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 NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0021
Phase:	Phase 2
Status / Date:	Original protocol (Version 1; 23 May 2016)
Sponsor:	Akebia Therapeutics, Inc. 245 First Street, Suite 1100 Cambridge, MA 02142, United States of America

NCT Number: NCT03054337
This NCT number has been applied to the document for purposes of posting on clinicaltrials.gov

1 SIGNATURE PAGES

1.1 Protocol Approval

[redacted] Medical Research
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 also 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.

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Signature of Investigator Date

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Investigator Name (print or type)

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Investigator's Title

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Full Address

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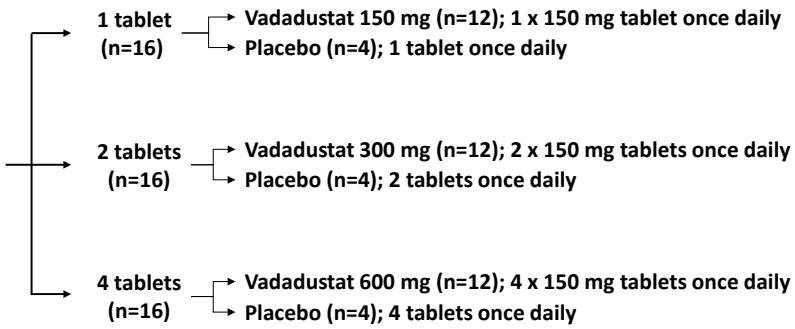
2 PROTOCOL SYNOPSIS

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 Non-Dialysis Dependent Chronic Kidney Disease
Protocol Number	AKB-6548-CI-0021
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 non-dialysis dependent chronic kidney disease (NDD-CKD) who are not currently being treated with an erythropoiesis-stimulating agent (ESA)
Investigative Sites	Approximately 25 sites in Japan
Planned Number of Subjects	Approximately 48 subjects will be enrolled in the study, with 36 subjects receiving one of the 3 doses of vadadustat and 12 subjects receiving placebo: • 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 (QD) dosing for 6 weeks and the change in hemoglobin (Hb) in Japanese subjects with anemia secondary to NDD-CKD; in order 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 QD dosing in Japanese subjects with anemia secondary to NDD-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 maintenance period
Study Design Overview	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 NDD-CKD. The study will include the following periods: • Eligibility screening period (up to 4 weeks) • Primary efficacy period (6 weeks; Weeks 1 to 6) • Dose adjustment and maintenance period (10 weeks), including the following: – Blinded dose adjustment and data cleaning period (4 weeks; Weeks 7 to 10): Individual subject data (from screening to Week 6) will be locked and individual subject unblinding will take place at the Week 10 visit – Open-label extension period (6 weeks; Weeks 11 to 16): Subjects randomized to receive vadadustat treatment during the blinded period will continue into this period • Safety follow-up period (2 weeks; Weeks 17 and 18): Subjects who complete participation in the open-label extension period and subjects who discontinue early during the blinded study periods will complete the safety follow-up

