CLINICAL PROTOCOL

PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-FINDING STUDY TO ASSESS THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF VADADUSTAT IN JAPANESE SUBJECTS WITH ANEMIA SECONDARY TO DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (DD-CKD)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0022
Phase:	Phase 2
Version Number; Date:	Version 1; 3 August 2016 (Original Protocol) Version 2; 23 November 2016
Sponsor:	Akebia Therapeutics, Inc. 245 First Street, Suite 1100 Cambridge, MA 02142 United States of America

NCT Number: NCT03054350
This NCT number has been applied to the document for purposes of posting on clinicaltrials.gov

1 SIGNATURE PAGES

1.1 Protocol Approval

[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 to 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 Conference on Harmonization Guidance for Industry, Good Clinical Practice E6.
- 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.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Phone Number

_____

Full Address

_____

_____

TABLE OF CONTENTS

LIST OF TABLES

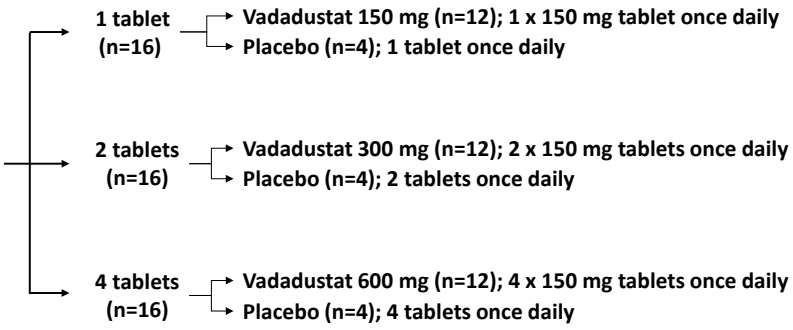
LIST OF FIGURES

2 PROTOCOL SYNOPSIS

Study Title	Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Assess the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Vadadustat in Japanese Subjects with Anemia Secondary to Dialysis-Dependent Chronic Kidney Disease (DD-CKD)
Protocol Number	AKB-6548-CI-0022
Study Phase	Phase 2
Investigational Product	Vadadustat; each tablet contains 150 mg of vadadustat for oral administration
Study Population	The study population will consist of male and female Japanese adults aged 20 years or older with anemia secondary to DD-CKD
Investigative Sites	Approximately 35 sites in Japan
Planned Number of Subjects	Approximately 48 subjects will be enrolled in the study, with 36 subjects receiving one of 3 doses of vadadustat and 12 subjects receiving placebo during the primary efficacy period: • 150 mg vadadustat once daily (n=12) • 300 mg vadadustat once daily (n=12) • 600 mg vadadustat once daily (n=12) • Placebo (n=12)
Study Objectives	• **Primary Objective:** To assess the dose-response relationship between oral vadadustat once daily dosing for 6 weeks and the change in hemoglobin (Hb) in Japanese subjects with anemia secondary to DD-CKD; this is to define the starting dose for use in Phase 3 clinical studies in Japan • **Secondary Objectives:** – To assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of oral vadadustat once daily dosing in Japanese subjects with anemia secondary to DD-CKD during the 6-week, primary efficacy period – To evaluate the effect of dose adjustments and demonstrate the maintenance effect on Hb during a 10-week dose adjustment and maintenance period – To assess the time to reach the target Hb level from baseline
Overview of Study Design	This is a Phase 2, randomized, double-blind, placebo-controlled, dose-finding study to assess the efficacy, safety, tolerability, PK, and PD of orally administered vadadustat in Japanese subjects with anemia secondary to DD-CKD. The study will include the following periods: • Eligibility screening period (up to 11 weeks) • Primary efficacy period (6 weeks; Weeks 1 to 6) • Dose adjustment and maintenance period (10 weeks; Weeks 7 to 16) • Follow-up period (2 weeks; Weeks 17 and 18) During the screening period, subjects who have recently received ESA therapy and otherwise meet eligibility criteria will be required to washout from ESA therapy prior to evaluation of screening Hb (see "Inclusion Criteria" below). Following the screening period, eligible subjects will be randomized to receive blinded study drug, either vadadustat (150, 300, or 600 mg vadadustat) or placebo. See "Dosage and Regimen" below for additional information regarding the randomization scheme.

	Fixed-dose treatment during the primary efficacy period will allow a dose-response relationship to be established. No increase in study drug dose is permitted during this period. However, if Hb level increases rapidly or if the Hb level exceeds 13.0g/dL the study drug dose can be decreased or interrupted following the dose adjustment guidelines listed under "Dosage and Regimen" (see below). After completing the primary efficacy period, subjects will continue to a 10-week dose adjustment and maintenance period. Subjects receiving placebo will be switched to vadadustat, and study drug dose will be adjusted to achieve a target Hb of 10.0-12.0 g/dL based on dose adjustment guidelines (see "Dosage and Regimen," below). Study drug will be discontinued after the dose adjustment and maintenance period has been completed (Week 16) and subjects will continue to a 2-week follow-up period (Week 17-18).
Study Duration	Study duration will depend on ESA use as follows: • For subjects who were not prescribed ESAs prior to study entry: Up to 22 weeks, including the eligibility screening period (up to 4 weeks, with 2 screening visits), primary efficacy period (6 weeks), dose adjustment and maintenance period (10 weeks), and follow-up period (2 weeks) • For subjects who were prescribed ESAs prior to study entry: Up to 29 weeks, including the eligibility screening period (up to 11 weeks, with 3 screening visits), primary efficacy period (6 weeks), dose adjustment and maintenance period (10 weeks), and follow-up period (2 weeks) Note: Subjects who discontinue prematurely from the study or permanently discontinue study medication will complete the end-of-treatment (Week 16) visit followed in two weeks by the Week 18 visit.
Key Inclusion Criteria (the complete list is provided in the protocol)	• Male and female Japanese subjects (20 years or older) • Receiving chronic maintenance hemodialysis for end-stage kidney disease for at least 8 weeks prior to screening • ESA status and screening Hb that meet one of the following criteria: – For subjects who are not being treated with ESAs: Mean Hb <10.0 g/dL; average of 2 measurements obtained during screening. These subjects must be off ESAs for at least the following periods of time prior to screening visit 1: • 2 weeks for epoetin alfa, epoetin beta, or epoetin kappa; • 4 weeks for darbepoetin alfa; • 8 weeks for epoetin beta pegol. – For subjects who are being treated with ESAs: Mean Hb <10.0 g/dL; average of 2 measurements obtained during screening after the protocol-defined ESA washout period. These subjects must washout ESA therapy for the following periods of time during the screening period, beginning at screening visit 1 and prior to screening visit 2: • 2 weeks for epoetin alfa, epoetin beta, and epoetin kappa; • 4 weeks for darbepoetin alfa; • 8 weeks for epoetin beta pegol. • Serum ferritin ≥50 ng/mL during screening • Transferrin saturation (TSAT) ≥20% during screening • Folate and vitamin B12 ≥lower limit of normal during screening • For subjects who are receiving oral or intravenous iron supplementation, the dose of iron supplementation must be stable for at least 28 days prior to the screening period. For subjects who are not receiving oral or intravenous iron supplementation, no iron supplementation may have been administered for at least 28 days prior to the screening

	period.
Key Exclusion Criteria (the complete list is provided in the protocol)	Anemia due to a cause other than CKD or presence of active bleeding or recent blood loss; sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia; red blood cell (RBC) transfusion within 4 weeks prior to or during screening; anticipated to recover adequate kidney function to no longer require hemodialysis during study participation; on peritoneal dialysis or expected to change dialysis modality during study participation; and hypo-responsiveness to ESA defined as any of the following ESA treatments within 8 weeks prior to screening: (i) intravenous epoetin dose ≥3000 units/dose 3 times a week (9000 units/week), (ii) intravenous darbepoetin alfa dose ≥60 µg once a week, or (iii) epoetin beta pegol ≥200 µg once a month or ≥100 µg once every 2 weeks
Retesting/ Rescreening	Subjects who initially fail to qualify for the study based on laboratory test results may be retested once within the screening period, at the investigator's discretion. Subjects who fail to meet the qualifying criteria for Hb during screening may be considered for rescreening at the discretion of the investigator, if it is felt 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 replacement therapy. Screening is limited to 3 attempts (initial screening and 2 additional rescreening attempts).
Efficacy and Pharmacokinetic Endpoints	Note that a pre-treatment average value for Hb is defined as the average of 3 values obtained prior to dosing, ie, the 2 qualifying screening values and the baseline value. **Primary Endpoint:** • Mean change in Hb levels from pre-treatment to the end of the primary efficacy period (Week 6) **Secondary Endpoints:** • Time to reach target Hb level of 10.0-12.0 g/dL from baseline • Mean Hb levels at the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16) • Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the dose adjustment and maintenance period (Week 16) • Mean change in Hb between pre-treatment and the end of the dose adjustment and maintenance period (Week 16) • Mean change in hematocrit, RBC count, and reticulocyte count from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16) • Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, and ferritin) and hepcidin from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16) • Proportion of subjects requiring rescue with RBC transfusion from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16) • Proportion of subjects requiring rescue with ESAs from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16) • Number of dose adjustments from baseline to the end of the dose adjustment and maintenance period (Week 16) • Plasma concentration profile of vadadustat and its metabolites using pre-dose sample from Week 4

Safety Endpoints	Safety assessments, including adverse events, vital signs, electrocardiograms (ECGs), and other laboratory assay results (eg, chemistry, components of the complete blood count [CBC] other than the ones noted above, and vascular endothelial growth factor [VEGF])
Dosage and Regimen	Study drug will be administered on an outpatient basis. Subjects should take the study medication with water or another beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food. **<u>Primary efficacy period (Day 1 to Week 6)</u>** Using a central randomization system, subjects will be randomized at a 1:1:1 ratio to receive 1 tablet (150 mg vadadustat or placebo), 2 tablets (300 mg vadadustat or placebo), or 4 tablets (600 mg vadadustat or placebo) of study drug. Within each tablet-count group, subjects will be randomized 3:1 to receive vadadustat or placebo as shown below. **Figure. Treatment Randomization Scheme**  The primary efficacy period involves fixed-dose treatment to establish a dose-response relationship. No increase in study drug dose is permitted during this period. However, the dose may be decreased or interrupted as described below. • If the Hb increases rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose by 1 tablet. • If the Hb exceeds 13.0 g/dL, interrupt study drug until the Hb decreases to 12.5 g/dL or below and then resume dosing with 1 fewer tablet. If dose reduction or interruption is recommended based on the central laboratory Hb result and protocol-specified guidelines, the investigative site will contact the subject within 1 business day of receiving the Hb result from the central laboratory. If possible, the subject will be scheduled for an additional visit within 3 business days. If scheduling the subject within this time frame is not possible, dosing instructions will be provided to the subject over the telephone. **<u>Dose adjustment and maintenance period (Weeks 7 to 16):</u>** Subjects who complete the primary efficacy period will enter the dose adjustment and maintenance period. Subjects receiving placebo will be switched to vadadustat. Dose adjustments for study drug will follow the dose adjustment guidelines listed below to achieve a target Hb of 10.0-12.0 g/dL. Dose adjustments will be based on central laboratory Hb results from study visits at Weeks 6, 8, 10, 12, and 14. • Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased based on Hb results from the Week 6 visit and the subject remains below the Hb target, the next opportunity to further increase the dose would be based on Hb results from the Week 10 visit. Decreases in dose can occur more frequently. Avoid frequent dose adjustments. • If the Hb has not increased by more than 0.5 g/dL above the baseline value after the

	first 6 weeks of treatment, increase the dose by 1 tablet. • Increase the dose by 1 tablet every 4 weeks until Hb is above 10.0 g/dL (maximum dose is 4 tablets). • If the Hb increases rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose by 1 tablet. • If the Hb falls below 10.0 g/dL, increase the dose by 1 tablet. • If the Hb exceeds 12.0 g/dL, reduce the dose by 1 tablet. • If the Hb exceeds 13.0 g/dL, interrupt study drug until the Hb decreases to 12.5 g/dL or below and then resume dosing with 1 fewer tablet. • If a dose adjustment is required to maintain Hb at the desired level, the dose adjustment is by 1 tablet. If dose adjustment is recommended based on the central laboratory Hb result and protocol-specified guidelines, the investigative site will contact the subject within 1 business day of receiving the Hb result from the central laboratory. If possible, the subject will be scheduled for an additional visit within 3 business days to discuss the dosing change and to dispense additional study drug if necessary (for subjects who receive a dose increase). If scheduling the subject within this time frame is not possible, dosing instructions will be provided to the subject over the telephone. Note: If subjects fail to achieve target Hb level despite administration of 4 tablets of study drug per day, this will not be considered a reason for subject discontinuation unless the subject initiates rescue therapy (see "Rescue Therapy Guidelines" below).
Rescue Therapy Guidelines	ESA Rescue Therapy In order to standardize the use of ESA rescue in the study, the following guidelines should be followed. ESA rescue therapy may be considered if: • ESA is considered warranted by the investigator's judgment, AND • The subject experiences a clinically significant worsening of anemia or symptoms of anemia, AND • The subject has a confirmed Hb level <9.0 g/dL as defined by two consecutive Hb levels <9.0 g/dL. The investigator may schedule the subject to return for an unscheduled visit to confirm Hb level <9.0 g/dL prior to the subsequent scheduled study visit. If clinically indicated, the investigator at his/her discretion may initiate ESA rescue therapy without a confirmatory Hb level <9.0 g/dL if the first two criteria above are met. Red Blood Cell Transfusions Investigators should use their local institution's transfusion guidelines when determining whether to transfuse a study subject. Subjects who initiate either rescue therapy, ESA Rescue Therapy or Red Blood Cell Transfusion, will be required to stop study drug treatment and will be discontinued from the study. See "Study Duration" for follow-up of subjects who discontinue early from the study.
Iron Supplementation	Subjects who are receiving a stable dose of oral or intravenous iron supplementation for at least 28 days prior to the screening period should continue their iron supplementation at the same dose and route of administration through the primary efficacy period (through Week 6). Changes to iron supplementation dose during the primary efficacy period will be considered protocol deviations but will not be considered a reason for subject discontinuation. After the Week 6 visit, investigators should prescribe iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT <20%, and the dose and route of iron administration will be

	selected at the investigator's discretion. Subjects who <u>are not receiving</u> iron supplementation at the beginning of the screening period <u>should not start</u> iron supplementation through the primary efficacy period (through Week 6). Initiation of iron supplementation during the primary efficacy period will be considered a protocol deviation but will not be considered a reason for subject discontinuation. After the Week 6 visit, investigators should prescribe iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT <20%, and the dose and route of iron administration will be selected at the investigator's discretion. **<u>Important</u>:** Because of the potential for oral iron to reduce the bioavailability of vadadustat, study drug (vadadustat or placebo) should not be administered concurrently with any oral iron supplement. Any oral iron supplements (including multivitamins containing iron) should be taken at least 2 hours before or 2 hours after the dose of study drug.
Statistical Considerations	An analysis of covariance (ANCOVA) model will be used to compare change from pre-treatment in Hb between the 3 vadadustat dosing groups and the placebo group. The model will include treatment assignment (3 dosed groups and 1 placebo group) and pre-treatment Hb value as a covariate. A step-down procedure will be used to control the overall type I error rate for the multiple comparisons. Testing of the highest dose compared with placebo will be conducted first. If and only if this comparison is significant, then testing will proceed to comparison of the next lower dose and placebo, and so on. Thus, no multiplicity adjustment will be needed for this analysis. The sample size and power calculations are based on results from Study AKB-6548-CI-0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to non-dialysis-dependent CKD. It is reasonable to extrapolate these data to the current study based on the following findings: • PK parameters of vadadustat are similar between CKD patients who are receiving hemodialysis (Study AKB-6548-CI-0009) and CKD patients who are not receiving dialysis (Study AKB-6548-CI-0003) • Hemodialysis procedure has no significant impact on the PK of vadadustat (Study AKB-6548-CI-0009) • The dose range of 150-600 mg of vadadustat to be used in the current study has been shown to be generally well-tolerated and efficacious in raising and/or maintaining Hb at the desired target level in CKD patients who were either on hemodialysis (Study AKB-6548-CI-0011) or CKD patients who were not on dialysis (Studies AKB-6548-CI-0005 and AKB-6548-CI-0007) The target enrollment will be approximately 48 subjects for the study with 12 subjects enrolled in each of the 4 treatment groups. The study is powered based on a comparison of the highest dose vadadustat group (600 mg daily) and the placebo group. Based on the results from Study AKB-6548-CI-0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to NDD-CKD, it is assumed that the expected mean Hb changes from pre-treatment to Week 6 will be approximately 0 mg/dL for the placebo group and 1.35 g/dL for the highest dose vadadustat group (600 mg daily). Based on the results from Study AKB-6548-CI-0011 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to DD-CKD, it is assumed that the common Hb standard deviation will be 0.9 g/dL across treatment groups. In addition, a dropout rate of 10% is assumed. With these assumptions, the study with n=12 subjects per group will have >85% power to detect the difference between treatment group and control group, at 2-sided alpha of 0.05. In addition to the final analysis which will take place when all subjects have completed the study and will include all data collected, the 6-week efficacy and safety data will be

	summarized for administrative planning purposes after the last patient completes the primary efficacy period (Week 6). The preliminary analysis will be performed and interpreted by sponsor and CRO study team personnel. Subjects and sites will not be unblinded to treatment allocation. Individuals from the sponsor and CRO study teams who are unblinded for the development and reporting of the preliminary analysis will not be involved in the conduct of the study after the preliminary analysis. As the study conduct and final analysis will not be modified by this analysis, no alpha adjustment is proposed. It is expected that this 6week data will be identical for the preliminary administrative analysis and the final analysis of the complete dataset. Any changes between the preliminary analysis and the final analysis will be documented.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
BV	baseline visit
C	Celsius
CBC	complete blood count
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
CV	cardiovascular
DD-CKD	dialysis-dependent chronic kidney disease
dL	deciliter
DVT	deep venous thrombosis
ECG	electrocardiogram
EDC	electronic data capture
EOT	end-of-treatment
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
Hb	hemoglobin
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl hydroxylase
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board

IV	intravenous
JSN	Japanese Society of Nephrology
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat (population)
µM	micromolar
mg	milligram
mL	milliliter
NDD-CKD	non-dialysis dependent chronic kidney disease
ng	nanogram
PD	pharmacodynamics(s)
PE	pulmonary embolism
PK	pharmacokinetic(s)
PP	per protocol
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SV	screening visit
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 Proposed Indication of Renal Anemia

Chronic kidney disease (CKD) is defined using the following criteria in accordance with the guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF 2002) and Kidney Disease Improving Global Outcomes (KDIGO 2012):

- Kidney damage for greater than 3 months, with or without decreased glomerular filtration rate (GFR) (ie, pathologic abnormalities or markers of damage, including abnormalities in composition of the blood or urine, or abnormalities in imaging tests)
- Decreased GFR levels (ie, less than 60 mL/min/1.73 m^2; GFR categories G3a-G5) for greater than 3 months, with or without kidney damage

CKD is a major public health problem worldwide. In Japan, the prevalence of GFR less than 60 mL/min/1.73 m^2 is estimated to be 20% of the adult population (Iseki 2008). The number of CKD patients in Japan who require dialysis is >300,000 and has been increasing continually over the last 30 years (Imai 2011).

