contraception methods	X (contraception methods should be reviewed at screening, as well as throughout the study as needed)													
Randomization [2]			X											
Clinical and Safety Assessments														
Demographics, medical history, physical exam		X												
Dry weight and dialysis treatment review			X	X	X	X	X	X	X	X	X	X	X	
Dialysis adequacy (Kt/V) [3]			X				X						X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead electrocardiography (on Day 1 or 1-3 days before Day 1)			X											
Adverse event review			X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluations														
Pregnancy test		X (serum)	X (urine)											

Study Period	**Screening**		**Study Treatment Period**										**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Week	**Week -4 to Day -4**		**Baseline/ Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**Week 20 (EOT) [8]**	**Week 24 (follow-up)**
Complete blood count (CBC)	X	X	X (CBC with diff)	X	X	X	X	X	X	X	X	X	X (CBC with diff)	X
Reticulocyte count			X		X		X		X		X		X	
Coagulation tests			X											
Folate and vitamin B12		X												
C-reactive protein			X				X						X	X
Serum chemistry		X	X		X		X				X		X	X
Liver function tests		X	X		X		X				X		X	X
Iron indices	X		X				X				X		X	X
Lipid panel			X										X	
Pharmacokinetics (vadadustat treatment arm only) [4]			X		X								X	
Biomarkers			X				X						X	X
Erythropoietin			X				X				X		X	
Exploratory analyses			X				X						X	
Procedures related to study drug treatment														
Epoetin alfa dosing (epoetin alfa treatment arm) [5]	X													
Vadadustat dosing (vadadustat treatment arm) [6]			X	X	X	X	X	X	X	X	X	X		
Vadadustat drug dispensation			X		X		X		X		X			
Review vadadustat dosing instructions			X	X	X	X	X	X	X	X	X	X		
Vadadustat drug reconciliation					X		X		X		X		X	
Review vadadustat dosing compliance				X	X	X	X	X	X	X	X	X	X	

Study Period	**Screening**		**Study Treatment Period**										**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Week	**Week -4 to Day -4**		**Baseline/ Day 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**Week 20 (EOT) [8]**	**Week 24 (follow-up)**
Resume epoetin alfa dosing (or another ESA) after EOT with vadadustat (vadadustat treatment arm) [7]													X	
Review use of rescue therapy (RBC transfusions and epoetin alfa rescue therapy)			X	X	X	X	X	X	X	X	X	X	X	X
Review use of iron supplementation			X	X	X	X	X	X	X	X	X	X	X	
Review use of therapeutic phlebotomy				X	X	X	X	X	X	X	X	X	X	X

Abbreviations: diff, differential; EOT, end-of-treatment visit; ESA, erythropoiesis-stimulating agent; SV1, screening visit 1; SV2, screening visit 2

[1] Written informed consent will be obtained prior to performing any study procedures. During screening or at any study visit thereafter, subjects will also be asked to provide optional written informed consent to obtain and store a blood sample for future genetic analyses.

[2] On Day 1, subjects will withhold dosing until it is confirmed which treatment arm (vadadustat or epoetin alfa) they are assigned to.

[3] Baseline dialysis adequacy will be reported from dialysis performed during screening.

[4] The first sample will be collected prior to vadadustat administration and the second sample will be collected at least 15 minutes post dialysis. If post dialysis collection is not possible, the second sample will be collected at least 3 hours after vadadustat administration. The time of the last dose of vadadustat taken prior to the PK sampling, as well as the timing of the PK sample collection, will be documented.

[5] Subjects randomized to the epoetin alfa arm will take the same dose of epoetin alfa they took during screening. During the study, the dose will be administered by site staff in the clinic on dialysis days. The dose may be titrated as clinically indicated based on the subject's central lab Hb value and the approved label for adult patients with CKD on dialysis.

[6] Subjects randomized to the vadadustat arm will discontinue their epoetin alfa and take their first dose of vadadustat in the clinic. During the study, subjects will self administer their assigned dose of vadadustat at approximately the same time each day (refer to Section 8.3.5). The dose will be titrated in accordance with the protocol dosing guidelines for vadadustat (Section 8.3.5). On days when PK samples are collected, subjects will administer their dose of vadadustat in the clinic. See foot note 4 above.

[7] After the end of vadadustat treatment at Week 20 (or following early discontinuation of vadadustat), subjects will resume dosing with epoetin alfa (or another ESA) based on the approved label for adult patients with CKD on dialysis and the investigative site's standard of care.

[8] In the event a subject discontinues early from the study prior to Week 20, the assessments listed under Week 20 (EOT) visit should be completed within 1 day of study discontinuation, followed by participation in a 4-week safety follow-up period, and a safety follow-up visit (which will include the assessments listed under Week 24 [follow-up] visit).

19 APPENDIX B: HISTORY OF AMENDMENTS TO THE PROTOCOL

Amendment 1 (Version 2; 18 July 2017)

The rationale for amending the protocol is to characterize the effect of vadadustat as a single agent versus epoetin alpha in subjects not responsive (also known as ESA hyporesponders) to epoetin alpha, [redacted] Understanding the ability of vadadustat alone to increase Hb concentrations is an important step in characterizing the effect of vadadustat in this population. This amendment also allows for characterization of the vadadustat dosing required to affect a Hb change. The safety profile of vadadustat in ESA hyporesponder patients will also be summarized. The data from this study, together with data from the ongoing Phase 3 INNO2VATE study, which is evaluating vadadustat in subjects on dialysis three times weekly, will inform Akebia on possible next steps in a hyporesponder population.

The major changes are summarized below:

1. The objectives and endpoints of the study were modified to be exploratory in nature and the statistical analysis was revised to be descriptive.
2. The total number of subjects to be evaluated was reduced from 78 (39 per arm) to 50 (25 per arm).
3. The starting dose was changed from [redacted] to further explore [redacted] as a starting dose in this difficult to treat (ESA hyporesponder) DD-CKD population. Subjects will initiate dosing with vadadustat at a dose of [redacted] daily with the flexibility to adjust doses as required [redacted] to maintain Hb between 10 to 11 g/dL. This allows for a wide range of doses that can be used to treat this challenging population who previously were unable to maintain Hb within the target range of 10.0 11.0 g/dL despite receiving high doses of epoetin alfa.

   [redacted]
4. To minimize the potential risk for Hb excursions from the add-on effect of vadadustat with epoetin alfa, and to better understand the effect of vadadustat alone in raising Hb in this population, subjects randomized to the vadadustat arm will discontinue treatment with epoetin alfa and be directly switched to vadadustat on Day 1.

5. In order to limit enrollment of subjects who may require adjustment of their baseline ESA dose or transfusion in the near term, inclusion criteria #4 was expanded to include subjects with a Hb between 8.5 and 10 g/dl.
6. To be consistent with the vadadustat Phase 3 program, requirements for serum ferritin levels were lowered to ≥100 ng/mL from ≥200 ng/mL throughout the document, and exclusion criteria #9 and #10 regarding histories for DVT and active malignancies, respectively, were modified.
7. A clarification that an Akebia internal Safety Monitoring Committee (SMC) will review safety on an ongoing basis was added.
8. This amendment also includes administrative clarifications.