	period. Subjects identified as having received placebo during the Week 10 unblinding visit will not participate in this safety follow-up period. Following the screening period, eligible subjects will be randomized to receive blinded study drug treatment during a 6-week primary efficacy period, with subjects randomized at a 3:1 ratio to receive vadadustat (150, 300, or 600 mg vadadustat) or placebo. See "Dosage and Regimen" in the synopsis for additional information regarding the randomization scheme. Fixed-dose treatment during the blinded primary efficacy period will allow a dose-response relationship to be established. However, if Hb levels increase too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose can be decreased or discontinued (see "Dosage and Regimen" for additional information). After completing the primary efficacy period, subjects will continue to a 10-week dose adjustable maintenance period which will include a 4-week, blinded dose adjustment and data cleaning period and a 6-week, open-label extension period. Dose can be adjusted during the open-label period to achieve a target Hb of 10-12 g/dL, and the dose adjustments will be guided by an interactive web response (IWR) system based on Hb concentration and programmed dose adjustment algorithms (see "Dosage and Regimen" for additional information). Individual subject's study data (from screening to Week 6) will be cleaned and locked during the 4-week, blinded, dose adjustment and data cleaning period. At the Week 10 visit, treatment assignment will be unblinded on an individual subject basis. Subjects who were randomized to receive placebo will end study participation after unblinding at the Week 10 visit. Subjects who were randomized to receive 1 of the 3 vadadustat doses will continue receiving vadadustat during the open-label extension period. Vadadustat treatment will stop after the extension period has been completed (Week 16) and subjects will continue in a 2-week follow-up safety period (Week 17-18).
Study Duration	Up to 22 weeks, including the eligibility screening period (up to 4 weeks), primary efficacy period (6 weeks), blinded dose adjustment and data cleaning period (4 weeks), open-label extension period (6 weeks), and safety follow-up period (2 weeks). Only subjects who are randomized to receive vadadustat will continue in the maintenance period and the safety follow-up period.
Key Inclusion Criteria (the complete list is provided in the protocol)	• Male and female Japanese subjects (20 years or older) • Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009) • Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening • Hb ≤10.5 g/dL • Serum ferritin ≥50 ng/mL • Transferrin saturation (TSAT) ≥20% • Folate and vitamin B12 ≥lower limit of normal
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; intravenous iron within 4 weeks prior to or during screening; and any ESA use within 6 weeks prior to or during screening.
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 or eGFR 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 B12 values may be considered for rescreening after receiving replacement therapy. Screening is limited to 3 attempts (initial screening and 2 additional rescreening attempts).
Study Endpoints	Note that a pre-treatment value for Hb, hematocrit, RBC count, reticulocyte count, and iron metabolism markers is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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:** • Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the open-label extension period (Week 16) • Mean change in Hb between pre-treatment and the end of the open-label extension period (Week 16) • Mean change in hematocrit, RBC count, and reticulocyte count from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, ferritin, and hepcidin) from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Proportion of subjects with confirmed Hb values <10.0 or >12.0 g/dL from pre-treatment to the end of the open-label extension 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 open-label extension 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 open-label extension period (Week 16) • Number of dose adjustments from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Plasma concentration profile of vadadustat and its metabolites using pre-dose sample from Week 4 • Safety assessments, including adverse events, vital signs, electrocardiograms (ECGs), and other laboratory assay results (eg, serum 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 other oral beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food. Note: Hb will be assessed at the central laboratory and also monitored using point-of-care HemoCue®. Note that the point-of-care HemoCue Hb value will be used to determine if the dose of study medication will be adjusted or discontinued. **Primary efficacy period (Day 1 to Week 6)** 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.  The primary efficacy period includes a fixed-dose treatment to establish a dose-response relationship. However, if Hb level increases too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose will be decreased or discontinued as presented below. • Subjects who meet the following criteria for excess Hb response will undergo a dose reduction by 1 tablet: – Hb increase >1 g/dL within any 2-week period, OR – Hb increase >2 g/dL within any 4-week period, OR – Hb level >13 g/dL • Subjects who meet the following criteria will discontinue study drug: – Excess Hb response as defined by any of the aforementioned criteria, AND – Current dose 1 tablet OR subject had previously decreased study drug dose due to excess Hb response **Blinded dose adjustment and data cleaning period (Week 7 to 10)** During this period, data from screening through the Week 6 visit will be cleaned and locked in preparation for the Week 10 unblinding visit. Blinded study drug dosage will be adjusted to achieve a target Hb 10-12 g/dL. Starting at the Week 6 visit, adjustments to doses will be guided by an IWR system based on Hb concentration

	and programmed dose adjustment algorithms. See the dose adjustment guidelines below. **Open-label extension period (Weeks 11 to 16):** Subjects who were randomized to receive vadadustat will enter this open-label extension period, and vadadustat dosage will continue to be adjusted to achieve a target Hb 10-12 g/dL. Dose adjustments will continue to be guided by an IWR system based on Hb concentration and programmed dose adjustment algorithms. See the dose adjustment guidelines below. **Dose adjustment guidelines from Week 7 to Week 16** The programmed dose adjustment algorithm for blinded study drug (from Week 7 to 10) and open-label vadadustat (from Week 11 to 16) will follow the dose adjustment guidelines listed below to achieve a target Hb of 10-12 g/dL, and will be guided by an IWR system. The point-of-care HemoCue Hb value will be used to determine if the dose of study drug will be adjusted. • Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased at Week 10 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 14. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the IWR system dosing recommendation to maintain the Hb within the target range.
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**: 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 – Exhibits Hb level <9.0 g/dL • **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.
Oral Iron Supplementation	Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be

	considered a reason for subject discontinuation. Subjects who are not taking oral iron supplementation at baseline should not start oral iron during their study participation. **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.
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. The target enrollment will be approximately 48 subjects for the study with 12 subjects enrolled in each of the 4 treatment groups. 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.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
CV	cardiovascular
dL	deciliter
DVT	deep venous thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
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
GFR	glomerular filtration rate
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(ly)
IWR	interactive web response
JSN	Japanese Society of Nephrology
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
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)
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.

A number of 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.