The prevalence and severity of renal anemia in CKD increases as renal function deteriorates. Anemia generally exists when hemoglobin (Hb) is less than 13 g/dL in men or less than 12 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 erythropoietin (EPO) to adjust the production of red blood cells (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.

As CKD progresses, the combined effect of decreased RBC production from lower EPO signaling, increased rate of RBC destruction, and reduced iron availability to the bone marrow results in the increased prevalence and severity of anemia.

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 Available Therapies for Anemia in Patients with CKD

Erythropoiesis-stimulating agent (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 trials in patients with CKD (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 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 trials have led to changes in prescribing information and clinical practice guidelines in the USA and Europe.

In the USA, 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 European Union (EU) Summary of Product Characteristics (SmPC) for ESAs suggests caution with the use of ESAs with a recommendation to keep Hb levels between 10-12 g/dL. Furthermore, recent clinical practice guidelines (Locatelli 2013) recommended that risk factors for stroke (including a past history of stroke) and the presence of active malignancy or a past history of malignancy should be taken into account when making treatment decisions to use ESAs for the treatment of anemia.

Although the CV risk is lower in Japanese subjects compared with Caucasian subjects, guidelines from the Japanese Society of Nephrology (JSN 2014) stated that ESA treatment targeting Hb levels 12–13 g/dL did not seem to be effective for preventing CKD progression or decreasing the incidence of CV disease compared to the Hb level of 9-11.5 g/dL, but rather had the potential to lead to an increase in the incidence of CV disease.

The risks associated with currently available recombinant ESAs, including an increased risk for death and CV events, highlight the need for novel therapies that may potentially minimize or avoid such risks and slow CKD progression.

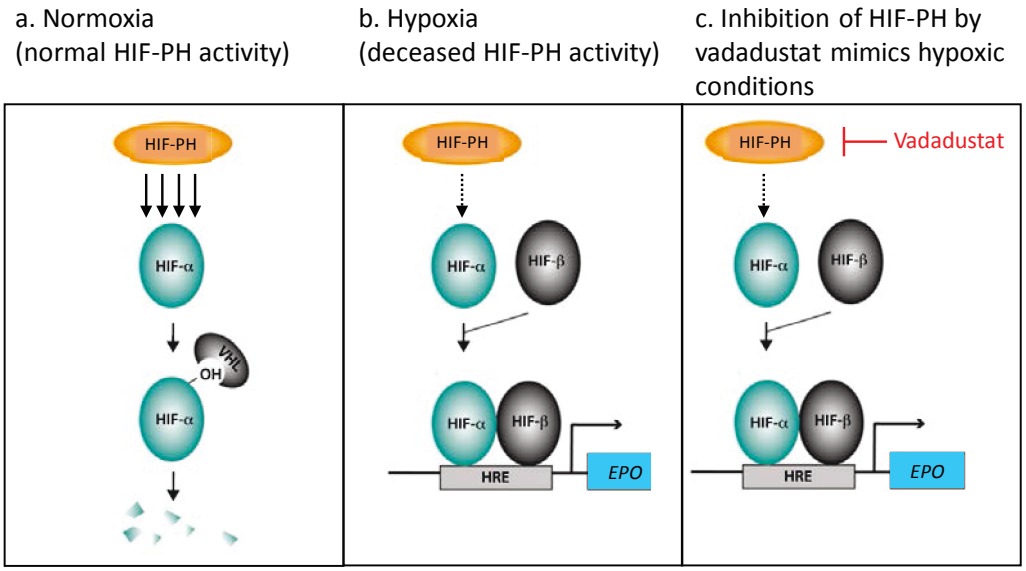
4.3 Hypoxia-Inducible Factor

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

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.

Vadadustat has compelling clinical data with several potential safety and efficacy advantages over current injectable recombinant ESA therapy for the treatment of renal anemia:

- *Vadadustat significantly increases and maintains Hb levels in CKD patients with anemia:* We have successfully completed two Phase 2 trials in patients with non-dialysis dependent chronic kidney disease (NDD-CKD) which 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 Phase 2b study (AKB-6548-CI-0007), vadadustat effectively increased Hb while minimizing Hb excursions ≥13.0 g/dL. Only 4.3% of patients on

vadadustat had a single excursion ≥ 13.0 g/dL. In addition, a third Phase 2 trial (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.

- *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 trials, vadadustat has demonstrated improved iron mobilization as reflected by a decrease in hepcidin and ferritin levels and an increase in total iron binding capacity. 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 program in DD-CKD patients.
- *Differentiated safety profile:* Vadadustat's novel 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 and/or excursions (McCullough 2013). The incidence of CV adverse events on vadadustat as compared with ESAs will be assessed in the global Phase 3 program. 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.

Overall, vadadustat has demonstrated consistent, dose-proportional pharmacodynamics (PD), producing the desired and anticipated effects of raising EPO concentrations in a dose-dependent manner in both Phase 1 and Phase 2 studies. The changes in EPO have been accompanied by dose-responsive increases in iron mobilization (increased total iron binding capacity [TIBC] and transferrin, and decreased hepcidin and ferritin). Together, these effects stimulated an increase in reticulocytes and Hb. Thus, current data support both an efficacious dose range and a controlled means of dose adjustment for vadadustat that optimizes individualized patient dosing. Additionally, vadadustat has been generally well tolerated.

Vadadustat is eliminated from the body by dual routes of 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. In a clinical

study in hemodialysis patients, it was determined that dialysis treatment did not have a notable effect on the PK parameters of vadadustat, indicating that vadadustat can be administered irrespective of the dialysis treatment.

A Phase 2a randomized, placebo-controlled, 6-week, dose range-finding study was performed in subjects with anemia (HGB ≤10.5 g/dL) secondary to NDD-CKD. The results demonstrated a significant dose-related increase in Hb and TIBC and decreases in hepcidin and ferritin. The plasma concentrations of vadadustat and the glucuronide metabolites exhibited a dose-related increase. Vadadustat was generally well tolerated.

A completed Phase 2b, randomized, double-blind, placebo-controlled study to assess the hematologic PD response, safety, and tolerability of oral vadadustat for 20 weeks was performed in 210 subjects with anemia associated with NDD-CKD (AKB-6548-CI-0007). Subjects were assigned to a study group based on their ESA status at screening (naïve, previously treated, or actively treated) and were randomized 2:1 to receive either vadadustat at a starting dose of 450 mg/day or placebo. The dose of vadadustat was adjusted based on Hb levels and changes in Hb. A significantly higher proportion of subjects with a successful Hb response at the end of treatment was observed with vadadustat treatment when compared with placebo ($p<0.0001$). The dosing algorithm was effective in minimizing excessive Hb levels (>13.0 g/dL) and a consistent and sustained improvement in iron mobilization was observed with vadadustat treatment. The safety profile of vadadustat in this study was generally consistent with that observed in prior clinical studies.

Based on the Phase 1 and Phase 2 study results, vadadustat is a suitable candidate for continued development as a treatment for anemia in patients with CKD.

4.6 Ethno-Bridging Data from a Study of Healthy Japanese and Caucasian Volunteers

Study AKB-6548-CI-0020 was a randomized, double-blind, placebo-controlled, dose escalation study conducted at a single clinical site in the United States. The study was conducted to compare the pharmacokinetics (PK) and PD of vadadustat in healthy adult male and female volunteers of Japanese and Caucasian descent.

Brief Overview of Study Design

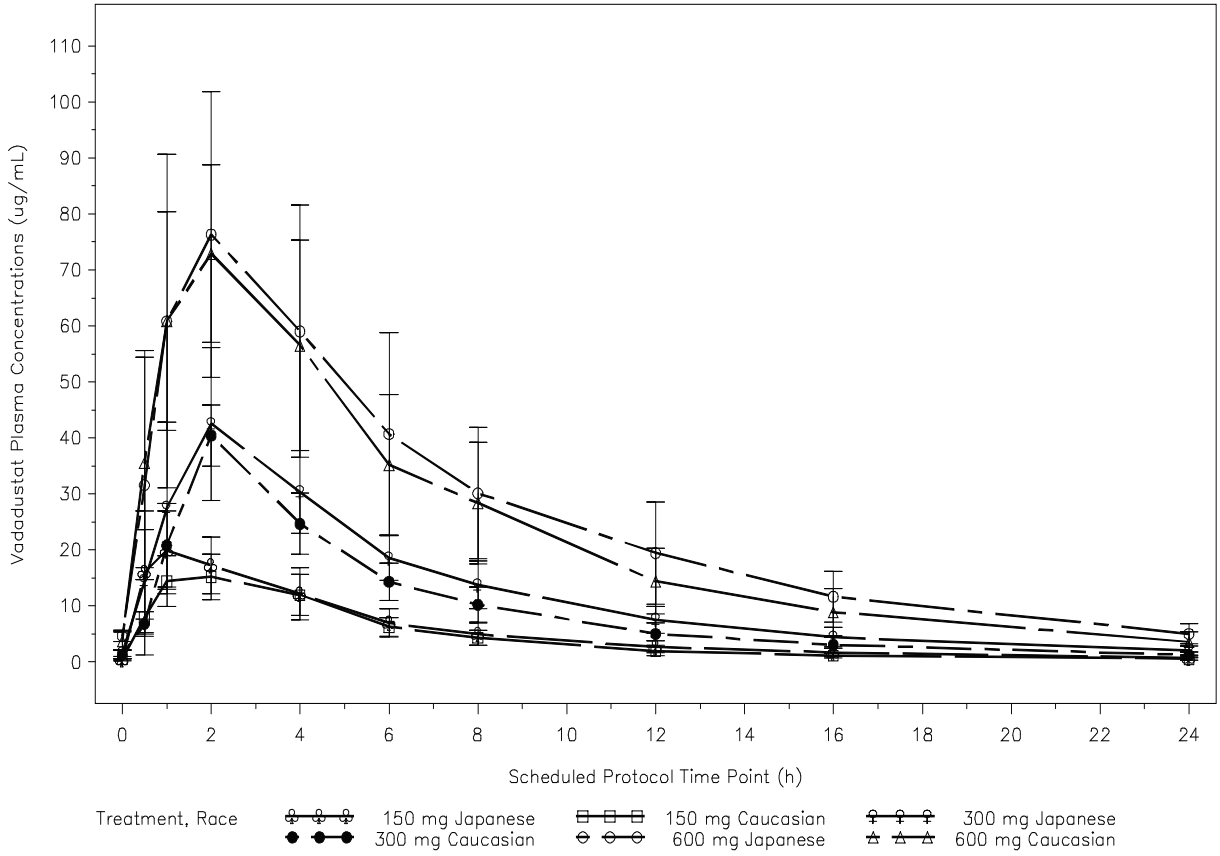
The primary study entry criteria included male or female subjects between 20 and 55 years of age, with a body mass index of 18-30 kg/m^2, and a body weight of 45-90 kg for Japanese subjects and a body weight of 50-100 kg for Caucasian subjects. For study eligibility, the Caucasian subjects had to be Caucasian of European or Latin American descent. The Japanese subjects had to fulfill the following eligibility criteria: Must have been born in Japan; must have had 2 biological Japanese parents and 4 Japanese grandparents as confirmed by interview; must have been living outside of Japan for up to 10 years at the time of the screening visit; and the subject's lifestyle, including diet, must not have changed significantly since leaving Japan.

Eligible subjects were enrolled into one of 3 dose cohorts: 150, 300, or 600 mg daily oral doses of vadadustat (or placebo). Subjects received daily doses of study drug (either vadadustat or placebo) for 10 days. Each of the 3 dose cohorts enrolled 8 Japanese and 8 Caucasian subjects. Within each dose cohort assignment, subjects were randomized at a 3:1 ratio to receive either vadadustat (n=6) or placebo (n=2).

Brief Overview of Study Results

Based on the study results, the PK and PD of vadadustat are similar in healthy Caucasian and Japanese subjects with no ethnic factors identified. The mean plasma concentration versus time plot for vadadustat is shown in Figure 2. Although there is a slight increase in the EPO exposure in Japanese subjects at the highest dose (600 mg); this increase is not clinically meaningful. The mean reticulocyte concentrations in subjects of both ethnicities is also similar. EPO levels following vadadustat dosing were within normal physiologic range, at a concentration below EPO receptor saturation, and substantially lower than EPO levels following ESA dosing. Vadadustat was generally well tolerated in this study.

Figure 2 Mean (± Standard Error) Plasma Concentration versus Time Profiles Following Administration of a Repeated Once Daily Oral Dose of Vadadustat to Healthy Caucasian and Japanese Subjects on Day 10 (Study AKB-6548-CI-0020)



4.7 Potential Benefits and Risks

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

Vadadustat offers the potential of flexible oral dosing that is easier to adjust than injectable hormone ESAs. This alternate therapeutic approach may avoid the excursions 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 suggestion from the US Food and Drug Administration (FDA) that fluctuations in Hb concentrations, rapidly increasing Hb levels, and excursions above the target level are associated with an increased risk of CV events (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, a prominent effect on iron metabolism was noted with the dosing of vadadustat, including a rapid increase in iron uptake, a dose responsive increase in TIBC, decreases in hepcidin and ferritin, and an increase in transferrin. A similar pattern was observed in the Phase 2a and 2b studies, with dose responsive increases in TIBC and decreases in ferritin and hepcidin.

To date, the acute findings observed at doses less than the maximum tolerated dose (MTD) in animals have been shown to be reversible and dose-related. In addition, most of the findings have followed a pattern that would have been predicted based on the known HIF and HIF-PH biochemistry, pharmacology, and human genetic variations (eg, Chuvash polycythemia). In the completed clinical studies, vadadustat has been generally well-tolerated.

5 STUDY OBJECTIVES AND ENDPOINTS

Note that a pre-treatment average value for Hb is defined as the average of 3 values obtained prior to dosing, ie, the 2 qualifying screening values and the baseline value.

5.1 Primary Objective and Endpoint

The primary objective of this study is to assess the dose-response relationship between oral vadadustat once daily dosing for 6 weeks and the change in hemoglobin (Hb) in Japanese subjects with anemia secondary to DD-CKD; this is to define the starting dose for use in Phase 3 clinical studies in Japan.

The primary endpoint that will be used to assess this objective is the mean change in Hb levels from pre-treatment to the end of the primary efficacy period (Week 6).

5.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of oral vadadustat once daily dosing in Japanese subjects with anemia secondary to DD-CKD during the 6-week, primary efficacy period
    - To evaluate the effect of dose adjustments and demonstrate the maintenance effect on Hb during a 10-week dose adjustment and maintenance period

The efficacy endpoints that will be used to assess these objectives include the following:

- Time to reach target Hb level of 10.0-12.0 g/dL from baseline
- Mean Hb levels at the end of the primary efficacy period (Week 6) and at the end of the dose adjustment and maintenance period (Week 16)

- Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the dose adjustment and maintenance period (Week 16)
- Mean change in Hb between pre-treatment and the end of the dose adjustment and maintenance period (Week 16)
- Mean change in hematocrit, RBC count, and reticulocyte count from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16)
- Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, and ferritin) and hepcidin from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16)
- Proportion of subjects requiring rescue with RBC transfusion from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16)
- Proportion of subjects requiring rescue with ESAs from baseline to the end of the primary efficacy period (Week 6) and the end of the dose adjustment and maintenance period (Week 16)
- Number of dose adjustments from baseline to the end of the dose adjustment and maintenance period (Week 16)
- Plasma concentration profile of vadadustat and its metabolites using pre-dose sample from Week 4

The safety endpoints that will be used to assess these objectives include the following:

- Safety assessments, including adverse events, vital signs, electrocardiograms (ECGs), and other laboratory assay results (eg, chemistry, components of the complete blood count [CBC] other than the ones noted above, and vascular endothelial growth factor [VEGF])

6 STUDY DESIGN

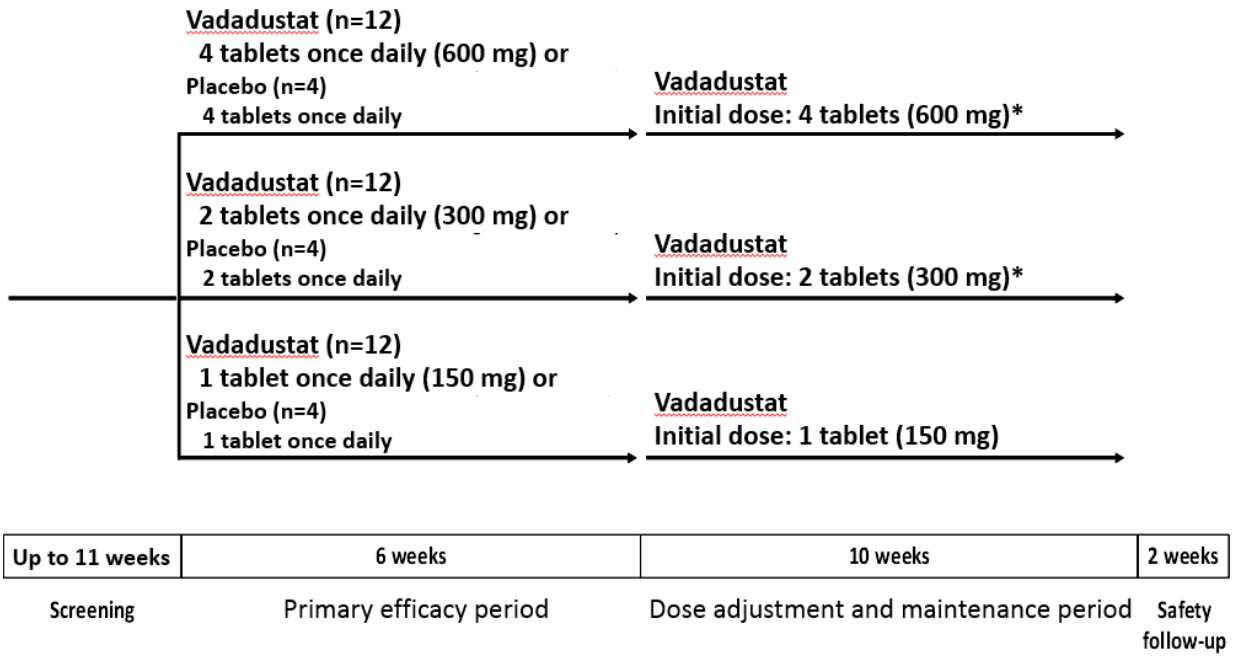
6.1 Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-finding study to assess the efficacy, safety, tolerability, PK, and PD of orally administered vadadustat in Japanese male and female subjects with anemia secondary to DD-CKD. The study does not include a pre-specified male-to-female ratio.