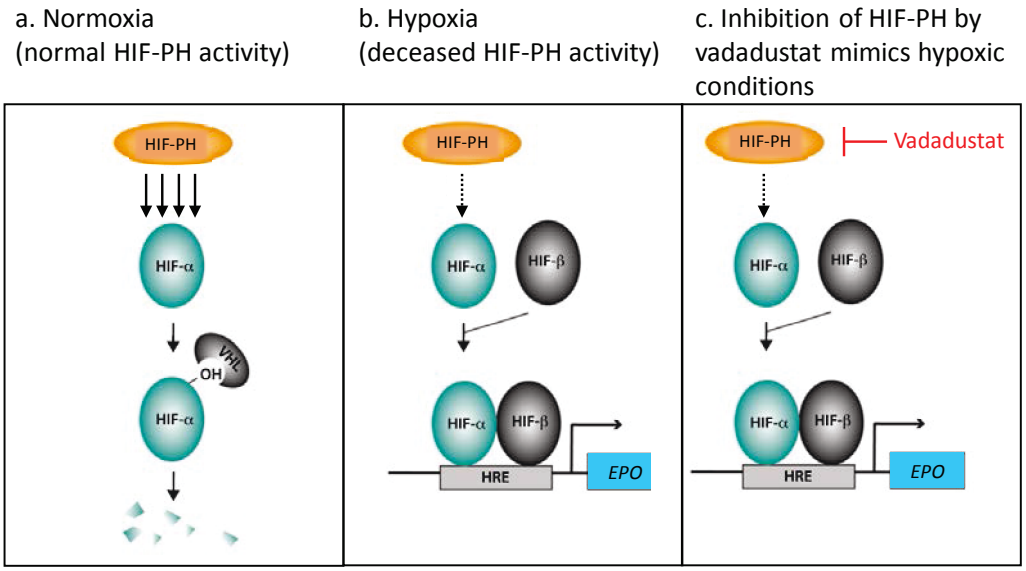
4.3 Hypoxia-Inducible Factor

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 patients with DD-CKD 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. As a result, 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 recently 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.

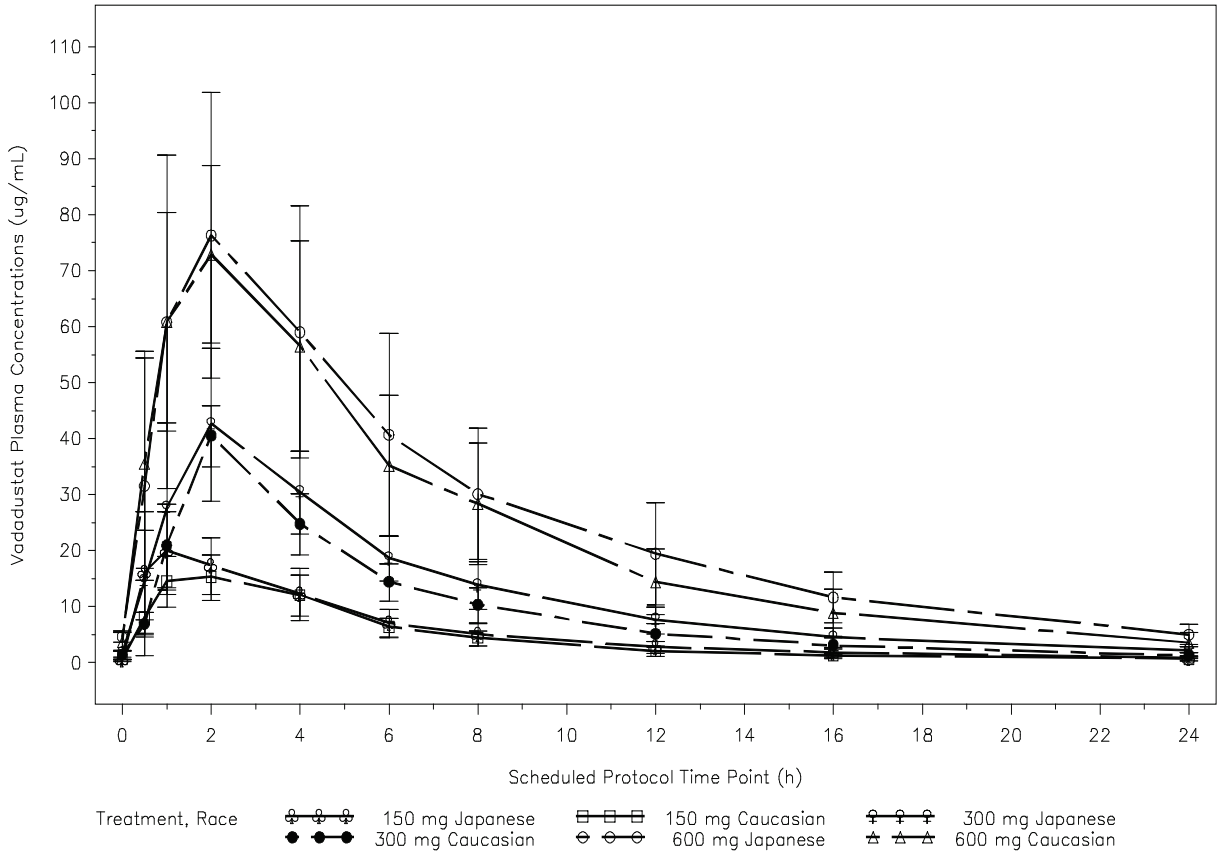
Eligible subjects were enrolled into one of 3 dose cohorts: 150, 300, or 600 mg daily oral doses of vadadustat (or placebo). Subjects received daily doses of study drug (either vadadustat or placebo) for 10 days. Each of the 3 dose cohorts enrolled 8 Japanese and 8 Caucasian subjects.

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.

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 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 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, all of 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 HIFPH 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 value for Hb, hematocrit, RBC count, reticulocyte count, and iron metabolism markers is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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 Hb in Japanese subjects with anemia secondary to NDD-CKD; in order 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 NDD-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 maintenance period

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

- Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the open-label extension period (Week 16)
- Mean change in Hb between pre-treatment and the end of the open-label extension period (Week 16)
- Mean change in hematocrit, RBC count, and reticulocyte count from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, ferritin, and hepcidin) from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Proportion of subjects with confirmed Hb values <10.0 or >12.0 g/dL from pre-treatment to the end of the open-label extension 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 open-label extension 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 open-label extension period (Week 16)
- Number of dose adjustments from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Plasma concentration profile of vadadustat and its metabolites using pre-dose sample from Week 4
- Safety assessments, including adverse events, vital signs, electrocardiograms (ECGs), and other laboratory assay results (eg, serum chemistry, components of the complete blood count [CBC] other than the ones noted above, and vascular endothelial growth factor [VEGF])

6 STUDY DESIGN

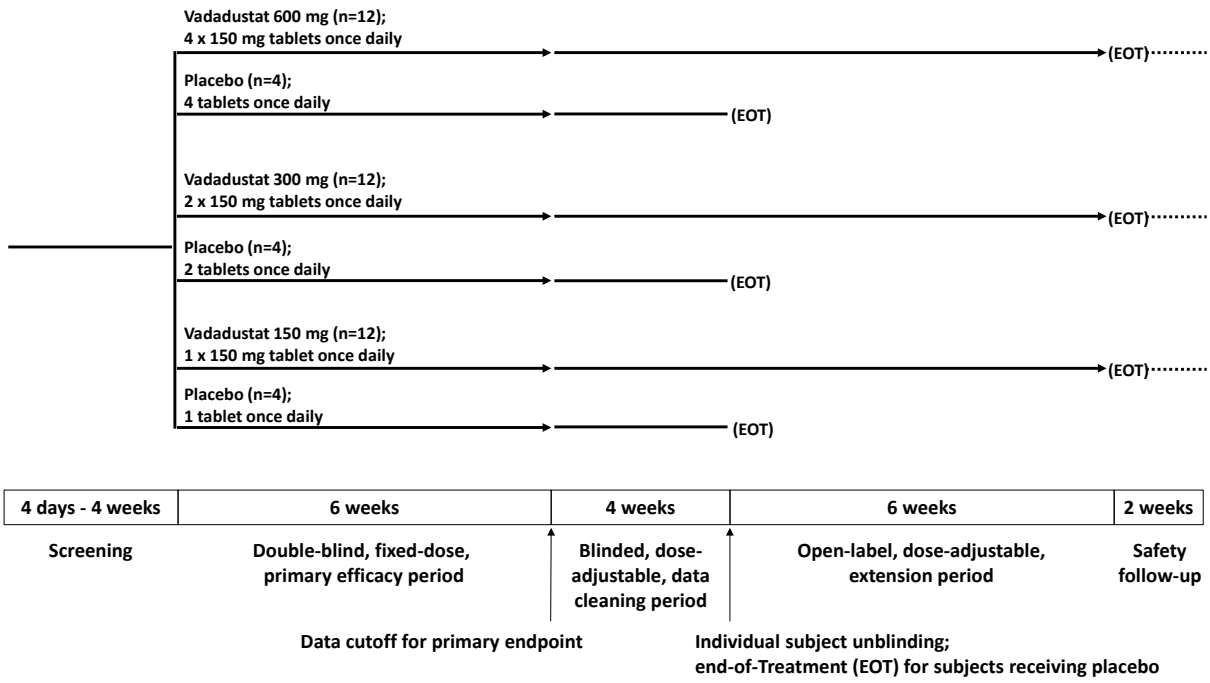
6.1 Study Design

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 subjects with anemia secondary to NDD-CKD.

The study has a planned enrollment of 48 subjects to be enrolled at approximately 25 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



The study will include the following periods:

- Eligibility screening period (up to 4 weeks)
- Primary efficacy period (6 weeks; Weeks 1 to 6)
- Dose adjustment and maintenance period (10 weeks) include the following:
  - Blinded dose adjustment and data cleaning period (4 weeks; Weeks 7 to 10): Individual subject data (from screening to Week 6) will be cleaned and locked and individual subject unblinding will take place at the Week 10 visit
  - Open-label extension period (6 weeks; Weeks 11 to 16): Subjects randomized to receive vadadustat treatment during the blinded period will continue into this period
- Safety follow-up period (2 weeks; Weeks 17 and 18): Subjects who complete participation in the open-label extension period and subjects who discontinue early during the blinded study periods will complete the safety follow-up period. Subjects identified as having received placebo during the Week 10 unblinding visit will not participate in this safety follow-up period.