The study has a planned enrollment of 48 subjects to be enrolled at approximately 35 sites in Japan. There will be 16 subjects in each of the 3 tablet-count groups.

An overview of the study design is presented in Figure 3.

Figure 3: Overview of Study Design



* For subjects who develop an excess Hb response during the primary efficacy period, the number of tablets of study drug will be decreased (see Section 8.2.4). For these subjects, the number of tablets of vadadustat initiated at the Week 6 visit will be lower than indicated.

The study will include the following periods:

- Eligibility screening period (see Section 9.1 for additional information regarding screening visits and ESA washout period for subjects who were prescribed ESAs at study entry)
  - Up to 4 weeks for subjects who were not prescribed ESAs prior to study entry (Day -28 to Day 0)
  - Up to 6 weeks for subjects who were prescribed epoetin alfa, epoetin beta, and epoetin kappa prior to study entry (Day -42 to Day 0)
  - Up to 8 weeks for subjects who were prescribed darbepoetin alfa prior to study entry (Day -56 to Day 0)
  - Up to 11 weeks for subjects who were prescribed epoetin beta pegol prior to study entry (Day -77 to Day 0)
- Primary efficacy period (6 weeks; Weeks 1 to 6)
- Dose adjustment and maintenance period (10 weeks; Weeks 7 to 16)
- Follow-up period (2 weeks; Weeks 17 and 18)

Subjects will participate in a screening period to determine study eligibility. Subjects who have not recently received ESA therapy will participate in 2 screening visits. Subjects who have recently received ESA therapy and otherwise meet eligibility criteria will be required to washout

from ESA therapy prior to evaluation of screening Hb, and will participate in 3 screening visits (see Section 7.2).

Eligible subjects will be randomized following the screening period using a central randomization system. Subjects will be randomized 1:1:1 to receive 1, 2, or 4 tablets at their baseline visit (Day 1). Within each tablet-count group, subjects will be randomized 3:1 to receive vadadustat (150, 300, or 600 mg vadadustat) or placebo. See Section 8.2.2 for information regarding the randomization scheme.

Study drug treatment will be administered during a 6-week primary efficacy period. See Section 8.2.4 for information on study drug administration. The primary efficacy period includes fixed-dose treatment to establish a dose-response relationship. However, if Hb level increases rapidly or if the Hb levels exceeds 13 g/dL, the study drug dose can be decreased or interrupted (see Section 8.2.4).

After completing the primary efficacy period, subjects will continue to a 10-week dose adjustment and maintenance period (see Section 8.2.5). Subjects receiving placebo will be switched to vadadustat, and study drug dose will be adjusted to achieve a target Hb of 10.0-12.0 g/dL based on dose adjustment guidelines (see Section 8.2.5).

Vadadustat treatment will stop after the dose adjustment and maintenance period has been completed (Week 16) and subjects will continue in a 2-week follow-up period (Week 17-18).

For subjects who were not being treated with ESAs, the clinical and safety assessments will be performed as described in Section 9.4 and as listed in Appendices

Appendix A. For subjects who were being treated with ESAs prior to study entry, the clinical and safety assessments will be performed as described in Section 9.5 and as listed in Appendix B.

6.2 Study Duration

Study duration will depend on ESA use as follows:

- For subjects who were not prescribed ESAs at study entry: Up to 22 weeks, including the eligibility screening period (up to 4 weeks, with 2 screening visits), primary efficacy period (6 weeks), dose adjustment and maintenance period (10 weeks), and follow-up period (2 weeks)
- For subjects who were prescribed ESAs prior to study entry: Up to 29 weeks, including the eligibility screening period (up to 11 weeks, with 3 screening visits), primary efficacy period (6 weeks), adjustment and maintenance period (10 weeks), and follow-up period (2 weeks)

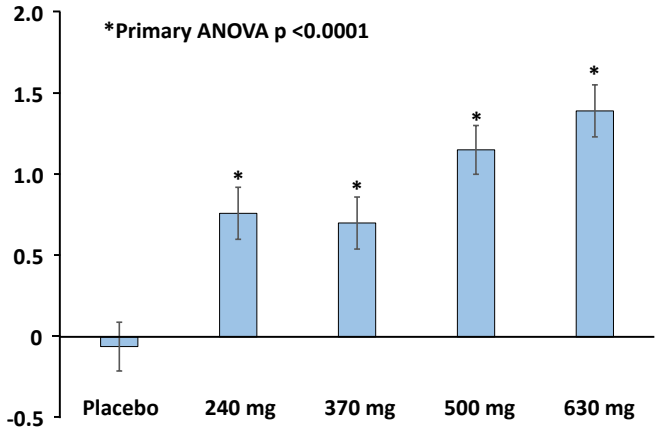
Note: See Section 7.6.3 for subjects who discontinue study drug or withdraw early from the study.

6.3 Rationale for Study Design

The study design of this randomized, double-blind, placebo-controlled, dose-finding study in Japanese subjects with anemia secondary to DD-CKD is modeled on a previously completed dose-finding study in subjects with anemia secondary to NDD-CKD that included a majority of Caucasian and Black/African American subjects (Study AKB-6548-CI-0005).

A treatment duration of 6 weeks will be adequate to demonstrate the dose-response relationship of vadadustat with change in Hb, as 6 weeks of treatment with vadadustat in Study AKB-6548-CI-0005 was adequate to establish a statistically significant dose-response relationship (as shown in Figure 4). An additional 10-week dose adjustment and maintenance period will be conducted to evaluate the effect of dose adjustments and demonstrate the maintenance effect on Hb.

Figure 4: Absolute Change in Hemoglobin (± Standard Error of Mean, g/dL) at Week 6 Compared to Baseline (Study AKB-6548-CI-0005)



Note: 25% of the subjects in the 630 mg vadadustat treatment group and 10% of subjects in the 500 mg vadadustat treatment group had their doses reduced by Week 4.

Note: Two tailed paired t-test of hemoglobin: Baseline versus Week 6, $p < 0.01$

6.4 Dose Justification

The doses to be used in the present study (150, 300, and 600 mg once daily) were previously evaluated in the ethno-bridging study (Study AKB-6548-CI-0020). The results from Study AKB-6548-CI-0020 showed that the doses are generally well tolerated, and similar PK and PD responses to vadadustat were demonstrated between the Caucasian and Japanese healthy subjects.

Furthermore, the same dose range of 150 mg to 600 mg was previously tested in US-based studies enrolling more than 200 subjects with either NDD-CKD (Phase 2 studies AKB-6548-CI-0005 and AKB-6548-CI-0007) or DD-CKD (Phase 2 study AKB-6548-CI-0011). In these completed studies, the dose range of 150-600 mg was shown to be generally well-tolerated, and efficacious in raising and/or maintaining Hb at the desired target level in patients with anemia secondary to NDD-CKD or DD-CKD. Importantly, the dose range provides great flexibility in enabling adjustment of vadadustat dose per an individual patient's Hb response. The product labeling for NESP® and ESPO® in Japan also allow for adjustable dosing based on Hb response in individual patients.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 General Criteria

To be eligible for this study, a subject or their legally acceptable representative must have provided valid informed consent and must meet the following criteria. No study procedures (including screening tests) may be performed until after the informed consent has been legally signed.

7.2 Inclusion Criteria

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

1. Male and female Japanese subjects (20 years or older)

2. Receiving chronic maintenance hemodialysis for end-stage kidney disease for at least 8 weeks prior to screening

3. ESA status and screening Hb that meet one of the following criteria:

    a. For subjects who are not being treated with ESAs: Hb <10.0 g/dL, average of 2 measurements obtained during screening. These subjects must be off ESAs for at least the following periods of time prior to screening visit 1 (refer to Appendix C for examples):

        i. 2 weeks for epoetin alfa, epoetin beta, or epoetin kappa;

        ii. 4 weeks for darbepoetin alfa;

        iii. 8 weeks for epoetin beta pegol.

    b. For subjects who are being treated with ESAs: Hb <10.0 g/dL, average of 2 measurements obtained during screening after the protocol-defined ESA washout period. These subjects must washout ESA therapy for the following periods of time during the screening period, beginning at screening visit 1 and prior to screening visit 2 (refer to Appendix C for examples):

        i. 2 weeks for epoetin alfa, epoetin beta, and epoetin kappa;

        ii. 4 weeks for darbepoetin alfa;

        iii. 8 weeks for epoetin beta pegol.

4. Serum ferritin ≥50 ng/mL during screening

5. Transferrin saturation (TSAT) ≥20% during screening

6. Folate and vitamin B12 ≥lower limit of normal during screening

7. For subjects who are receiving oral or intravenous iron supplementation, the dose of iron supplementation must be stable for at least 28 days prior to the screening period. For subjects who are not receiving oral or intravenous iron supplementation, no iron

supplementation may have been administered for at least 28 days prior to the screening period.

8. Understands the procedures and requirements of the study 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 study participation:

1. Anemia due to a cause other than CKD or presence of active bleeding or recent blood loss.

2. 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 hemodialysis during study participation.

5. On peritoneal dialysis or expected to change dialysis modality during study participation.

6. Hypo-responsiveness to ESA defined as any of the following ESA treatments within 8 weeks prior to screening: (i) intravenous epoetin dose ≥3,000 units/dose 3 times a week (9,000 units/week), (ii) intravenous darbepoetin alfa dose ≥60 µg once a week, or (iii) epoetin beta pegol ≥200 µg once a month or ≥100 µg once every 2 weeks.

7. 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 during screening. A history of Gilbert's syndrome is not an exclusion criterion.

8. Uncontrolled hypertension (defined as confirmed pre-dialysis systolic blood pressure [BP] >190 mmHg or diastolic BP >110 mmHg at rest) during screening.

9. Body mass index (BMI) >42.0 kg/m2.

10. Severe heart failure during screening (New York Heart Association Class III or IV).

11. History of untreated proliferative diabetic retinopathy, diabetic macular edema, age-related macular degeneration, central retinal vein occlusion, active retinal hemorrhage, or ongoing ocular treatment with laser photocoagulation or anti-VEGF therapies.

12. 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.

13. 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, cervical carcinoma in situ, or resected benign colonic polyps.

14. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) requiring active treatment within 8 weeks prior to or during screening. Note: Active treatment indicates treatment with an anticoagulant (blood thinner), such as heparin, enoxaparin, warfarin, rivaroxaban, apixaban, edoxaban, argatroban, and fondaparinux. Aspirin is not considered active treatment for DVT or PE.

15. History of hemosiderosis or hemochromatosis.

16. History of prior organ transplantation or scheduled organ transplant, or prior hematopoietic stem cell or bone marrow transplant. Note: Subjects on kidney transplant wait-list, or with a history of failed kidney transplant, corneal transplants, or stem cell therapy for knee arthritis are not exclusion criteria.

17. 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.

18. Previous participation in a study with a hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI), other than vadadustat, within 90 days prior to screening.

19. Hypersensitivity to vadadustat, or to any of its excipients.

20. Females who are pregnant or breast-feeding.

21. Females of childbearing potential who are unable or unwilling to use an acceptable method of contraception.

22. Non-vasectomized males who are unable or unwilling to use an acceptable method of contraception.

23. Any other reason that 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

All screening laboratory tests, including any repeat measurements, must be performed within the screening window (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 within the 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.

7.4.2 Rescreening

Subjects who fail to meet the qualifying criteria for Hb during screening may be considered for rescreening at the discretion of the investigator, if it is felt 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 replacement therapy.

Screening is limited to 3 attempts (during 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 adverse event (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. 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. 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

7.6.1 Subject Completion

A subject will be considered as having completed the study after completing participation in the Week 18 visit (end of the 2-week follow-up period).

Note: See Section 7.6.3 for subjects who discontinue study drug or withdraw early from the study.

See Section 10.3.6 for information regarding follow-up of unresolved events.

7.6.2 Conditions and Documentation of Individual Subject Study Drug Discontinuation

Subjects may discontinue study medication for any of the following conditions:

- Completion of the protocol-defined dosing period (see Appendices
- Appendix A and Appendix B)
- Worsening of anemia requiring ESA rescue or blood transfusion

- Unacceptable toxicity or drug intolerability
- Investigator discretion
- Subject withdrawal of consent
- Subject becomes pregnant
- Subject receives kidney transplant
- Other reasons

The investigator must document the primary reason for discontinuation in the appropriate case report form (CRF).

7.6.3 Individual Subject Discontinuation

Subjects permanently discontinuing study drug or withdrawing early from the study prior to the Week 16 visit should complete the Week 16 (EOT) clinical and laboratory assessments within 1 day of stopping study medication, if possible. Such subjects should also complete the 2-week follow-up period and complete the Week 18 visit assessments (see Appendices

Appendix A and Appendix B).

For subjects who discontinue study medication, the investigator should resume standard of care treatment, as deemed appropriate.

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

8 STUDY DRUGS AND TREATMENT OF SUBJECTS

8.1 Study Drugs

The study drugs will be vadadustat and placebo (Table 1).

Table 1: Identity of Study Drugs

Study Drug	Formulation	Strength	Route of Administration
Vadadustat	Tablet	150 mg per tablet	Oral
Placebo	Tablet	Not applicable	Oral

8.1.1 Formulation

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

Vadadustat is formulated for oral dosing. The tablets are white to off-white, round, bi-convex film-coated tablets (8.0 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.

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

8.1.2 Storage and Accountability

Vadadustat and placebo should be stored at 1–30 ºC. All study medication supplies must be kept in a locked facility and accessible only to authorized study personnel. A temperature log should be maintained with drug storage temperatures recorded per the Pharmacy Manual. A min-max thermometer is preferred for this study.

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

8.1.3 Dispensing of Study Drugs

Based on the randomized treatment assignment, individual subjects will be provided with 1 bottle of study drug (placebo or vadadustat) at the baseline visit (Day 1). Each bottle will contain 100 tablets of study drug. Subjects will be instructed to finish 1 bottle before opening a new bottle.

At the Week 6 visit, sites will collect all unused study drug tablets dispensed during the primary efficacy period. Each subject will then be provided with 1 bottle of vadadustat. Each bottle will contain 100 tablets of vadadustat.

Resupply of additional study drug as needed will be dependent on the dose level and the number of tablets remaining in the subject's current supply at a given study visit. Subjects will be instructed to finish 1 bottle before opening a new bottle.

To allow for some flexibility in study visit scheduling, sites should ensure that subjects have an adequate supply of study medication.

Subjects should be instructed to bring unused and empty bottles to each study visit for product accountability. Empty bottles will be collected at these study visits. Previously dispensed bottles (whether opened or unopened) with remaining tablets may be re-dispensed to the subject depending on the dosing period of the study.

8.1.4 Product Accountability and Destruction

Product accountability should be an ongoing process throughout the study. All study drug 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 will be maintained that accurately reflect the drug accountability.

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, and/or destruction, and copies will be sent to the sponsor or designee.

All unused and/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 per local procedures.

8.2 Treatment of Subjects

8.2.1 Dosing Instructions

Study drug will be administered on an outpatient basis. Subjects should take the study drug with water or another beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food.

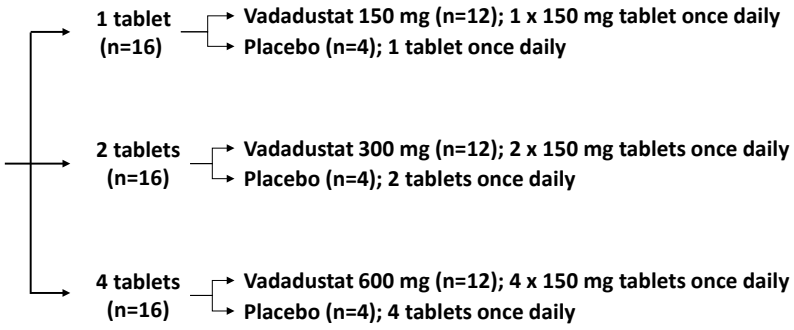
Subjects should be instructed to take the study medication at approximately the same time each day, preferably between 7 am and 2 pm, with the following exception: On the day of the Week 4 visit, the dose of study medication should be held until after the pre-dose PK sample has been obtained.

8.2.2 Randomization

Prior to start of dosing on Day 1, a central randomization system will be used to randomize subjects at a 1:1:1 ratio to receive 1, 2, or 4 tablets.

Within each tablet-count group, subjects will be randomized 3:1 to receive vadadustat or placebo as shown in Figure 5.

Figure 5: Randomization Scheme of Study Treatment



8.2.3 Blinding During the Study and Breaking the Blind

Throughout the study, all subjects, investigators, site personnel, and site pharmacists will be blinded to subject randomization status. All sponsor and CRO personnel will be blinded to randomization until the last subject completes the primary efficacy period (Week 6). At that time, the preliminary analysis will be performed and interpreted by sponsor and CRO study team personnel. Individuals from the sponsor and CRO study teams who are unblinded for the development and reporting of the preliminary analysis will not be involved in the conduct or interpretation of the study after the preliminary analysis. These activities will be transitioned to sponsor and CRO personnel who will remain blinded to randomization status throughout the remainder of the study.

The blind may be broken for individual subjects in the case of a medical emergency (where knowledge of the study drug administered would affect the treatment of the emergency). The decision to break the blind will be made on a case-by-case basis, at the discretion of the site investigator in collaboration with the sponsor's medical monitor/medical director (or designee).

The sponsor's and/or the CRO's safety medical monitor/medical director (or designee) and related safety personnel will be unblinded for safety data that would require assessment for expedited reporting.

8.2.4 Study Drug Administration during the Primary Efficacy Period (Week 1 to Week 6)

The primary efficacy period involves fixed-dose treatment to establish a dose-response relationship. No increase in study drug dose is permitted during this period. However, the dose may be decreased or interrupted as described below:

- If the Hb increases rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose by 1 tablet.
- If the Hb exceeds 13.0 g/dL, interrupt study drug until the Hb decreases to 12.5 g/dL or below and then resume dosing with 1 fewer tablet.

If dose reduction or interruption is recommended based on the central laboratory Hb result and protocol-specified guidelines, the investigative site will contact the subject within 1 business day of receiving the Hb result from the central laboratory. If possible, the subject will be scheduled

for an additional visit within 3 business days. If scheduling the subject within this time frame is not possible, dosing instructions will be provided to the subject over the telephone.

8.2.5 Study Drug Administration during the Dose Adjustment and Maintenance Period (Week 7 to Week16)

Subjects who complete the primary efficacy period will enter the dose adjustment and maintenance period. Subjects receiving placebo will be switched to vadadustat at the Week 6 visit. Specifically, at the Week 6 visit, sites will collect all unused study drug tablets dispensed during the primary efficacy period. Each subject will then be provided with 1 bottle of vadadustat. Each subject will initially take the same number of tablets of study drug after the Week 6 visit as before the Week 6 visit. For example, subjects taking 2 tablets of study drug (vadadustat or placebo) prior to the Week 6 visit will initially take 2 tablets of vadadustat after the Week 6 visit.

Subsequently, study drug dose will be adjusted to achieve a target Hb of 10.0-12.0 g/dL based on central laboratory Hb results and dose adjustment guidelines described below. Dose adjustments will be based on central laboratory Hb results from study visits at Weeks 6, 8, 10, 12, and 14.

- Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased based on Hb results from the Week 6 visit and the subject remains below the Hb target, the next opportunity to further increase the dose would be based on Hb results from the Week 10 visit. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the Hb has not increased by more than 0.5 g/dL above the baseline value after the first 6 weeks of treatment, increase the dose by 1 tablet.
- Increase the dose by 1 tablet every 4 weeks until Hb is above 10.0 g/dL (maximum dose is 4 tablets).
- If the Hb increases rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose by 1 tablet.
- If the Hb falls below 10.0 g/dL, increase the dose by 1 tablet.
- If the Hb exceeds 12.0 g/dL, reduce the dose by 1 tablet.
- If the Hb exceeds 13.0 g/dL, interrupt study drug until the Hb decreases to 12.5 g/dL or below and then resume dosing with 1 fewer tablet.
- If a dose adjustment is required to maintain Hb at the desired level, the dose adjustment is by 1 tablet.

When adjusting therapy, investigators should consider Hb rate of rise, rate of decline, and variability as well as the subject's clinical condition (including recent illness, volume depletion, and volume overload). As clinically indicated, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range. In such cases, the clinical circumstances must be documented in the subject's record.

If dose adjustment is recommended based on the central laboratory Hb result and protocol-specified guidelines, the investigative site will contact the subject within 1 business day of receiving the Hb result from the central laboratory. If possible, the subject will be scheduled for

an additional visit within 3 business days. If scheduling the subject within this time frame is not possible, dosing instructions will be provided to the subject over the telephone.

Note: If subjects fail to achieve target Hb level despite administration of 4 tablets of study drug per day, this will not be considered a reason for subject discontinuation unless the subject initiates rescue therapy (see Section 8.2.6).

8.2.6 Rescue Therapy Guidelines

ESA Rescue Therapy

In order to standardize the use of ESA rescue in the study, the following guidelines should be followed. ESA rescue therapy may be considered if:

- ESA is considered warranted by the investigator's judgment, AND
- The subject experiences a clinically significant worsening of anemia or symptoms of anemia, AND
- The subject has a confirmed Hb level <9.0 g/dL as defined by two consecutive Hb levels <9.0 g/dL. The investigator may schedule the subject to return for an unscheduled visit to confirm Hb level <9.0 g/dL prior to the subsequent scheduled study visit.

If clinically indicated, the investigator at his/her discretion may initiate ESA rescue therapy without a confirmatory Hb level <9.0 g/dL if the first two criteria above are met.

Red Blood Cell Transfusions

Investigators should use their local institution's transfusion guidelines when determining whether to transfuse a study subject.

Subjects who initiate either rescue therapy, ESA Rescue Therapy or Red Blood Cell Transfusion, will be required to stop study drug treatment and will be discontinued from the study. See Section 7.6.3 for subjects who discontinue study drug or withdraw early from the study.

8.2.7 Iron Supplementation (Information on Allowed Use)

Subjects who are receiving a stable dose of oral or intravenous iron supplementation for at least 28 days prior to the screening period should continue their iron supplementation at the same dose and route of administration through the primary efficacy period (through Week 6). Changes to iron supplementation dose during the primary efficacy period will be considered protocol deviations but will not be considered a reason for subject discontinuation. After the Week 6 visit, investigators should prescribe iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT <20%, and the dose and route of iron administration will be selected at the investigator's discretion.

Subjects who are not receiving iron supplementation at the beginning of the screening period should not start iron supplementation through the primary efficacy period (through Week 6). Initiation of iron supplementation during the primary efficacy period will be considered a protocol deviation but will not be considered a reason for subject discontinuation. After the Week 6 visit, investigators should prescribe iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT <20%, and the dose and route of iron administration will be selected at the investigator's discretion.

Important: Because of the potential for oral iron to reduce the bioavailability of vadadustat, study drug (vadadustat or placebo) should not be administered concurrently with any oral iron supplement. Any oral iron supplements (including multivitamins containing iron) should be taken at least 2 hours before or 2 hours after the dose of study drug.

8.2.8 Late or Missed Doses

Subjects should be instructed to take the study medication at roughly the same time each day, preferably between 7 am and 2 pm.

If a dose is forgotten, subjects should be instructed to take the dose as soon as they remember until 11 pm the same day. If a forgotten dose is not remembered until after 11 pm, the subject should skip the dose and resume the normal dosing schedule on the following day.

8.2.9 Compliance with Study Drug Dosing

Subjects will be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study drug. 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 treatment compliance.

Subjects will also be questioned regarding the timing of their last dose of vadadustat during PK sample collection. The date and time of these doses will be recorded on the CRF.

8.2.10 Continuation of Treatment

Subjects participating in this study will not be considered for continuation of treatment with the study medication past the maximum duration of treatment of approximately 16 weeks.

8.3 Prior and Concomitant Therapy

All medications taken within 30 days prior to the start of study drug and during study participation should be recorded on the appropriate case report form.

8.4 Prohibited Treatments

8.4.1 Investigational Medications

Study subjects should not have received any investigational medications or participated in an investigational study within 30 days or 5 half-lives of the investigational medication, whichever is longer, prior to Day 1.

Additionally, subjects should not take another investigational medication while participating in this study.

8.4.2 ESAs and Blood Transfusion

Note: ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.6 for the rescue therapy guidelines. Subjects who initiate rescue therapy will be required to stop

study drug treatment and will be discontinued from the study. See Section 7.6.3 for subjects who discontinue study drug or withdraw early from the study.

- Prohibitions related to ESA use: See Section 9.1 for washout period for ESAs.
  - For subjects who are not currently being treated with ESAs:
    - Subjects may not receive any ESA during the screening, treatment, and follow-up study periods except in the context of ESA rescue (see ESA rescue guidelines, section 8.2.6).
  - For subjects who are currently being treated with ESAs:
    - After screening visit 1 and prior to screening visit 2, subjects must not receive ESAs for at least the following time periods:

ESA	ESA washout period (Minimum duration of time without ESA treatment after screening visit 1 and prior to screening visit 2)
Epoetin alfa	2 weeks
Epoetin beta	
Epoetin kappa	
Darbepoetin alfa	4 weeks
Epoetin beta pegol	8 weeks

    - After screening visit 2 and through the remaining screening period, subjects must not use any ESA. Any ESA use during this period would result in exclusion from the study.

During the treatment and follow-up study periods, subjects may not receive any ESA except in the context of ESA rescue (see ESA rescue guidelines, section 8.2.6).

- Prohibitions related to blood transfusions: Subjects may not receive blood transfusion within 4 weeks prior to the screening period and through the follow-up period.

8.4.3 Iron Supplementation (Information on Prohibition)

Subjects who are not receiving iron supplementation at the beginning of the screening period should not start iron supplementation through the primary efficacy period (through Week 6). Initiation of iron supplementation during the primary efficacy period will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

See Section 8.2.7 for information on circumstances allowing use of oral iron supplementation.

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

9.1 Schedule of Visits

As presented in Appendices

Appendix A and Appendix B, this study includes the following visits:

- Eligibility screening period

  - For subjects who were not prescribed ESAs at study entry, the screening visits must be performed within 4 weeks (Day -28 to Day 0) prior to dosing on Day 1, in addition, screening visit 2 should be ≥4 days from screening visit 1, and baseline visit (Day 1) should be ≥4 days from screening visit 2.
  - For subjects who were prescribed epoetin alfa, epoetin beta, and epoetin kappa prior to study entry, the screening visits must be performed within 6 weeks (Day 42 to Day 0) prior to dosing on Day 1. There will be a 2-week ESA washout period between screening visit 1 and screening visit 2, in addition, screening visit 2 after the ≥2-wk ESA washout; screening visit 3 should be ≥4 days from screening visit 2; and baseline visit (Day 1) should be ≥4 days from screening visit 3.
  - For subjects who were prescribed darbepoetin alfa prior to study entry, the screening visits must be performed within 8 weeks (Day -56 to Day 0) prior to dosing on Day 1. There will be a 4-week ESA washout period between screening visit 1 and screening visit 2, in addition, screening visit 2 after the ≥4-wk ESA washout; screening visit 3 should be ≥4 days from screening visit 2; and baseline visit should be ≥4 days from screening visit 3.
  - For subjects who were prescribed epoetin beta pegol prior to study entry, the screening visits must be performed within 11 weeks (Day -77 to Day 0) prior to dosing on Day 1. There will be an 8-week washout period between screening visit1 and screening visit 2, in addition, screening visit 2 after the ≥8-wk ESA washout; screening visit 3 should be ≥4 days from screening visit 2; and baseline visit should be ≥4 days from screening visit 3.

- Primary efficacy period (from Day 1 to Week 6 visit)
  - Baseline visit (Day 1)
  - Week 2 visit ± 1 day
  - Week 4 visit ± 3 days
  - Week 6 visit ± 3 days
- Dose adjustment and maintenance period (after the Week 6 visit to Week 16 visit)
  - 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
- Follow-up period (after the Week 16 visit to the Week 18 visit)
  - Week 18 visit ± 3 days

Note: The following visits will be scheduled on the first hemodialysis session of the week.

- For subjects who were not prescribed ESAs at study entry: Screening visit 1, screening visit 2, baseline visit (Day 1), Week 6, and Week 16 visit

- For subjects who were prescribed ESAs prior to study entry: Screening visit 2, screening visit 3, baseline visit (Day 1), Week 6, and Week 16 visit

As visit scheduling permits, effort should be made to try to schedule other visits for the first hemodialysis of the week, acknowledging that this may not be feasible due to subject or site scheduling constraints.

9.2 Administrative Procedures

9.2.1 Informed Consent

Informed consent must be obtained and legally signed prior to a subject entering the study and before any protocol-directed procedures (including screening tests) are performed (see Section 15.3).

9.2.2 Documentation of Screen Failures

To account for screen failures throughout the screening process, investigators must maintain a log of subjects and their disposition beginning at the screening stage.

For each screened subject, investigators must indicate whether the subject enrolled in the study. Reasons for ineligibility and not proceeding to screening or study enrollment must be provided.

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. Information on acceptable methods of contraception is provided in Section 9.2.3.1.

9.2.3.1 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 medication. In addition, men must not donate sperm during the study and for at least 90 days after the last dose of study medication.

Acceptable methods of contraception are defined as follows:

- Female subjects must be surgically sterile, postmenopausal (no menses for at least 1 year), or have negative pregnancy test results at screening (assessed using serum pregnancy test).

- Female subjects who are not surgically sterile or postmenopausal (no menses for at least 1 year) 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 medication
    - 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 medication
    - Intrauterine contraception/device starting at the screening visit, throughout the study, and for 30 days after the last dose of study medication
    - Double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap together with spermicidal foam/gel/film/suppository) starting at the screening visit, throughout the study, and for 30 days after the last dose of study medication

9.3 Study Procedures and Evaluations

9.3.1 Clinical Evaluations

The following clinical evaluations will be conducted during the study.

For subjects who were not prescribed ESAs at study entry, detailed information regarding the timing of the assessments is presented in Section 9.4 and summarized in Appendices

Appendix A. For subjects who were prescribed ESAs prior to study entry, detailed information regarding the timing of the assessments is presented in Section 9.5 and summarized in Appendix B.

- 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 assessments
- Dry weight assessment
- Dialysis adequacy: Dialysis adequacy (measured as Kt/V), as available from local collection, will be recorded.
- Dialysis treatment review: Review of dialysis treatment should include frequency of dialysis and vascular access type (eg, AV fistula, AV 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 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, serious adverse events (SAEs), and non-serious events is described in Section 10.3.6.
- Rescue therapy (ESA rescue and RBC transfusion) review: Beginning with the first post-baseline visit (after Day 1) and through the follow-up visit, the investigator and study personnel will review whether a subject received rescue therapy (ESA rescue or RBC transfusion).
- 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. In addition, the ESA and iron treatment regimen prior to randomization and date of last dose will be recorded.

  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 in the CRFs.

9.3.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis. 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:

- Serum pregnancy tests: Female subjects who are of childbearing potential (ie, are not surgically sterile or postmenopausal) will participate in serum pregnancy tests (to be analyzed by the central lab). The screening pregnancy test results must be available and must be negative for a subject to initiate study drug.
- Note: Additional serum or local urine (if possible) pregnancy tests may be conducted, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study. Coagulation tests: Blood sample will be collected to assess the prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).

- Folate and vitamin B12: Blood sample will be collected to assess folate and Vitamin B12 levels.
- CBC: Blood sample will be collected to assess CBC, including 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, bands, lymphocytes, monocytes, eosinophils, and basophils), platelets, and automated reticulocyte count (both absolute and percent).

  Blood samples for CBC/Hb assessment will be collected with the patient in the supine position and prior to hemodialysis (per the Japanese Society for Dialysis Therapy [JSDT] guidelines). As noted in Appendices

  Appendix A and Appendix B, the following visits will be scheduled for the first hemodialysis of the week:

  - For patients not prescribed ESAs: Screening visit 1, screening visit 2, baseline visit/Day 1, Week 6, Week 16
  - For patients prescribed ESAs: Screening visit 2, screening visit 3, baseline visit/Day 1, Week 6, Week 16

  As visit scheduling permits, effort should be made to try to schedule other visits for the first hemodialysis of the week, acknowledging that this may not be feasible due to subject or site scheduling constraints. The CRF will describe how blood samples for central Hb analysis are drawn (ie, supine, prior to hemodialysis, on the day of the first hemodialysis session of the week).
- Chemistry: Including sodium, potassium, bicarbonate, chloride, calcium, phosphorus, glucose, creatinine, blood urea nitrogen, creatine phosphokinase, uric acid, albumin, total protein, total bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), lactate dehydrogenase (LDH), and total cholesterol. Glucose will be measured using plasma samples and the other chemistry parameters will be measured using serum samples.
- Iron indices: Blood samples will be collected to assess serum iron, TIBC, TSAT, and ferritin.
- Hepcidin: Blood samples will be collected to assess hepcidin.
- C-reactive protein: Blood sample will be collected to assess C-reactive protein.
- VEGF: Blood sample will be collected to assess VEGF levels.
- PK analysis: Week 4 pre-dose sample will be analyzed for vadadustat and its metabolites. Study drug dose on this day should be held until after the pre-dose PK sample has been obtained. After the labs are drawn, the subject should take their scheduled dose of study drug.

  Blood samples will be collected in tubes with K2EDTA anticoagulant, plasma prepared, and frozen within 1 hour of blood collection. Analysis of samples for vadadustat and metabolite concentration determinations will be performed by a sponsor-designated contract research organization (CRO) using a validated Liquid Chromatography-Mass Spectrometry and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method. 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.

9.4 Schedule of Activities (For Subjects Who Were Not Prescribed ESAs Prior to Study Entry)

The Schedule of Events in Appendices

Appendix A shows the timing of planned study procedures. Every effort should be made to adhere to this procedure schedule and all assessments should be completed at each study visit.

Note: The following visits will be scheduled on the day of the first hemodialysis session of the week, in keeping with JSDT Guidelines from Hb measurement: Screening visit 1, screening visit 2, baseline visit (Day 1), Week 6, and Week 16. As visit scheduling permits, effort should be made to try to schedule other visits on the day of the first hemodialysis session of the week, acknowledging that this may not be feasible due to subject or site scheduling constraints.

Note: Blood samples for CBC/Hb assessment should be collected with the patient in the supine position and prior to hemodialysis.

See Section 7.4 for information regarding retesting and rescreening.

9.4.1 Screening Visit 1

This visit will be scheduled on the day of the first hemodialysis session of the week.

Informed consent must be obtained and legally signed before performing any protocol-directed procedures (including screening tests).

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo screening procedures. The investigator will maintain a log of subjects and indicate who was enrolled or excluded and the reason for exclusion (see Section 9.2.2).

At screening visit 1, the following activities/procedures will be performed:

- Signing of informed consent
- Review study inclusion and exclusion criteria
- Demographics, medical history, and physical examination
- Vital signs
- Dry weight
- AE review
- Laboratory procedures:
    - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The serum pregnancy test will be analyzed by the central lab. The screening results must be available and must be negative before the subject takes the first dose of study drug.
    - Iron indices
    - Folate and vitamin B12 levels
    - CBC
    - Chemistry

9.4.2 Screening Visit 2

This visit will be scheduled on the day of the first hemodialysis session of the week.

At screening visit 2, the following activities/procedures will be performed:

- Review study inclusion and exclusion criteria
- Vital signs
- Dry weight
- AE review
- Laboratory procedures:
    - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The serum pregnancy test must be performed within 4-8 days prior to visit 1/Day 1 to allow sufficient time to obtain the pregnancy test result prior to randomization, and the screening results must be available and must be negative before the subject takes the first dose of study drug. In the event screening visit 2 is >8 days prior to Day 1, the subject will be asked to return to the study site for an unscheduled serum pregnancy test to verify eligibility prior to Day 1. The serum pregnancy test will be analyzed by the central lab.
    - CBC

9.4.3 Baseline Visit (Day 1)

This visit will be scheduled on the day of the first hemodialysis session of the week.

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

- Review study inclusion and exclusion criteria
- Vital signs
- Dry weight
- Randomization
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)
- Dialysis treatment review
- Dialysis adequacy (Kt/V)
- AE review
- Laboratory procedures:
    - CBC
    - Iron indices
    - Chemistry
    - Coagulation tests
    - Hepcidin
    - C-reactive protein
    - VEGF
- Concomitant medication review
- Dispense one bottle of study drug
- Review dosing instructions

9.4.4 Week 2 Visit

At the Week 2 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - CBC
  - Iron indices
  - Chemistry
- Concomitant medication review
- Dispense study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose reduction if central lab Hb result demonstrates excess Hb response
- Remind/instruct subjects to hold their dose of study medication on the day of the Week 4 visit until after the pre-dose PK blood sample has been collected
- If central lab Hb result demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.4.5 Week 4 Visit

When possible, this visit should be scheduled in the morning due to the pre-dose PK evaluation. The morning dose of study medication should be held until after the pre-dose PK sample is drawn.