Subjects will participate in a screening period (4 days to 4 weeks) to determine study eligibility, and 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.

Blinded 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 levels increase too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose can be decreased or discontinued (see Section 8.2.4).

After completing the primary efficacy period, subjects will continue to a 10-week dose adjustment and maintenance period including a 4-week, blinded dose adjustment and data cleaning period and a 6-week, open-label extension period (see Sections 8.2.5 and 8.2.6). Dose will be adjusted to achieve a target Hb of 10-12 g/dL, and the dose adjustments will be guided by an interactive web response (IWR) system based on Hb concentration and programmed dose adjustment algorithms (see Section 8.2.7).

Individual subject's study data (from screening to Week 6) will be cleaned and locked during the 4-week, blinded, dose adjustment period.

At the Week 10 visit, treatment assignment will be unblinded on an individual subject basis. Subjects who were randomized to receive placebo will end study participation after unblinding at the Week 10 visit. Subjects who were randomized to receive 1 of the 3 vadadustat doses will continue receiving vadadustat during the 6-week, open-label extension period.

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

The clinical and safety assessments will be performed as described in Section 9.3 and as listed in Appendix A.

6.2 Study Duration

Individual subjects will participate in the study for up to 22 weeks, including the eligibility screening period (up to 4 weeks), primary efficacy period (6 weeks), blinded dose adjustment and data cleaning period (4 weeks), open-label extension period (6 weeks), and safety follow-up period (2 weeks).

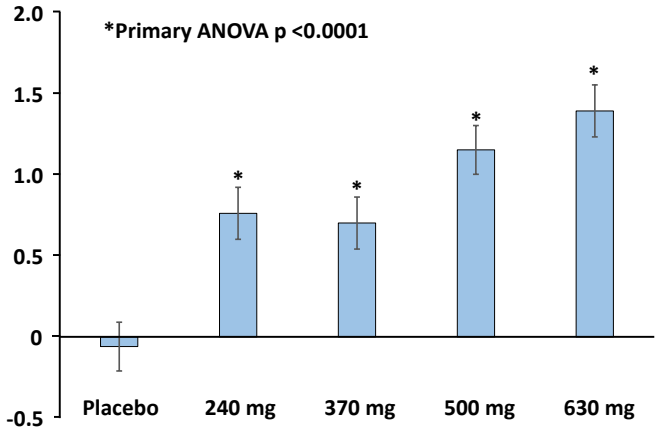
Only subjects who are randomized to receive vadadustat will continue in the open-label extension period and the safety follow-up period. Subjects who are randomized to receive placebo during the blinded treatment period will discontinue from the study after unblinding at Week 10.

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 NDD-CKD is modeled on a previously completed dose-finding study in Caucasian subjects with anemia secondary to NDD-CKD (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 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 safe and 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 safe, 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 according to 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

The study population will consist of male and female Japanese adults aged 20 years or older with anemia secondary to NDD-CKD who are not currently being treated with an ESA.

To be eligible for this study, a subject or their legally acceptable representative must have provided valid informed consent and must meet all of 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 all of the following inclusion criteria to be eligible for study participation:

1. Male and female Japanese subjects, aged 20 years or older
2. Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009)
3. Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening
4. Hemoglobin (Hb) ≤10.5 g/dL during screening
5. Serum ferritin ≥50 ng/mL during screening
6. TSAT ≥20% during screening
7. Folate and vitamin B12 greater than or equal to the lower limit of normal during screening
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. RBC transfusion within 4 weeks prior to or during screening
4. Intravenous iron within 4 weeks prior to or during screening

5. Any ESA use within 6 weeks prior to or during screening (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta)

6. 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.

7. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mm Hg or systolic blood pressure >180 mm Hg) during screening

8. Body mass index (BMI) >42.0 kg/m^2

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

10. 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

11. 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

12. 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

13. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) requiring active treatment within 8 weeks prior to or during screening

14. History of hemosiderosis or hemochromatosis

15. History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list are not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis are not excluded)

16. 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

17. Previous participation in a study with vadadustat or another hypoxia-inducible factor prolyl-hydroxylase inhibitor

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

19. Females who are pregnant or breast-feeding

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

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

22. 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.

The screening period can last up to 4 weeks long, with a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1), ie, the screening period window is from Day -28 to Day -4.

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 or eGFR 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 B12 values may be considered for rescreening after receiving replacement therapy.

If intravenous (IV) iron is used to replete iron stores, the last dose of IV iron must be administered at least 4 weeks prior to rescreening.

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 randomized to receive placebo will be considered as having completed the study after completing participation in the Week 10 (unblinding) visit.

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

Note that for subjects who discontinue study drug due to an excess Hb response during the primary efficacy period, Hb levels will be monitored weekly via lab evaluation until the subject no longer exhibits an excess Hb response.

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 will discontinue study medication for any of the following conditions:

- Completion of the protocol-defined dosing period (see Appendix A)
- Meets discontinuation criteria related to excess Hb response during the primary efficacy period (defined in Section 8.2.4)
- Major toxicity considered to be related to study medication
- Worsening of anemia requiring ESA rescue or blood transfusion
- Administrative reasons, such as, subject non-compliance or a major protocol violation
- Upon request of the sponsor or regulatory agency
- If, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject
- Study termination (see Section 14)

Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be considered a reason for subject discontinuation.

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

7.6.3 Individual Subject Discontinuation during the Primary Efficacy Period or Blinded Dose Adjustment and Data Cleaning Period

Subjects discontinuing study medication or withdrawing early from the study during the blinded periods should undergo the Week 10 (EOT for blinded period) clinical and laboratory assessments within 1 day of stopping study medication, if possible. Such subjects should also complete the 2-week safety follow-up period (see Appendix A). 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.

7.6.4 Individual Subject Discontinuation during the Open-Label Extension Period

Only subjects randomized to vadadustat will continue to the open-label extension period. Subjects discontinuing vadadustat or withdrawing from the study during the open-label period should complete the Week 16 (EOT for open-label period) clinical and laboratory assessments within 1 day of stopping study medication, if possible. Such subjects should also complete the 2-week safety follow-up period and complete the Week 18 visit assessments (see Appendix A). 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 according to 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 at the baseline visit. Each bottle will contain 100 tablets of study drug. Subjects will be instructed to finish 1 bottle before opening a new bottle.

Resupply of additional study drug at subsequent 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.

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 at all times.

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 according to 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 other oral beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food.

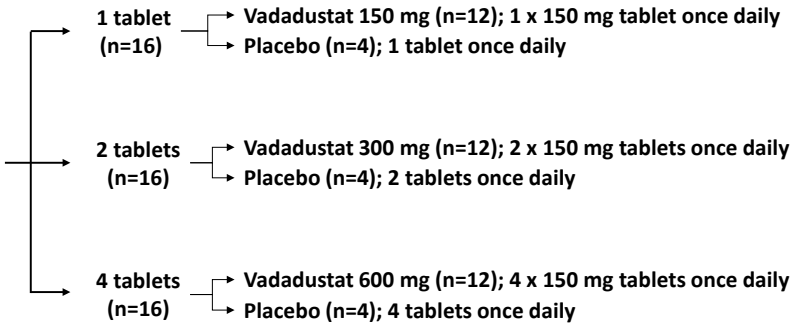
Subjects should be instructed to take the study medication at approximately the same time each day, preferably between 7 am and 2 pm, with the exception of the Week 4 visit. On the day of the Week 4 visit, the dose of study medication should be held until after the pre-dose PK sample has been obtained.

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 Primary Efficacy Period and Breaking the Blind

During the blinded periods, all subjects and personnel involved with the conduct and interpretation of the study will be blinded to the study drug treatment, including investigators, site personnel, site pharmacist, and sponsor's staff and designees.

The study blind should be broken for individual subjects after a subject completes the Week 6 visit and the subject's data (from screening to Week 6) is cleaned and locked.

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.

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. The applicable standard operating procedure will be followed for blind-breaking procedures. After each subject's data is cleaned and locked, their individual randomization code will be broken to determine eligibility for continuation to the open-label extension period.

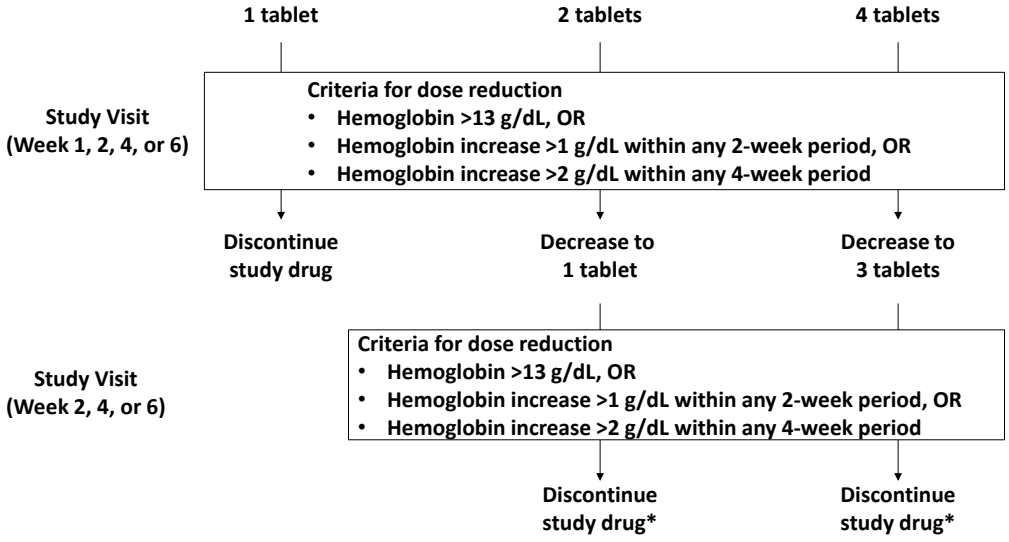
8.2.4 Study Drug Administration during the Primary Efficacy Period

To establish a dose-response relationship, the primary efficacy period includes a blinded fixed-dose treatment regimen. However, if Hb levels increase too rapidly or if the Hb levels exceed the desired range, the dose will be decreased or discontinued as presented below (and as depicted in Figure 6).