At the Week 4 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - CBC
  - Chemistry
  - Iron indices
  - Pre-dose PK sample
- Record date and time of the last dose of the study drug that was taken prior to the pre-dose PK sample
- Concomitant medication review
- Dispense study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose reduction if central lab Hb result demonstrates excess Hb response

- If central lab Hb result demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.4.6 Week 6 Visit

This visit will be scheduled on the day of the first hemodialysis session of the week.

At the Week 6 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - CBC
  - Chemistry
  - Iron indices
  - Hepcidin
  - C-reactive protein
  - VEGF
- Concomitant medication review
- Collect study bottle and all remaining study drug tablets remaining from the primary efficacy period (last dose to be taken on day of Week 6 visit)
- Dispense one bottle of vadadustat (first dose to be taken day after Week 6 visit)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose adjustment depending on central lab Hb result
- If central lab Hb result obtained from this visit supports dose adjustment based on dose adjustment guidelines, contact subject for dose adjustment (Section 8.2.5)

9.4.7 Week 8, 10, 12, 14 Visits

At these visits, the following activities/procedures will be performed:

- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- Dry weight
- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry
  - Iron indices (Week 8 and Week 12 visits only)
- Dispense vadadustat (as necessary)
- Subjects should be questioned regarding dosing compliance

- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose adjustment depending on central lab Hb result
- If central lab Hb result obtained from this visit supports dose adjustment based on dose adjustment guidelines, contact subject for dose adjustment (Section 8.2.5)

9.4.8 Week 16 Visit (End-of-Treatment Visit for Subjects Who Complete the Dose Adjustment and Maintenance Period or for Subjects Who Withdraw Early from the Study Prior to Week 16)

This visit will be scheduled on the day of the first hemodialysis session of the week.

All subjects should complete the Week 16 (end of treatment) assessments.

Subjects who withdraw prematurely from the study prior to the Week 16 visit should undergo the clinical and laboratory assessments specified below within 1 day of stopping study medication, if possible. Such subjects should also complete the requisite 2-week follow-up period (see Section 9.4.9).

At the Week 16 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - Serum pregnancy test
  - Iron indices
  - CBC
  - Chemistry
  - Hepcidin
  - C-reactive protein
  - VEGF
- Concomitant medication review
- Subjects should be questioned regarding dosing compliance

9.4.9 Week 18 Follow-Up Visit (or 2 Weeks after End-of-Treatment Follow-Up Visit)

For subjects who complete the dose adjustment and maintenance period, the follow-up visit will be conducted 2 weeks after their end-of-treatment visit (Week 16).

For subjects who discontinue the study prematurely (ie, prior to Week 16), the follow-up visit will be conducted 2 weeks after their end-of-treatment visit.

At the follow-up visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Rescue therapy (ESA rescue and RBC transfusion) review

- Laboratory procedures:
  - CBC
  - Chemistry

9.5 Schedule of Activities (For Patients Who Were Prescribed ESAs Prior to Study Entry)

The Schedule of Events in Appendix B shows the timing of planned study procedures. Every effort should be made to adhere to this procedure schedule and all assessments should be completed at each study visit.

Note: The following visits will be scheduled on the day of the first hemodialysis session of the week, in keeping with JSDT Guidelines from Hb measurement: Screening visit 2, screening visit 3, baseline visit, Week 6, and Week 16. As visit scheduling permits, effort should be made to try to schedule other visits on the day of the first hemodialysis of the week, acknowledging that this may not be feasible due to subject or site scheduling constraints.

Note: Blood samples for Hb assessment should be collected with the patient in the supine position and prior to hemodialysis.

See Section 7.4 for information regarding retesting and rescreening.

9.5.1 Screening Visit 1

Informed consent must be obtained and legally signed before performing any protocol-directed procedures (including screening tests).

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo several screening activities. The investigator will maintain a log of subjects and indicate who was enrolled or excluded and the reason for exclusion (see Section 9.2.2).

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

- Signing of informed consent
- Review study inclusion and exclusion criteria
- Demographics, medical history, and physical examination
- Vital signs
- Dry weight
- AE review
- Laboratory procedures:
  - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The serum pregnancy test will be analyzed by the central lab. The screening results must be available and must be negative before the subject takes the first dose of study drug.
  - CBC
  - Chemistry
  - Iron indices
  - Folate and vitamin B12

Subjects who remain eligible for the study after screening visit 1 will undergo ESA washout. Subjects who were prescribed epoetin alfa, epoetin beta, and epoetin kappa will undergo ESA

washout for 2 weeks prior to screening visit 2. Subjects who were prescribed darbepoetin alfa will undergo ESA washout for 4 weeks prior to screening visit 2. Subjects who were prescribed epoetin beta pegol will undergo ESA washout for 8 weeks prior to screening visit 2.

9.5.2 Screening Visit 2

This visit will be scheduled on the day of the first hemodialysis session of the week after the ESA washout periods described above.

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

- Review study inclusion and exclusion criteria
- Vital signs
- Dry weight
- AE review
- Laboratory procedures:
  - CBC

9.5.3 Screening Visit 3

This visit will be scheduled on the day of the first hemodialysis session of the week.

At screening visit 3, the following activities/procedures will be performed:

- Review study inclusion and exclusion criteria
- Vital signs
- Dry weight
- AE review
- Laboratory procedures:
  - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The serum pregnancy test must be performed within 4-8 days prior visit 1/Day 1 to allow sufficient time to obtain the pregnancy test result prior to randomization, and the screening results must be available and must be negative before the subject takes the first dose of study drug. In the event screening visit 3 is >8 days prior to Day 1, the subject will be asked to return to the study site for an unscheduled serum pregnancy test to verify eligibility prior to Day 1. The serum pregnancy test will be analyzed by the central lab.
  - CBC

9.5.4 Baseline Visit (Day 1)

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

- Review study inclusion and exclusion criteria
- Vital signs
- Dry weight
- Randomization
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)

- Dialysis treatment review
- Dialysis adequacy (Kt/V)
- AE review
- Laboratory procedures:
  - Iron indices
  - CBC
  - Chemistry
  - Coagulation tests
  - Hepcidin
  - C-reactive protein
  - VEGF
- Concomitant medication review
- Dispense one bottle of study drug
- Review dosing instructions

9.5.5 Week 2 Visit

At the Week 2 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - CBC
  - Chemistry
  - Iron indices
- Concomitant medication review
- Dispense study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose reduction if central lab Hb result demonstrates excess Hb response
- Remind/instruct subjects to hold their dose of study medication on the day of the Week 4 visit until after the pre-dose PK blood sample has been collected
- If central lab Hb result demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.5.6 Week 4 Visit

When possible, this visit should be scheduled in the morning due to the pre-dose PK evaluation. The morning dose of study medication should be held until after the pre-dose PK sample is drawn.

At the Week 4 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight

- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - CBC
  - Chemistry
  - Iron indices
  - Pre-dose PK sample
- Record date and time of the last dose of the study drug that was taken prior to the pre-dose PK sample
- Concomitant medication review
- Dispense blinded study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose reduction if central lab Hb result demonstrates excess Hb response
- If central lab Hb result demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.5.7 Week 6 Visit

This visit will be scheduled on the day of the first hemodialysis session of the week.

At the Week 6 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - CBC
  - Chemistry
  - Iron indices
  - Hepcidin
  - C-reactive protein
  - VEGF
- Concomitant medication review
- Collect study bottle and all remaining study drug tablets remaining from the primary efficacy period (last dose to be taken on day of Week 6 visit)
- Dispense one bottle of vadadustat (first dose to be taken day after Week 6 visit)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose adjustment depending on central lab Hb result
- If central lab Hb result obtained from this visit supports dose adjustment based on dose adjustment guidelines, contact subject for dose adjustment (Section 8.2.5)

9.5.8 Week 8, 10, 12, and 14 Visits

At these visits, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry
  - Iron indices (Week 8 and Week 12 visits only)
- Dispense vadadustat (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose adjustment depending on central lab Hb result
- If central lab Hb result obtained from this visit supports dose adjustment based on dose adjustment guidelines, contact subject for dose adjustment (Section 8.2.5)

9.5.9 Week 16 Visit (End-of-Treatment Visit for Subjects Who Complete the Dose Adjustment and Maintenance Period or for Subjects Who Withdraw Early from the Study Prior to Week 16)

This visit will be scheduled on the day of the first hemodialysis session of the week.

All subjects should complete the Week 16 (end of treatment) assessments.

Subjects who withdraw prematurely from the study prior to the Week 16 visit or permanently discontinue study medication prior to the Week 16 visit, should undergo the clinical and laboratory assessments specified below within 1 day of stopping study medication, if possible. Such subjects should also complete the requisite 2-week safety follow-up period (see Section 9.4.9).

At the Week 16 visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- Dialysis treatment review
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - Serum pregnancy test
  - Iron indices
  - CBC
  - Chemistry
  - Hepcidin
  - C-reactive protein

  - VEGF
- Concomitant medication review
- Subjects should be questioned regarding dosing compliance

9.5.10 Week 18 Follow-Up Visit (or 2 Weeks after End-of-Treatment Follow-Up Visit)

For subjects who complete the dose adjustment and maintenance period, the follow-up visit will be conducted 2 weeks after their end-of-treatment visit (Week 16).

For subjects who discontinue the study prematurely (ie, prior to Week 16), the follow-up visit will be conducted 2 weeks after their end-of-treatment visit.

At the follow-up visit, the following activities/procedures will be performed:

- Vital signs
- Dry weight
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Rescue therapy (ESA rescue and RBC transfusion) review
- Laboratory procedures:
  - CBC
  - Chemistry

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.

Preexisting 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. The investigator will utilize his/her 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 and/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/medical director or CRO designee within 24 hours of awareness as an SAE with 'other medically important event' criterion selected, if the following conditions are met:

- New elevation in ALT or AST >3 times the upper limit of normal (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.

Kidney Transplantation – During this study, some subjects may receive a kidney transplant. Kidney transplantation will not be recorded as an AE.

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/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/incapacity (see paragraph below on Disability)
- Congenital anomaly/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.

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.

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 reporting period for all non-serious AEs and all SAEs not related to protocol procedures begins upon receiving the first dose of study medication and ends at the final protocol-required visit.

SAEs that are assessed by the investigator to be related to protocol procedures (eg, ESA washout) must be reported after signing of the informed consent form.

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 CRFs.

10.3.3 Reporting SAEs

Any SAE, regardless of causal relationship, must be reported to the sponsor's medical monitor/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 number/ID, sex, and age/date of birth
- The date of report
- Name of the reporter
- 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 SAE Report Form. The investigator must assess the relationship to each specific component of the study treatment. If the event meets serious criteria, SAE Report Form should be sent to the CRO via email or fax, or the investigator should call the CRO SAE

hotline within 24 hours of being made aware of the SAE (reference the site manual for contact information).

The investigator must report follow-up information relating to an SAE to the sponsor's medical monitor/medical director or CRO designee within 24 hours of awareness by submitting a new SAE Report Form. 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 and/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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) 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 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/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 trial ends.

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 trial 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.

10.3.7 Special Situations

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

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

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.

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 study participant 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).

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.

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

11 DATA ANALYSIS

An overview of the statistical approach to the primary endpoint and safety analyses are provided below. The details of the planned analysis of the primary endpoint as well as the planned analyses of secondary endpoints, PK, PD, and safety will be documented in the statistical analysis plan (SAP).

11.1 Primary Endpoint – Mean Change in Hb from Pre-treatment to the End of the Primary Efficacy Period (Week 6)

The primary objective of this study is to evaluate the dose-response relationship between oral vadadustat once daily dosing for 6 weeks and the change in Hb in Japanese subjects with anemia secondary to DD-CKD; this is to define the starting dose for use in Phase 3 clinical studies in Japan.

The primary endpoint is the mean change in Hb from pre-treatment to the end of the primary efficacy period (Week 6). Pre-treatment Hb is defined as the average of 3 Hb values obtained prior to treatment based on 2 qualifying screening Hb values and the Hb value at the baseline visit (Day 1).

11.2 Primary Efficacy Analysis and Sample Size Determination

An analysis of covariance (ANCOVA) model will be used to compare change from pre-treatment in Hb between the three vadadustat dosing groups and the placebo group. The model will include treatment assignment (3 dosed groups and one placebo group) and pre-treatment Hb value as a covariate. A step-down procedure will be used to control the overall type I error rate for the multiple comparisons. Testing of the highest dose compared with placebo will be conducted first. If and only if this comparison is significant, then testing will proceed to comparison of the next lower dose and placebo, and so on. Thus, no multiplicity adjustment will be needed for this analysis.

The sample size and power calculations are based on results from Study AKB-6548-CI-0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to non-dialysis-dependent CKD. It is reasonable to extrapolate these data to the current study based on the following findings:

- PK parameters of vadadustat are similar between CKD patients who are receiving hemodialysis (Study AKB-6548-CI-0009) and CKD patients who are not receiving dialysis (Study AKB-6548-CI-0003)
- Hemodialysis procedure has no significant impact on the PK of vadadustat (Study AKB-6548-CI-0009)
- The dose range of 150-600 mg of vadadustat to be used in the current study has been shown to be generally well-tolerated, and efficacious in raising and/or maintaining Hb at the desired target level in CKD patients who were either on hemodialysis (Study AKB-6548-CI-0011) or CKD patients who were not on dialysis (Studies AKB-6548-CI-0005 and AKB-6548-CI-0007)

The target enrollment will be approximately 48 subjects for the study with 12 subjects enrolled in each of the 4 treatment groups.

The study is powered based on a comparison of the highest dose vadadustat group (600 mg daily) and the placebo group.

Based on the results from Study AKB-6548-CI-0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to NDD-CKD, it is assumed that the expected mean Hb changes from pre-treatment to Week 6 will be approximately 0 mg/dL for the placebo group and 1.35 g/dL for the highest dose vadadustat group (600 mg daily).

Based on the results from Study AKB-6548-CI-0011 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to DD-CKD, it is assumed that the common Hb standard deviation will be 0.9 g/dL across treatment groups. In addition, a dropout rate of 10% is assumed. With these assumptions, the study with n=12 subjects per group will have >85% power to detect the difference between treatment group and control group, at 2-sided alpha of 0.05.

11.3 Preliminary (6-Week) Analysis

In addition to the final analysis which will take place when all subjects have completed the study and will include all data collected, the 6-week efficacy and safety data will be summarized for administrative planning purposes after the last patient completes the primary efficacy period (Week 6). The preliminary analysis will be performed and interpreted by the sponsor and CRO study team personnel. Subjects and sites will not be unblinded to treatment allocation. Individuals from the sponsor and CRO study teams who are unblinded for the development and reporting of the preliminary analysis will not be involved in the conduct of the study after the preliminary analysis. As the study conduct and final analysis will not be modified by this analysis, no alpha adjustment is proposed. It is expected that this 6-week data will be identical for the preliminary administrative analysis and the final analysis of the complete dataset. Any changes between the preliminary analysis and the final analysis will be documented.

11.4 Study Populations

11.4.1 Analysis Population for the Safety Analyses

The safety population is defined as all enrolled subjects who receive at least 1 dose of study medication. The safety population will be based on the actual treatment that patients received. All safety analyses will be performed using the safety population.

11.4.2 Analysis Populations for the Efficacy Analyses

The modified intent-to-treat (MITT) population is defined as all randomized subjects who receive at least 1 dose of study medication, have a pre-treatment Hb average, and at least one post-baseline Hb measurement. A pre-treatment average value for Hb is defined as the average of 3 values obtained prior to dosing, ie, the 2 qualifying screening values and the baseline value. The MITT population will be based on the treatment to which patients are randomized.

The per-protocol (PP) population will consist of the subjects in the MITT population who have completed the study and have efficacy data through Week 6, have a study medication compliance of ≥80%, and do not have any major protocol deviations expected to significantly affect the primary efficacy endpoint. Subjects with major protocol deviations expected to significantly affect the primary efficacy endpoint will be identified and documented prior to data unblinding.

As sensitivity analyses, efficacy endpoints will also be analyzed using the PP population.

11.5 Analysis of Demographics and Pretreatment Variables

Descriptive statistics (eg, number of subjects, mean, standard deviation (SD), median, minimum, and maximum) will be generated for selected continuous variables (including age, selected laboratory assays, and vital signs). The number and percentage of subjects in each class of categorical demographic and baseline variables (eg, gender, ethnicity, race, and CKD stage) will be tabulated. Individual subject demographic and baseline characteristic data will be listed.

11.6 Disposition of Subjects

The number of subjects who are randomized, discontinued, or complete the study and reasons for discontinuation will be summarized in tabular format.

11.7 Safety Analyses

The reporting of safety data is descriptive, and will include all subjects who receive at least one dose of study medication. The following variables are the safety endpoints: Adverse events, vital signs, ECGs, and laboratory parameters.

AEs will be summarized based on the frequency of AEs and their severity for all treated subjects. Overall safety and tolerability will be assessed with treatment-emergent AEs, laboratory results, and other safety variables including summaries of vital signs and ECGs. As appropriate, summaries may also include change from baseline and shift tables. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by dose level. Data will be summarized using preferred term and primary system organ class.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms (CRFs)

This study will utilize an EDC system to manage data collection during this trial. 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 and/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 Conference on Harmonisation (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/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 to quality assurance audits performed by the sponsor or its designees, and/or review by the IRB/IEC, and/or to 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 or IEC, 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 or IEC, 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/INVESTIGATIVE STUDY SITE TERMINATION

The sponsor reserves the right to discontinue the trial 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 trial.

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 medication 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.
- Major violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

The sponsor reserves the right to discontinue the trial for other valid administrative reasons.

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 major 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, and applicable local regulatory requirements and laws.

15.2 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

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/IEC. All correspondence with the IRB/IEC should

be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the sponsor.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC 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 trial and the possible risks involved. The subjects must be informed about their right to withdraw from the trial 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 trial. 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 study, must be prospectively approved by both the IRB/IEC 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 (i.e., 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 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 and IECs 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 (i.e., 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 and/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/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.

17 REFERENCES

Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584-90.

Bigham AW, Lee FS. Human high-altitude adaptation: forward genetics meets the HIF pathway. *Genes Dev* 2014;28:2189-204.

Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355:2071-84.

Goodkin DA, Fuller DS, Robinson BM, et al. Naturally occurring higher hemoglobin concentration does not increase mortality among hemodialysis patients. *J Am Soc Nephrol* 2011;22:358-65.

Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. *Blood Rev* 2013;27:41-53.

Imai E, Yasuda Y, Makino H. Japan Association of Chronic Kidney Diease Initiatives (J-CKDI). *JMAJ* 2011;54:403-5.

Iseki K. Chronic Kidney Disease in Japan. *Internal Medicine* 2008;47:681-9.