- Subjects who meet the following criteria for excess Hb response will undergo a dose reduction by 1 tablet:
  - Hb level >13 g/dL, OR
  - Hb increase >1 g/dL within any 2-week period, OR
  - Hb increase >2 g/dL within any 4-week period
- Subjects who meet the following criteria will discontinue study drug:
  - Excess Hb response as defined by any of the aforementioned criteria, AND
  - Current dose of 1 tablet daily OR subject had previously decreased study drug dose due to excess Hb response

Hb will be assessed at the central laboratory and also monitored using point-of-care HemoCue® (as listed in Appendix A). Note that the point-of-care HemoCue Hb value will be used to determine if the dose of study medication will be adjusted or discontinued.

Figure 6: Algorithm for Dose Reduction or Discontinuation of Study Drug During the Primary Efficacy Period



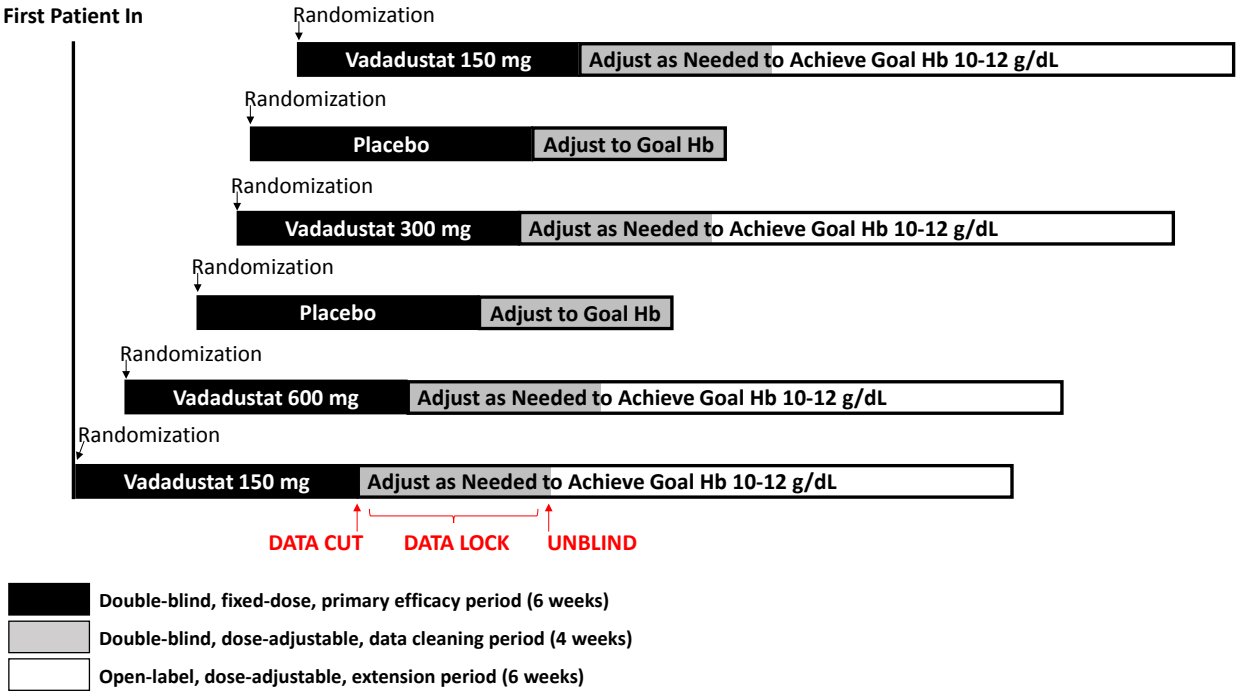
*Note: A subject who had previously decreased study drug dose due to an excess Hb response and meets the criteria for excess Hb response at a subsequent visit during the primary efficacy period (Week 2, 4, or 6) will discontinue study drug

8.2.5 Study Drug Administration during the Blinded Dose Adjustment and Data Cleaning Period

After completing the Week 6 visit, subjects will continue blinded study treatment for an additional 4 weeks during which time their data from screening through the Week 6 visit will be cleaned and locked. Individual subjects will be unblinded at their Week 10 visit. Potential scenarios for individual subject unblinding is shown in Figure 7.

Point-of-care Hb levels will be monitored via HemoCue to determine if the dose of study medication will be adjusted (as listed in Appendix A). Dose adjustments will be guided by an IWR system based on Hb concentration and programmed dose adjustment algorithms (see Section 8.2.7).