Iseki K, Kohagura K. Anemia as a risk factor for chronic kidney disease. *Kidney Int Suppl* 2007;107:S4-9.

JSN. Japanese Society of Nephrology, Evidence-Based Clinical Practice Guideline for CKD 2013. *Clin Exp Nephrol* 2014;18:346-423.

KDIGO. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int* 2012;2:1-64.

Liu Q, Davidoff O, Niss K, et al. Hypoxia-inducible factor regulates hepcidin via erythropoietin-induced erythropoiesis. *J Clin Invest* 2012;122:4635-44.

Locatelli F, Barany P, Covic A, et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant* 2013;28:1346-59.

McCullough PA, Barnhart HX, Inrig JK, et al. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. *Am J Nephrol* 2013;37:549-58.

Metivier F, Marchais SJ, Guerin AP, et al. Pathophysiology of anaemia: focus on the heart and blood vessels. *Nephrol Dial Transplant* 2000;15 Suppl 3:14-8.

NICE. Anaemia management in people with chronic kidney disease. *National Institute for Health and Care Excellence* 20111-39.

NKF. National Kidney Foundation, K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 2002;39:S1-S266.

Nurko S. Anemia in chronic kidney disease: causes, diagnosis, treatment. *Cleve Clin J Med* 2006;73:289-97.

Peyssonnaux C, Zinkernagel AS, Schuepbach RA, et al. Regulation of iron homeostasis by the hypoxia-inducible transcription factors (HIFs). *J Clin Invest* 2007;117:1926-32.

Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009a;361:2019-32.

Pfeffer MA, Burdmann EA, Chen CY, et al. Baseline characteristics in the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT). *Am J Kidney Dis* 2009b;54:59-69.

Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.

Solomon SD, Uno H, Lewis EF, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med* 2010;363:1146-55.

Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014;9:e84943.

Szczech LA, Barnhart HX, Inrig JK, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 2008;74:791-8.

Tacchini L, Bianchi L, Bernelli-Zazzera A, et al. Transferrin receptor induction by hypoxia. HIF-1-mediated transcriptional activation and cell-specific post-transcriptional regulation. *J Biol Chem* 1999;274:24142-6.

Unger EF, Thompson AM, Blank MJ, et al. Erythropoiesis-stimulating agents--time for a reevaluation. *N Engl J Med* 2010;362:189-92.

18 APPENDICES

APPENDIX A: SCHEDULE OF ACTIVITIES FOR SUBJECTS WHO WERE NOT PRESCRIBED ESAS PRIOR TO STUDY ENTRY

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.

Screening Visits and Study Week	**Screening period (Week -4 to 0)**		**Primary efficacy period (Day 1-Week 6)**				**Dose adjustment and maintenance period (Week 7-16)**					**Follow-up (Week 17-18)**
	SV1 [a]	**SV2 [a]**	**BV [a]**	**2**	**4**	**6 [a]**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**SV2 ≥4 days from SV1 BV ≥4 days from SV2**		**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Visit Window (Days)	**—**	**—**	**—**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X											
Review inclusion/ exclusion criteria	X	X	X									
Demographics, medical history, physical exam	X											
Vital signs, dry weight	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X									
12-lead ECG			X									
Dialysis treatment review			X	X	X	X	X	X	X	X	X	
Dialysis adequacy (Kt/V)			X									
Adverse event review [b]	X	X	X	X	X	X	X	X	X	X	X	X
Rescue therapy (ESA rescue and RBC transfusion) review				X	X	X	X	X	X	X	X	X

Screening Visits and Study Week	Screening period (Week -4 to 0)		Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18)
	SV1 [a]	SV2 [a]	BV [a]	2	4	6 [a]	8	10	12	14	16 (EOT)	18
Study Day	**SV2 ≥4 days from SV1 BV ≥4 days from SV2**		**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Serum pregnancy test [c]	X	X									X	
Iron indices	X		X	X	X	X	X		X		X	
Folate and vitamin B12	X											
CBC including Hb	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X		X	X	X	X	X	X	X	X	X	X
Coagulation tests			X									
Hepcidin			X			X					X	
C-reactive protein			X			X					X	
VEGF			X			X					X	
Pre-dose PK sample					X							
Concomitant medication review			X	X	X	X	X	X	X	X	X	
Study drug dispensation			X									
Study drug dispensation, as necessary				X	X							
Vadadustat dispensation						X						
Vadadustat dispensation, as necessary							X	X	X	X		
Review dosing instructions			X	X	X	X	X	X	X	X		
Study drug compliance check				X	X	X	X	X	X	X	X	

Screening Visits and Study Week	Screening period (Week -4 to 0)		Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18)
	SV1 [a]	SV2 [a]	BV [a]	2	4	6 [a]	8	10	12	14	16 (EOT)	18
Study Day	SV2 ≥4 days from SV1 BV ≥4 days from SV2		1	15	29	43	57	71	85	99	113	127
Based on Hb results from the visits noted, dose reduction for excess Hb response as needed (Section 8.2.4)				X	X							
Based on Hb results from the visits noted, dose adjustment to achieve target Hb 10-12 g/dL (Section 8.2.5)						X	X	X	X	X		

Abbreviations: BV, baseline visit; CBC, complete blood count; ECG, electrocardiogram; EOT, end of treatment; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; PK, pharmacokinetics; RBC, red blood cells; SV1, screening visit 1; SV2, screening visit 2; VEGF, vascular endothelial growth factor

[a] The following visits will be scheduled on the day of the first hemodialysis session of the week, in keeping with JSDT Guidelines from Hb measurement: Screening visit 1, screening visit 2, baseline visit, Week 6, and Week 16. As visit scheduling permits, effort should be made to try to schedule other visits on the day of the first hemodialysis session of the week, acknowledging that this may not be feasible due to subject or site scheduling constraints.

[b] SAEs that are deemed by the investigator to be related to protocol procedures must be reported after signing of the informed consent form. The reporting period for all non-serious AEs and all SAEs not related to protocol procedures begins upon receiving the first dose of study medication and ends at the final protocol-required visit.

[c] In the event screening visit 2 is >8 days prior to Day 1, the subject will be asked to return to the study site for an unscheduled serum pregnancy test to verify eligibility prior to Day 1.

APPENDIX B: SCHEDULE OF ACTIVITIES FOR SUBJECTS WHO WERE PRESCRIBED ESAS PRIOR TO STUDY ENTRY (ESA WASHOUT IS REQUIRED)

Please refer to Section 9.1 for information regarding the visit schedule (including duration of the screening period and the washout period), Section 9.3 for detailed information regarding the study procedures and evaluations, and Section 9.5 for detailed information regarding the activities to be performed at each study visit.

- For subjects who were prescribed epoetin alfa, epoetin beta, and epoetin kappa prior to study entry: Screening visits must be performed within 6 weeks (Day -42 to Day 0) prior to dosing on baseline visit (BV); screening visit 2 (SV2) after ≥2-weeks ESA washout; SV3 should be ≥4 days from SV2; and BV should be ≥4 days from SV3.
- For subjects who were prescribed darbepoetin alfa prior to study entry: Screening visits must be performed within 8 weeks (Day -56 to Day 0) prior to dosing on Day 1; SV2 after ≥4-wk ESA washout; SV3 should be ≥4 days from SV2; and BV should be ≥4 days from SV3.
- For subjects who were prescribed epoetin beta pegol prior to study entry: Screening visits must be performed within 11 weeks (Day -77 to Day 0) prior to dosing on Day 1; SV2 after ≥8-wk ESA washout; SV3 should be ≥4 days from SV2; and BV should be ≥4 days from SV3.

	Screening period			**Primary efficacy period (Day 1-Week 6)**				**Drug adjustment and maintenance period (Week 7-16)**					**Follow-up (Week 17-18)**
Screening Visits and Study Week	**SV1**	**SV2 [a]**	**SV3 [a]**	**BV [a]**	**2**	**4**	**6 [a]**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**See bullet points above**			**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Visit Window (Days)	**—**	**—**	**—**	**—**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X												
Review inclusion/ exclusion criteria	X	X	X	X									
Demographics, medical history, physical exam	X												
Vital signs, dry weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization				X									
12-lead ECG				X									

	Screening period			Primary efficacy period (Day 1-Week 6)				Drug adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18)
Screening Visits and Study Week	**SV1**	**SV2 [a]**	**SV3 [a]**	**BV [a]**	**2**	**4**	**6 [a]**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Dialysis treatment review				X	X	X	X	X	X	X	X	X	
Dialysis adequacy (Kt/V)				X									
Adverse event review [b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Rescue therapy (ESA rescue and RBC transfusion) review					X	X	X	X	X	X	X	X	X
Serum pregnancy test	X		X									X	
Iron indices	X			X	X	X	X	X		X		X	
Folate and vitamin B12	X												
CBC including Hb	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X			X	X	X	X	X	X	X	X	X	X
Coagulation tests				X									
Hepcidin				X			X					X	
C-reactive protein				X			X					X	
VEGF				X			X					X	
Pre-dose PK sample						X							
Concomitant medication review				X	X	X	X	X	X	X	X	X	
Study drug dispensation				X									
Study drug dispensation, as necessary					X	X							

	Screening period			Primary efficacy period (Day 1-Week 6)				Drug adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18)
Screening Visits and Study Week	**SV1**	**SV2 [a]**	**SV3 [a]**	**BV [a]**	**2**	**4**	**6 [a]**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Vadadustat dispensation							X						
Vadadustat dispensation, as necessary								X	X	X	X		
Review dosing instructions				X	X	X	X	X	X	X	X		
Study drug compliance check					X	X	X	X	X	X	X	X	
Based on Hb results from the visits noted, dose reduction for excess Hb response as needed (Section 8.2.4)					X	X							
Based on Hb results from the visits noted, dose adjustment to achieve target Hb 10-12 g/dL (Section 8.2.5)							X	X	X	X	X		

Abbreviations: BV, baseline visit; CBC, complete blood count; ECG, electrocardiogram; EOT, end of treatment; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; PK, pharmacokinetics; SV1, screening visit 1; SV2, screening visit 2; SV3, screening visit 3; VEGF, vascular endothelial growth factor

[a] The following visits will be scheduled on the day of the first hemodialysis session of the week, in keeping with JSDT Guidelines from Hb measurement: Screening visit 2, screening visit 3, baseline visit, Week 6, and Week 16. As visit scheduling permits, effort should be made to try to schedule other visits on the day of the first hemodialysis of the week, acknowledging that this may not be feasible due to subject or site scheduling constraints.

[b] SAEs that are deemed by the investigator to be related to protocol procedures (eg, ESA washout) must be reported after signing of the informed consent form. The reporting period for all non-serious AEs and all SAEs not related to protocol procedures begins upon receiving the first dose of study medication and ends at the final protocol-required visit.

[c] In the event screening visit 3 is >8 days prior to Day 1, the subject will be asked to return to the study site for an unscheduled serum pregnancy test to verify eligibility prior to Day 1.

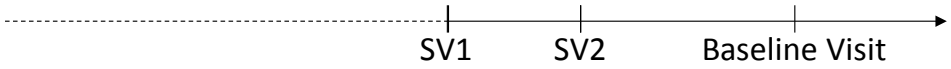
APPENDIX C: DEFINITIONS OF ESA STATUS INCLUSION CRITERIA AND ESA WASHOUT PERIOD

Subjects <u>who are not being treated</u> with ESAs:

Example 1:

ESA use No prior ESA use

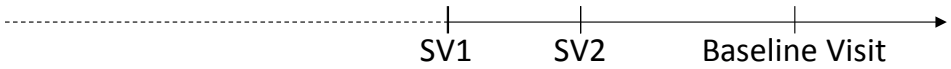
ESA washout No ESA washout required



Example 2:

ESA use Last ESA dose before SV1 ≥2w for epoetin alfa, beta, or kappa; ≥4w for darbepoetin alfa; or ≥8w for epoetin beta pegol

ESA washout No ESA washout required

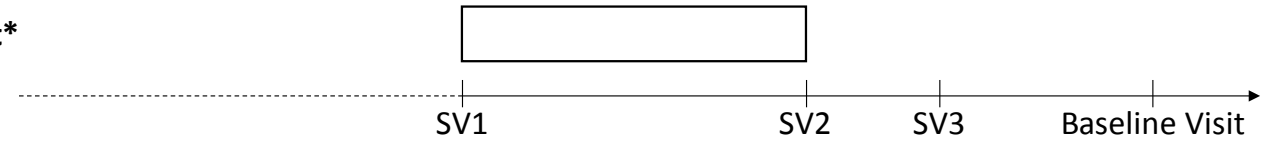


Subjects <u>who are being treated</u> with ESAs:

Example 1:

ESA use Last ESA dose before SV1 <2w for epoetin alfa, beta, or kappa; <4w for darbepoetin alfa; or <8w for epoetin beta pegol

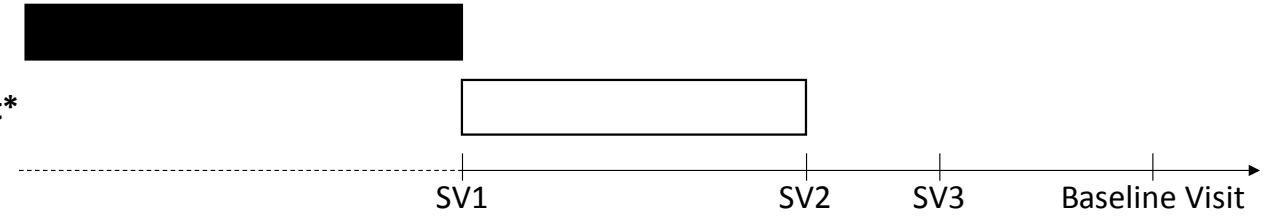
ESA washout*



Example 2:

ESA use

ESA washout*



*After SV1 and before SV2, ≥2w off of epoetin alfa, beta, or kappa; ≥4w off of darbepoetin alfa; or ≥8w off of epoetin beta pegol

1 IDENTIFYING INFORMATION FOR AMENDMENT

Protocol Title:	Phase 2, Randomized, Double-blind, Placebo-Controlled, Dose-Finding Study to Assess the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Vadadustat in Japanese Subjects with Anemia Secondary to Dialysis-Dependent Chronic Kidney Disease (DD-CKD)
Protocol Number:	AKB-6548-CI-0022
Compound:	Vadadustat (AKB-6548)
Status / Date:	Version 1; 3 August 2016 (Original Protocol)
	Version 2; 23 November 2016

2 SPECIFIC CHANGES

Amendments to the protocol are detailed below, except for editorial changes and minor clarification changes. If it is necessary to clarify the edits, newly added text is identified using **bold underlined** font and deleted text is identified by ~~strikethrough~~ font.

Protocol Section	Text in Version 1	Changes in Version 2	Rationale for Change
Synopsis, overview of Study Design, **Synopsis, Dosage and Regimen** **8.2.4, Study Drug Administration during the Primary Efficacy Period (Week 1 to Week 6)**	Fixed dose treatment during the primary efficacy period will allow a dose response relationship to be established. No increase in study drug dose is permitted during this period. However, if Hb level increases rapidly or if the Hb level ~~exceed the desired range~~, the study drug dose can be decreased or interrupted following the dose adjustment guidelines listed under "Dosage and Regimen" (see below). The primary efficacy period involves fixed-dose treatment to establish a dose-response relationship. No increase in study drug dose is permitted during this period. However, ~~if Hb levels increase too rapidly or if Hb levels exceed the desired range based on Hb results from the Week 2 and/or Week 4 study visits, the study drug dose will be decreased as described below~~. • If the Hb rises rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose by 1 tablet. • If the Hb exceeds 13.0 g/dL, interrupt study drug until the Hb decreases to 12.5 g/dL or below and then resume dosing with 1 fewer tablet.	Fixed dose treatment during the primary efficacy period will allow a dose response relationship to be established. No increase in study drug dose is permitted during this period. However, if Hb level increases rapidly or if the Hb level **exceeds 13.0g/dL** the study drug dose can be decreased or interrupted following the dose adjustment guidelines listed under "Dosage and Regimen" (see below). The primary efficacy period involves fixed-dose treatment to establish a dose-response relationship. No increase in study drug dose is permitted during this period. However, **the dose may be decreased or interrupted as described below**. • If the Hb increases rapidly (eg, more than 1 g/dL in any 2-week period), reduce the dose by 1 tablet. • If the Hb exceeds 13.0 g/dL, interrupt study drug until the Hb decreases to 12.5 g/dL or below and then resume dosing with 1 fewer tablet If dose reduction or **interruption** is recommended based on the central laboratory Hb result and protocol-specified guidelines, the investigative site will contact the subject within 1	To clarify the Hb level at which the dose will be interrupted (>13.0 g/dL)

	If dose reduction is recommended based on the central laboratory Hb result and protocol-specified guidelines, the investigative site will contact the subject within 1 business day of receiving the Hb result from the central laboratory.	business day of receiving the Hb result from the central laboratory.	
Synopsis, Study Duration **6.2, Study Duration**	• For subjects who <u>were not prescribed</u> ESAs prior to study entry: Up to 22 weeks, including the eligibility screening period (up to 4 weeks), primary efficacy period (6 weeks), dose adjustment and maintenance period (10 weeks), and follow-up period (2 weeks) • For subjects who <u>were prescribed</u> ESAs prior to study entry: Up to 29 weeks, including the eligibility screening period (up to 11 weeks), primary efficacy period (6 weeks), dose adjustment and maintenance period (10 weeks), and follow-up period (2 weeks) Note: Subjects who discontinue prematurely from the study will complete the end-of-treatment Week 16 visit followed in two weeks by the Week 18 visit.	• For subjects who <u>were not prescribed</u> ESAs prior to study entry: Up to 22 weeks, including the eligibility screening period (up to 4 weeks, **<u>with 2 screening visits</u>**), primary efficacy period (6 weeks), dose adjustment and maintenance period (10 weeks), and follow-up period (2 weeks) • For subjects who <u>were prescribed</u> ESAs prior to study entry: Up to 29 weeks, including the eligibility screening period (up to 11 weeks**<u>, with 3 screening visits</u>**), primary efficacy period (6 weeks), dose adjustment and maintenance period (10 weeks), and follow-up period (2 weeks) Note: Subjects who discontinue prematurely from the study **or permanently discontinue study medication** will complete the end-of-treatment Week 16 visit followed in two weeks by the Week 18 visit.	To clarify the number of screening visits that subjects will undergo during screening. To clarify which subjects will participate prematurely in end-of-treatment visit assessments in alignment with the protocol
Synopsis, Study Duration **6.2, Study Duration** **7.6.1, Subject Completion** **9.3.2, Laboratory Evaluations**	For subjects with Hb >13.0 g/dL at the follow-up visit, Hb will be assessed every 2 weeks until the Hb <13.0 g/dL.	*Text has been deleted*	Excursions in Hb >13 g/dL occurred in only 6 of 138 vadadustat-treated subjects and 1 of 94 vadadustat-treated subjects in the US Phase 2b NDD-CKD (AKB-6548-CI-0007) and Phase 2 DD-CKD (AKB-6548-CI-0011) studies, respectively. In these 2 trials, no

9.4.9, Week 18 Follow-up Visit **9.5.10, Week 18 Follow-up Visit**			elevations in Hb >13 g/dL were observed in the follow-up visit performed 4 weeks after vadadustat cessation. These excursions were not affiliated with any adverse events.
Synopsis, Study Design **6.1 Study Design**	Subjects will participate in a screening period to determine study eligibility. Subjects who have recently received ESA therapy and otherwise meet eligibility criteria will be required to washout from ESA therapy prior to evaluation of screening Hb.	Subjects will participate in a screening period to determine study eligibility. **Subjects who have not recently received ESA therapy will participate in 2 screening visits**. Subjects who have recently received ESA therapy and otherwise meet eligibility criteria will be required to washout from ESA therapy prior to evaluation of screening Hb, **and will participate in 3 screening visits**.	To clarify that the number of screening visits is either 2 or 3 depending on whether subjects recently received ESA therapy.
Synopsis, Key Inclusion Criteria **6.1, Study Design** **7.2, Inclusion Criteria** **8.4.2, ESAs and Blood Transfusion** **9.1, Schedule of Visits** **9.5.1, Screening Visit 1** **Appendix B, Schedule of Activities**	*Previously, ESA washout periods were specified as a 2-week washout for short-acting ESAs and an 8-week washout for long-acting ESAs* • ESA status and screening Hb that meet one of the following criteria: – For subjects <u>who are not being treated</u> with ESAs: Mean Hb <10.0 g/dL; average of 2 measurements obtained during screening. – For subjects <u>who are being treated</u> with ESAs: mean Hb <10.0 g/dL; average of 2 measurements obtained during screening ~~after the protocol-defined ESA washout period~~ (~~ie, a 2-week washout period for short-acting ESA~~	*Protocol has been updated to specify 2-week washout period for epoetin alfa, epoetin beta, and epoetin kappa, 4-week washout for darbepoetin alfa, and 8-week washout for epoetin beta pegol* *Screening visit times in relation to ESA washout periods have been specified* For subjects <u>who are being treated</u> with ESAs: Mean Hb <10.0 g/dL; average of 2 measurements obtained during screening. **<u>These subjects must be off ESAs for at least the following periods of time prior to screening visit 1(refer to Appendix C for examples):</u>** • **<u>2 weeks for epoetin alfa, epoetin beta, or epoetin kappa;</u>** • **<u>4 weeks for darbepoetin alfa;</u>**	A re-evaluation of the published literature (eg, Macdougall KI 2002) and ongoing discussions with nephrology experts in Japan indicated that an 8-week washout period for darbepoetin alfa was too long, and that a 4-week washout period for darbepoetin alfa would be optimal. Text was also edited to clarify ESA washout periods for subjects who are and are not taking ESAs.

	~~and an 8-week washout period for long-acting ESA~~)	• **8 weeks for epoetin beta pegol.** For subjects who are being treated with ESAs: Mean Hb <10.0 g/dL; average of 2 measurements obtained during screening after the protocol-defined ESA washout period. **These subjects must washout ESA therapy for the following periods of time during the screening period, beginning at screening visit 1 and prior to screening visit 2 (refer to Appendix C for examples):** • **2 weeks for epoetin alfa, epoetin beta, and epoetin kappa;** • **4 weeks for darbepoetin alfa;** • **8 weeks for epoetin beta pegol**.	
Synopsis, Key Exclusion Criteria **Section 7.3, Exclusion Criteria**	Hypo-responsiveness to ESA defined as an epoetin equivalent dose >23,000 IU per week within the prior 8 weeks	Hypo-responsiveness to ESA defined **as any of the following ESA treatments within 8 weeks prior to screening: (i) intravenous epoetin dose ≥3000 units/dose 3 times a week (9000 units/week), (ii) intravenous darbepoetin alfa dose ≥60 µg once a week, (iii) epoetin beta pegol ≥200 µg once a month or ≥100 µg once every 2 weeks** ~~as an epoetin equivalent dose >23,000 IU per week within the prior 8 weeks~~	The definition of ESA hyporesponsiveness was updated to be consistent with the 2008 renal anemia guidelines provided by the Japanese Society of Dialysis Therapy
Synopsis, Rescue Therapy Guidelines **Section 8.2.6, Rescue Therapy Guidelines**	~~The following rescue therapy guidelines are provided to ensure the safety of study subjects and~~ to standardize the use of rescue in the study.	**ESA Rescue Therapy** **In order to** standardize the use of ESA rescue in the study**, the following guidelines should be followed.** ESA rescue therapy may be considered if**:** 1) **ESA is considered warranted by the** investigator's judgment, AND	Text was updated to clarify that (a) the rescue guidelines are in place to standardize the use of rescue therapy across study sites (b) clarify when a confirmatory Hb level <9.0 g/dL will be taken and (c) add a provision to initiate rescue therapy if clinically indicated by the investigator.

	• ~~ESA rescue~~: ESA rescue therapy may be considered ~~based on the~~ investigator's judgment if ~~a subject~~: -Experiences a clinically significant worsening of anemia or symptoms of anemia, AND -Has a confirmed Hb level <9.0 g/dL If a subject has one Hb result <9.0 g/dL, the subject should return to the site within 1 week for repeat Hb measurement through the central laboratory. If the second Hb result is also <9.0 g/dL, the subject qualifies for initiation of ESA rescue therapy. •RBC transfusion: Investigators should use their local institution's transfusion guidelines when determining whether to transfuse a study subject. Subjects who initiate rescue therapy will be required to stop study drug treatment and will be discontinued from the study.	2) **The subject** experiences a clinically significant worsening of anemia or symptoms of anemia, AND 3) **The subject** has a confirmed Hb level <9.0 g/dL as defined by two consecutive Hb levels <9.0 g/dL. **The investigator may schedule the subject to return for an unscheduled visit to confirm Hb level <9.0 g/dL prior to the subsequent scheduled study visit.** **If clinically indicated, the investigator at his/her discretion may initiate ESA rescue therapy without a confirmatory Hb level <9.0 g/dL if the first two criteria above are met.** Red Blood Cell Transfusions Investigators should use their local institution's transfusion guidelines when determining whether to transfuse a study subject. Subjects who initiate **either** rescue therapy, **ESA Rescue Therapy or Red Blood Cell Transfusion**, will be required to stop study drug treatment and will be discontinued from the study.	
Synopsis, Statistical Considerations	The primary analysis will use a linear regression analysis to quantify the association between vadadustat dose and mean change in Hb (ie, to assess the vadadustat dose-response relationship). Comparison of each vadadustat dose group versus baseline will be performed. All tests of significance will be performed using a 0.05 two-sided significance level.	*[Text shown in the left cell has been deleted and replaced with the following text]* **An analysis of covariance (ANCOVA) model will be used to compare change from baseline in Hb between the 3 vadadustat dosing groups and the placebo group. The model will include treatment assignment (3 dosed groups and 1**	Update of statistical approach to primary endpoint. Use of ANCOVA instead of linear regression is considered more appropriate for this dose-finding study. For comparison of more than 2 treatment groups, with baseline metric as a covariate, ANCOVA analysis is a common and traditional method to assess change from baseline, the primary endpoint. This change in statistical

		placebo group) and baseline Hb value as a covariate. A step-down procedure will be used to control the overall type I error rate for the multiple comparisons. Testing of the highest dose compared with placebo will be conducted first. If and only if this comparison is significant, then testing will proceed to comparison of the next lower dose and placebo, and so on. As a result, no multiplicity adjustment will be needed for this analysis.	analysis method does not affect the study design.

Synopsis, Statistical Considerations	Based on the results from Study AKB-6548-CI-0005, the expected changes in mean Hb from baseline to Week 6 will be 0, 0.5, 0.7, and 1.2 g/dL for the placebo, 150 mg, 300 mg, and 600 mg vadadustat dose groups, respectively, with a common standard deviation of 0.68 g/dL among the 4 treatment groups. With these assumptions, the study will have >85% power to detect a non-zero slope in a dose-response relationship using linear regression analysis and α=0.05, based on simulation of 10,000 repetitions using SAS® software, Version Number 9.4.	*[Text shown in the left cell has been deleted and replaced with the following text]* **The study is powered based on a comparison of the highest dose vadadustat group (600 mg daily) and the placebo group.** **Based on the results from Study AKB 6548 CI 0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to NDD-CKD, it is assumed that the expected mean Hb changes from baseline to Week 6 will be approximately 0 mg/dL for the placebo group and 1.35 g/dL for the highest dose vadadustat group (600 mg daily).** **Based on the results from Study AKB 6548 CI 0011 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to DD-CKD, it is assumed that the common Hb standard deviation will be 0.9 g/dL across treatment groups. In addition, a dropout rate of 10% is assumed. With these assumptions, the study with n=12 subjects per group will have >85% power to detect the difference between treatment group and control group, at 2-sided alpha of 0.05.**	The common Hb standard deviation is increased from 0.68 to 0.9 g/dL based on the US Phase 2 DD-CKD study (AKB-6548-CI-0011) to better reflect the DD-CKD population. In addition, the assumed dropout rate is increased from 0 to 10%. With these changes in assumptions, the study power has changed from >95% to >85%. This change does not impact study conduct.
Synopsis, Statistical Considerations	Sponsor and CRO study team personnel involved in the preliminary analysis will not be involved in the conduct of the study after the preliminary analysis.	**Individuals from the** sponsor and CRO study teams ~~team personnel involved in~~ **who are unblinded for the development and reporting of the** preliminary analysis will not be	To clarify that individuals who are unblinded during the primary analysis will not be involved in study conduct following the preliminary analysis.

8.2.3, Blinding During the Study and Breaking the Blind		involved in the conduct of the study after the preliminary analysis.	
4.6, Ethno-Bridging Data from a Study of Healthy Japanese and Caucasian Volunteers	*Not applicable*	**Vadadustat was generally well tolerated in this study.**	Overall safety results from the study was added
4.7, Potential Benefits and Risks	In addition, HIF activation promotes iron mobilization through upregulation of ferroportin and transferrin and downregulation of hepcidin (Peyssonnaux 2007). As a result, vadadustat will likely improve iron availability and enhance EPO responsiveness.	In addition, HIF activation **is associated with increased expression of** ~~promotes iron mobilization through upregulation of~~ ferroportin and transferrin and ~~downregulation~~ **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** ~~As a result, vadadustat will likely improve iron availability and enhance EPO responsiveness~~.	Editorial change to accurately quote the referenced articles
6.2, Study Duration **7.6.1, Subject Completion**	Subjects who discontinue prematurely from the study will complete the end-of-treatment Week 16 visit followed in two weeks by the Week 18 visit.	*[Text in the left cell has been deleted and replaced with the following text]* **See Section 7.6.3 for subjects who discontinue study drug or withdraw early from the study.**	To clarify which subjects will participate prematurely in end-of-treatment visit assessments in alignment with the protocol
6.3, Rationale for Study Design	…completed dose-finding study in Caucasian subjects with anemia secondary to NDD-CKD…	…completed dose-finding study in ~~Caucasian~~ subjects with anemia secondary to NDD-CKD **that included a majority of Caucasian and Black/African American subjects**…	Clarification of the ethnic distribution of the subjects who participated in Study AKB-6548-CI-0005
7.6.3, Individual Subject Discontinuation	Subjects discontinuing study drug or withdrawing from the study should complete the Week 16 (EOT) clinical and laboratory assessments within	Subjects **permanently** discontinuing study drug or withdrawing **early** from the study **prior to the Week 16 visit** should complete the Week 16 (EOT) clinical and laboratory assessments	To clarify which subjects will participate prematurely in end-of-treatment visit assessments in alignment with the protocol

	1 day of stopping study medication, if possible.	within 1 day of stopping study medication, if possible.	
8.1.3, Dispensing of Study Drugs	At the Week 6 visit, sites will collect from subjects from all dosing cohorts study drug bottles and all remaining study drug tablets remaining from the primary efficacy period. Each subject will then be provided with 1 bottle of vadadustat. Each bottle will contain 100 tablets of vadadustat. Subjects will be instructed to finish 1 bottle before opening a new bottle. Resupply of additional study drug at other visits will be dependent on the dose level and the number of tablets remaining in the subject's current supply at a given study visit. To allow for some flexibility in study visit scheduling and possible dropped doses, sites should ensure that subjects have an adequate supply of study medication.	At the Week 6 visit, sites will collect ~~from subjects from all dosing cohorts study drug bottles and~~ all **unused** remaining study drug tablets ~~remaining from~~ **dispensed during** the primary efficacy period. Each subject will then be provided with 1 bottle of vadadustat. Each bottle will contain 100 tablets of vadadustat. ~~Subjects will be instructed to finish 1 bottle before opening a new bottle.~~ Resupply of additional study drug ~~at other visits~~ **as needed** will be dependent on the dose level and the number of tablets remaining in the subject's current supply at a given study visit. **Subjects will be instructed to finish 1 bottle before opening a new bottle.** To allow for some flexibility in study visit scheduling ~~and possible dropped doses~~, sites should ensure that subjects have an adequate supply of study medication.	Editorial change to clarify the drug dispensing and return process.
8.2.3, Blinding During the Study and Breaking the Blind	The applicable standard operating procedure will be followed for blind-breaking procedures.	*The sentence has been deleted*	Statement is not necessary to be included in the protocol as information related to SOPs will be addressed in the Trial Master File.
8.2.5, Study Drug Administration during the Dose Adjustment and Maintenance Period (Week 7 to Week16)	Specifically, at the Week 6 visit, sites will collect from subjects from all dosing cohorts study drug bottles and all remaining study drug tablets remaining from the primary efficacy period.	Specifically, at the Week 6 visit, sites will collect ~~from subjects from all dosing cohorts study drug bottles and~~ all ~~remaining~~ **unused** study drug tablets ~~remaining~~ dispensed during ~~from~~ the primary efficacy period.	Editorial change to clarify the drug return process.

8.2.5, Study Drug Administration during the Dose Adjustment and Maintenance Period (Week 7 to Week16)	When adjusting therapy, investigators should consider Hb rate of rise, rate of decline, and variability as well as the subject's clinical condition (including recent illness, volume depletion, and volume overload). ~~In cases of extenuating clinical circumstances~~, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range.	*[Text shown in the left cell has been deleted and replaced with the following text]* **As clinically indicated,** the investigator may elect to dose outside the dose adjustment guidelines. **In such cases, the clinical circumstances must be documented in the subject's record**	The text was updated to mitigate any ambiguity or confusion regarding the adjustment of therapy.
8.2.6, Rescue Therapy Guidelines **8.4.2, ESAs and Blood Transfusion**	Note: ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.6 for the rescue therapy guidelines. Subjects who initiate rescue therapy will be required to stop study drug treatment and will be discontinued from the study. • Prohibitions related to ESA use: See Section 9.1 for washout period for ~~short acting ESAs and long acting~~ ESAs. ~~Subjects may not receive any short acting ESA treatment within 2 weeks of the Hb assessment at Screening Visit 2 or any long acting ESA treatment within 8 weeks of the Hb assessment at Screening Visit 2. In addition, subjects may not receive any ESA treatment through the follow up period.~~ • Prohibitions related to blood transfusions: Subjects may not receive blood transfusion within 4 weeks prior to the screening period and through the follow up period.	Note: ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.6 for the rescue therapy guidelines. Subjects who initiate rescue therapy will be required to stop study drug treatment and will be discontinued from the study. **See Section 7.6.3 for subjects who discontinue study drug or withdraw early from the study.** • **Prohibitions related to ESA use: See Section 9.1 for washout period for ESAs.** • **For subjects who are not currently being treated with ESAs:** ○ **Subjects may not receive any ESA during the screening, treatment, and follow-up study periods except in the context of ESA rescue (see ESA rescue guidelines, section 8.2.6).** • **For subjects who are currently being treated with ESAs:** ○ **After screening visit 1 and prior to screening visit 2, subjects must not**	Text was updated to provide additional clarification regarding: 1. When subjects, who discontinue early from the study, will participate in the end-of-treatment visit assessments. 2. When subjects must be off ESAs during the study.

<table>
<tr>
<td></td>
<td></td>
<td><u>receive ESAs for at least the following time periods:</u>
<table>
<tr><th><u>ESA</u></th><th><u>ESA washout period (Minimum duration of time without ESA treatment after SV1 and prior to SV2)</u></th></tr>
<tr><td><u>Epoetin alfa</u>
<u>Epoetin beta</u>
<u>Epoetin kappa</u></td><td><u>2 weeks</u></td></tr>
<tr><td><u>Darbepoetin alfa</u></td><td><u>4 weeks</u></td></tr>
<tr><td><u>Epoetin beta pegol</u></td><td><u>8 weeks</u></td></tr>
</table>

<u>After screening visit 2 and through the remaining screening period, subjects must not use any ESA. Any ESA use during this period would result in exclusion from the study.</u>

<u>During the treatment and follow-up study periods, subjects may not receive any ESA except in the context of ESA rescue (see ESA rescue guidelines, section 8.2.6).</u></td>
<td></td>
</tr>
<tr>
<td>8.2.9, Compliance with Study Drug Dosing</td>
<td>Subjects will be questioned regarding dosing compliance at all study visits</td>
<td>Subjects will be questioned regarding dosing compliance and whether they have questions or have experienced</td>
<td>Editorial change to clarify that dosing compliance is to be determined from</td>
</tr>
</table>

	from Week 1 through Week 16, and any missed doses will be recorded. Subjects will also be questioned regarding the date and time of their last dose of study drug prior to the PK sample at the Week 4 visit. The date and time of these doses will be recorded on the CRF.	**any problems related to the dosing of study drug. 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.**~~at all study visits from Week 1 through Week 16, and any missed doses will be recorded.~~ **Subjects who miss doses will be counseled on the importance of treatment compliance.** Subjects will also be questioned regarding **the timing of their last dose of vadadustat during PK sample collection.** ~~the date and time of their last dose of study drug prior to the PK sample at the Week 4 visit.~~ The date and time of these doses will be recorded on the CRF.	discussions with the subject following drug accountability.
9.3.1, Clinical Evaluations	*Not applicable*	**Rescue therapy (ESA rescue and RBC transfusion) review: Beginning with the first post-baseline visit (after Day 1) and through the follow-up visit, the investigator and study personnel will review whether a subject received rescue therapy (ESA rescue or RBC transfusion).**	This item was added to prompt sites to ask about ESA rescue and RBC transfusion at each post-baseline visit.
9.4, Schedule of Activities (For Subjects Who Were Not Prescribed ESAs Prior to Study Entry) **9.5, Schedule of Activities (For Patients Who Were**	*Not applicable*	*Added the following item to post-baseline visits:* **<u>Rescue therapy (ESA rescue and RBC transfusion) review</u>**	This item was added to prompt sites to ask about ESA rescue and RBC transfusion at each post-baseline visit.

Prescribed ESAs Prior to Study Entry) **Appendix A** **Appendix B**			
9.4, Schedule of Activities (For Subjects Who Were Not Prescribed ESAs Prior to Study Entry) **9.5, Schedule of Activities (For Patients Who Were Prescribed ESAs Prior to Study Entry)** **Appendix A** **Appendix B**	*Not applicable*	*Relevant sections have been updated to include "AE review" at the screening and baseline visits.* *Section 9.5.1 has been updated to list "Demographics, medical…"* *Related footnote has been added to Appendix A and Appendix B*	The SAE reporting period has been redefined specifically for SAEs related to protocol procedures, eg, ESA washout during screening. This was done because the screening period in this study requires withdrawal of ESA therapy in the study population of DD-CKD patients who are currently using ESAs. Section 9.4 and Appendix A were updated to ensure that the assessments are aligned across these 2 sections. Section 9.5 and Appendix B were updated to ensure that the assessments are aligned across these 2 sections.
9.2.3.1, Acceptable Methods of Contraception **9.3.2, Laboratory Evaluations** **9.4, Schedule of Activities (For Subjects Who Were Not Prescribed ESAs Prior to Study Entry)** **9.5, Schedule of Activities (For Patients Who Were Prescribed ESAs Prior to Study Entry)** **Appendix A** **Appendix B**	*Urine pregnancy test performed at baseline visit*	*Deleted urine pregnancy test* *Added serum pregnancy testing to the last scheduled screening visit prior to randomization*	A substantial proportion of DD-CKD subjects are anuric. Therefore, we replaced urine pregnancy testing at baseline with a serum pregnancy testing at screening.

9.3.2, Laboratory Evaluations **9.4.2, Screening Visit 2, Appendix A footnote [c]** **9.5.3 Screening Visit 3, Appendix B, footnote [c]**	Serum pregnancy tests: Female subjects who are of childbearing potential (ie, are not surgically sterile or postmenopausal) will participate in serum pregnancy tests (to be analyzed by the central lab). The screening pregnancy test results must be available and must be negative for a subject to initiate ~~or continue~~ study drug.	Serum pregnancy tests: Female subjects who are of childbearing potential (ie, are not surgically sterile or postmenopausal) will participate in serum pregnancy tests (to be analyzed by the central lab). The screening pregnancy test results must be available and must be negative for a subject to initiate study drug. **Note: Additional serum or local urine (if possible) pregnancy tests may be conducted, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the study** *Newly added text to section 9.4.2 and 9.5.3. Text was customized for visit.* • **Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The serum pregnancy test must be performed within 4-8 days prior visit 1/Day 1 to allow sufficient time to obtain the pregnancy test result prior to randomization, and the screening results must be available and must be negative before the subject takes the first dose of study drug. In the event screening visit 3 is >8 days prior to Day 1, the subject will be asked to return to the study site for an unscheduled serum pregnancy test to verify eligibility prior to Day 1. The**	The timing of the screening pregnancy test was changed from baseline to last screening visit to ensure the test results are available to verify subject eligibility prior to randomization and dosing on Day 1. As an additional precaution to avoid in utero exposure to study drug, language has been added to remind sites that pregnancy testing may be performed during the study as determined by investigator discretion.

		serum pregnancy test will be analyzed by the central lab.	
10.1.1, Adverse Events	*Not applicable*	*Newly added text:* **Kidney Transplantation – During this study, some subjects may receive a kidney transplant. These events will not be recorded as AEs.**	Clarification is provided that kidney transplantation will not be considered an AE in this study.
10.3.1, Reporting Period **Appendix A, Footnote [b]** **Appendix B, Footnote [b]**	~~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.	**The reporting period for all non-serious AEs and all SAEs not related to protocol procedures begins upon receiving the first dose of study medication and ends at the final protocol-required visit.** **SAEs that are assessed by the investigator to be related to protocol procedures (eg, ESA washout) must be reported after signing of the informed consent form.** 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.	The SAE reporting period has been redefined specifically for SAEs related to protocol procedures, eg, ESA washout during screening. This was done because the screening period in this study requires withdrawal of ESA therapy in the study population of DD-CKD patients who are currently using ESAs. Appendix A and B were updated to reflect the clarification.
10.4, Exposure in Utero	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, or the investigator should call the CRO SAE hotline within 24 hours of being made	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~~, or the investigator should call the CRO SAE hotline within 24 hours of being made~~	Editorial change to clarify the process for reporting pregnancy and its outcome.

	aware of the pregnancy (reference the site manual for contact information).	~~aware of the pregnancy~~ (reference the site manual for contact information).	
10.4, Exposure in Utero	*Not applicable*	**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.**	To clarify procedure for reporting pregnancy and its outcome.
10.4, Exposure in Utero	Neonates should be followed the first four weeks after birth.	*[The text shown in the left cell has been deleted and the following text has been added]* **Neonates should be followed through gestational age of 46 weeks.**	Specification of follow-up period for neonates based on gestational age to account for the possibility of premature births.

Section 11	*See deleted/added text in the cell below*	*See deleted/added text in the cell below*	Update of statistical approach to primary endpoint. Use of ANCOVA instead of linear regression is considered more appropriate for this dose-finding study. The common Hb standard deviation is increased from 0.68 to 0.9 g/dL based on the US Phase 2 DD-CKD study (CI-0011) to better reflect the DD-CKD population. In addition, the assumed dropout rate is increased from 0 to 10%. With these changes in assumptions, the study power has changed from >95% to >85%. This change does not impact study conduct.

This cell refers to the item in the above row. Rationale for change is provided in the row above in the far right cell.

Text added to Section 11:

An overview of the statistical approach to the primary endpoint and safety analyses are provided below. The details of the planned analysis of the primary endpoint as well as the planned analyses of secondary endpoints, PK, PD, and safety will be documented in the statistical analysis plan (SAP).

Section 11.1 Primary Endpoint – Mean Change in Hb from Pre-treatment to the End of the Primary Efficacy Period (Week 6)

The primary objective of this study is to evaluate the dose-response relationship between oral vadadustat once daily dosing for 6 weeks and the change in Hb in Japanese subjects with anemia secondary to DD-CKD; in order to define the starting dose for use in Phase 3 clinical studies in Japan.

The primary endpoint is the mean change in Hb from pre-treatment to the end of the primary efficacy period (Week 6). Pre-treatment Hb is defined as the average of 3 Hb values obtained prior to treatment based on the 2 qualifying screening Hb value and the Hb value at the baseline visit.

Section 11.2 Primary Efficacy Analysis and Sample Size Determination

An analysis of covariance (ANCOVA) model will be used to compare change from pre-treatment in Hb between the 3 vadadustat dosing groups and the placebo group. The model will include treatment assignment (3 dosed groups and 1 placebo group) and pre-treatment Hb value as a covariate. A step-down procedure will be used to control the overall type I error rate for the multiple comparisons. Testing of the highest dose compared with placebo will be conducted first. If and only if this comparison is significant, then testing will proceed to comparison of the next lower dose and placebo, and so on. As a result, no multiplicity adjustment will be needed for this analysis.

The study is powered based on a comparison of the highest dose vadadustat group (600 mg daily) and the placebo group.

Based on the results from Study AKB-6548-CI-0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to NDD CKD, it is assumed that the expected mean Hb changes from pre-treatment to Week 6 will be approximately 0 mg/dL for the placebo group and 1.35 g/dL for the highest dose vadadustat group (600 mg daily).

Based on the results from Study AKB 6548 CI 0011 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to DD-CKD, it is assumed that the common Hb standard deviation will be 0.9 g/dL across treatment groups. In addition, a dropout rate of 10% is assumed. With these assumptions, the study with n=12 subjects per group will have >85% power to detect the difference between treatment group and control group, at 2-sided alpha of 0.05.

Text deleted from Section 11:

~~**The primary objective of this study is to quantify the dose-response relationship between oral vadadustat once daily dosing for 6 weeks and change in Hb in Japanese subjects with DD-CKD in order to define the starting dose for use in Phase 3 clinical studies in Japan.**~~

~~**Change in Hb is defined as the Hb measured at the Week 6 visit minus the mean pre-treatment Hb. Note that a pre-treatment average value for Hb is defined as the average of 3 values obtained prior to dosing, ie, the 2 qualifying screening values and the baseline value.**~~

~~**Linear regression analysis will be used to calculate the relationship between vadadustat dose and change in Hb.**~~

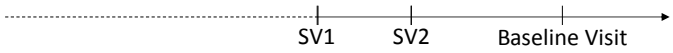
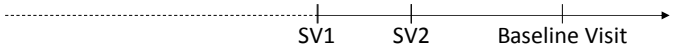
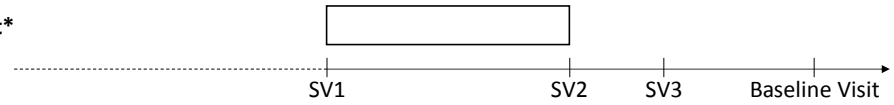
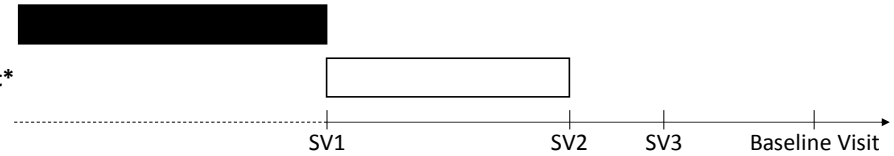
~~**The primary analysis will use a linear regression analysis to quantify the association between vadadustat dose and mean change in Hb (ie, to assess the vadadustat dose-response relationship). Comparison of each vadadustat dose group versus will be performed. All tests of significance will be performed using a 0.05 two-sided significance level.**~~

~~**Based on the results from Study AKB-6548-CI-0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to NDD-CKD, the expected mean Hb changes from baseline to Week 6 will be 0, 0.5, 0.7, and 1.2 g/dL for the placebo, 150 mg, 300 mg, and 600 mg vadadustat dose groups, respectively, with a common standard deviation of 0.68 g/dL among the 4 treatment groups. With these assumptions, the study will have >85% power to detect a non-zero slope in a dose-response relationship using linear regression analysis and α=0.05, based on simulation of 10,000 repetitions using SAS® software, Version Number 9.4.**~~

11.4.1, Analysis Populations for the Safety Analyses	The intent-to-treat (ITT) population will include all subjects assigned to study medication who receive at least 1 dose of study medication. All safety analyses will be performed using the ITT population.	The ~~intent-to-treat (ITT)~~ **safety** population **is defined as** ~~will include~~ all **enrolled** subjects ~~assigned to study medication~~ who receive at least 1 dose of study medication. **The safety population will be based on the actual treatment that patients received.** All safety analyses will be performed using the ~~ITT~~ **safety** population.	The various study populations were defined.
11.4.2, Analysis Populations for the Efficacy Analyses	The modified intent-to-treat (MITT) population will include subjects who receive at least 1 dose of study medication, have a pre-treatment Hb	The modified intent-to-treat (MITT) population **is defined as all randomized** subjects who receive at least 1 dose of study medication, have a	The various study populations were defined.

	average defined as the average of the qualifying screening value and the baseline value, and at least one post-baseline Hb measurement. The per-protocol (PP) population will consist of the subjects in the MITT population who have completed the study and have efficacy data through Week 6, have a study medication compliance of ≥80%, and do not have any major protocol deviations.	pre-treatment Hb average defined as the average of the qualifying screening value and the baseline value, and at least one post-baseline Hb measurement. **The MITT population will be based on the treatment to which patients are randomized.** The per-protocol (PP) population will consist of the subjects in the MITT population who have completed the study and have efficacy data through Week 6, have a study medication compliance of ≥80%, and do not have any major protocol deviations **expected to significantly affect the primary efficacy endpoint. Subjects with major protocol deviations expected to significantly affect the primary efficacy endpoint will be identified and documented prior to data unblinding.**	
11.5 Efficacy and PD Analyses	The entire set of efficacy outcomes will be defined in the statistical analysis plan (SAP). In addition to the primary endpoint analysis defined above, the following efficacy endpoints will also be assessed: • Actual values and change (absolute and percent) from baseline in Hb, HCT, RBC count, and reticulocyte count (both absolute and percent) • Actual values and change (absolute and percent) from baseline in iron, TIBC, TSAT, ferritin (both absolute and percent), and hepcidin	*This section has been deleted*	Editorial revision to focus protocol on statistical approach to primary efficacy analysis. Details related to all planned analyses will be provided in the statistical analyses plan as mentioned in the newly added paragraph at the beginning of Section 11.

	Changes from baseline of efficacy and PD parameters will be summarized using descriptive statistics by treatment groups and each scheduled assessment, and results will be displayed using box lots. Linear regression analysis will be performed for Hb change from baseline to Week 6, to quantify the association between vadadustat dose and mean change in Hb (ie, to assess the vadadustat dose response relationship).. Comparison of each vadadustat dose group versus baseline will be performed. All tests of significance will be performed using a 0.05 two sided significance level. Similar analysis will be performed for change from baseline to Week 6 of reticulocyte count (both absolute and percent), hematocrit, and RBC count. Also, similar linear regression analysis will be performed for change from baseline to Week 6 of the iron indices (ie, iron, TIBC, ferritin, and TSAT) and hepcidin will be evaluated. All tests of significance will be performed using a 0.05 two sided significance level.		
11.7, Safety Analyses	The following variables are the safety endpoints: adverse events, vital signs, ECGs, components of the CBC, and VEGF.	The following variables are the safety endpoints: adverse events, vital signs, ECGs, **and laboratory parameters** ~~components of the CBC, and VEGF~~.	Editorial revision
11.7, PK Analyses	At the Week 4 visit, pre-dose plasma concentrations of vadadustat and its metabolites will be obtained to evaluate for accumulation of study medication.	*This section has been deleted*	Editorial revision to focus protocol on statistical approach to primary efficacy analysis. Details related to all planned analyses will be provided in the

			statistical analyses plan as mentioned in the newly added paragraph at the beginning of Section 11.
18, Appendices	Appendix C: Definitions of ESA Status Inclusion Criteria and ESA Washout Period, was added to provide additional clarity regarding when subjects are to washout ESA therapy. **Subjects <u>who are not being treated</u> with ESAs:** **Example 1:** **ESA use** No prior ESA use **ESA washout** No ESA washout required  **Example 2:** **ESA use** Last ESA dose before SV1 ≥2w for epoetin alfa, beta, or kappa; ≥4w for darbepoetin alfa; or ≥8w for epoetin beta pegol **ESA washout** No ESA washout required  **Subjects <u>who are being treated</u> with ESAs:** **Example 1:** **ESA use** Last ESA dose before SV1 <2w for epoetin alfa, beta, or kappa; <4w for darbepoetin alfa; or <8w for epoetin beta pegol **ESA washout***  **Example 2:** **ESA use** **ESA washout***  *After SV1 and before SV2, ≥2w off of epoetin alfa, beta, or kappa; ≥4w off of darbepoetin alfa; or ≥8w off of epoetin beta pegol	

Akebia Therapeutics, Inc.
245 First Street, Suite 1100
Cambridge, MA 02142
T: +1 617.871.2098 F: +1 617.871.2099
www.akebia.com

NOTE TO FILE

Protocol Number: AKB-6548-CI-0022

Protocol Title: Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Assess the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Vadadustat in Japanese Subjects with Anemia Secondary to Chronic Kidney Disease (DD-CKD)

Protocol Section: 9.1 – Schedule of Events, **Appendix B** – Schedule of Activities for Subjects Who Were Prescribed ESAs Prior to Study Entry (ESA Washout is Required)

Subject: Clarification regarding administrative errors

Date: 16-Dec-2016

This is to confirm that the below editorial changes will made to the English version of protocol AKB-6548-CI-0022 (v.2.0, 23Nov2016) at the time of the next protocol amendment. Please note that these edits were made in the Japanese version of the protocol.

Section 9.1 – Schedule of Events: Day 42 will be updated to Day -42.

- **For subjects who were prescribed epoetin alfa, epoetin beta, and epoetin kappa prior to study entry, the screening visits must be performed within 6 weeks (Day 42 to Day 0) prior to dosing on Day 1. There will be a 2-week ESA washout period between screening visit 1 and screening visit 2, in addition, screening visit 2 after the ≥2-wk ESA washout; screening visit 3 should be ≥4 days from screening visit 2; and baseline visit (Day 1) should be ≥4 days from screening visit 3.**

Appendix B: Schedule of Activities for Subjects who were Prescribed ESAs Prior to Study Entry (ESA Washout is Required): A [c] will be added after Serum Pregnancy test in the Schedule of Events.

(ESA rescue and RBC transfusion) review					
Serum pregnancy test	X		X		
Iron indices	X			X	
Folate and	X				

[b] SAEs that are deemed by the investigator to be related to protocol procedures (eg, ESA washout) must be reported after signing of the informed consent form. The reporting period for all non-serious AEs and all SAEs not related to protocol procedures begins upon receiving the first dose of study medication and ends at the final protocol-required visit.

[c] In the event screening visit 3 is >8 days prior to Day 1, the subject will be asked to return to the study site for an unscheduled serum pregnancy test to verify eligibility prior to Day 1.

Printed Name: [redacted] Role: [redacted]

Signature: [redacted] Date: 16-Dec-2016

Akebia Therapeutics, Inc.
245 First Street, Suite 1100
Cambridge, MA 02142
T: +1 617.871.2098 F: +1 617.871.2099
www.akebia.com

NOTE TO FILE

Protocol Number: AKB-6548-CI-0022

Protocol Title: Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Assess the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Vadadustat in Japanese Subjects with Anemia Secondary to Dialysis Dependent Chronic Kidney Disease

Subject: Administrative errors in Protocol Version 2.0 and Summary of Changes (SOC)

Date: 03 February 2017

This is to clarify that the following administrative errors were noted in Protocol version 2.0 and the corresponding Summary of Changes (SOC) document, dated 23 November 2016.

- **The following highlighted text the protocol synopsis, protocol section 11.2, and the SOC, is incorrect: "mg/dL" should be "g/dL"**
  - *Based on the results from Study AKB-6548-CI-0005 that was conducted in the United States and evaluated vadadustat in patients with anemia secondary to NDD-CKD, it is assumed that the expected mean Hb changes from baseline to Week 6 will be approximately 0 mg/dL for the placebo group and 1.35 g/dL for the highest dose vadadustat group (600 mg daily), with a common standard deviation of 0.68 g/dL across treatment groups.*

Printed Name: _____ **Role:** Clinical Project Manager

Signature: _____ **Date:** _____