Figure 7: Potential Scenarios for Individual Subject Unblinding



8.2.6 Vadadustat Administration during the Open-Label Extension Period

During the 6-week, open-label extension period, vadadustat dosage will be adjusted to achieve a target Hb level of 10-12 g/dL. Point-of-care Hb will be monitored via HemoCue to determine if the dose of study medication will be adjusted (see Appendix A). Dose adjustments will be guided by an IWR system based on Hb concentration and programmed dose adjustment algorithms (see Section 8.2.7).

8.2.7 Dose Adjustment Guidelines

The programmed dose adjustment algorithm for blinded study drug (from Week 7 to 10) and open-label vadadustat (from Week 11 to 16) will follow the dose adjustment guidelines listed below to achieve a target Hb of 10-12 g/dL, and will be guided by an IWR system. The point-of-care HemoCue Hb value will be used to determine if the dose of study drug will be adjusted.

- Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased at Week 10 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 14. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the IWR system dosing recommendation to maintain the Hb within the target range.

8.2.8 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**: 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
  - Exhibits Hb level <9.0 g/dL
- **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.

8.2.9 Oral Iron Supplementation (Information on Allowed Use)

Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be considered a reason for subject discontinuation.

Subjects who are not taking oral iron supplementation at baseline should not start oral iron during their study participation (see Section 8.4.3).

Important: Because of the potential for oral iron to reduce the bioavailability of vadadustat, the 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.

8.2.10 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.

Subjects should be questioned regarding dosing compliance and the information should be recorded.

8.2.11 Treatment Compliance

Subjects will be questioned regarding dosing compliance at all study visits from Week 1 through Week 18, 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.

8.2.12 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 through the course of 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, Intravenous Iron, and Blood Transfusion

Subjects may not receive any ESA treatment within 6 weeks prior to the screening period and through the safety follow-up period (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta). See Section 8.2.8 for the rescue therapy guidelines.

Subjects may not receive intravenous iron or blood transfusion within 4 weeks prior to the screening period and through the safety follow-up period. Use of intravenous iron supplementation after Day 1 will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.8 for the rescue therapy guidelines. Note that subjects who initiate rescue therapy will be required to stop study drug treatment and will be discontinued from the study.

8.4.3 Oral Iron Supplementation (Information on Prohibition)

Subjects who are not taking oral iron supplementation at baseline should not start oral iron during study participation. Use of oral iron supplementation by such subjects will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

See Section 8.2.9 for information on circumstances allowing use of oral iron supplementation.

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

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

- Eligibility screening period (Day -28 to Day -4)
- Baseline visit (Day 1)
- Primary efficacy period (Week 1 ± 1 day, Week 2 ± 1 day, Week 4 ± 3 days, and Week 6 ± 3 days)
- Blinded dose adjustment and data cleaning period (Week 10 ± 3 days)
- Open-label extension period (Week 14 ± 3 days and Week 16 ± 3 days)
- Safety follow-up period (Week 18 ± 3 days)

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same investigator or site personnel whenever possible.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.2 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.

9.1.3 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 9.1.3.1.

9.1.3.1 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.

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) and at baseline (assessed using urine 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

9.2 Study Procedures and Evaluations

9.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study. Detailed information regarding the timing of the assessments is presented in Section 9.3 and summarized in Appendix A:

- Demographics and medical history: Relevant medical history (with particular 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
- Weight assessment
- 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.
- 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.

  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.

9.2.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis, with the exception of the urine pregnancy test at baseline which will be performed locally. 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 course of the study:

- Serum and urine pregnancy test: A serum pregnancy test for females of childbearing potential will be analyzed by the central lab (screening, Week 10, and Week 16 visits). A urine pregnancy test will be analyzed by the local lab (baseline visit). The screening and baseline pregnancy test results must be available and must be negative for a subject to initiate or continue study drug.
- 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.
- HemoCue®: Hb will be monitored via HemoCue point-of-care device to determine if the dose of study drug will be adjusted.

- 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).

  For subjects who discontinue study drug due to an excess Hb response during the primary efficacy period, Hb will be assessed weekly via lab evaluation until the subject no longer exhibits an excess Hb response.
- Serum chemistry and eGFR: The serum chemistry will include the following assays: 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. eGFR will be calculated from serum creatinine as described in Appendix B.
- Iron indices: Blood samples will be collected to assess serum iron, TIBC, TSAT, ferritin, and 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.

9.3 Schedule of Activities

The Schedule of Events in 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.

9.3.1 Screening Visit

The screening visit must be performed within 28 days prior to dosing and there must be a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1).

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo a number of screening activities. The investigator will maintain a log of subjects and indicate who was enrolled or excluded and the reason for exclusion (see Section 9.1.2).

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

- Review of study inclusion and exclusion criteria
- Demographics, medical history, and physical examination
- Weight assessment
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)
- Prior and current medication use
- 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.
    - Coagulation tests (including prothrombin time, partial thromboplastin time, and international normalized ratio)
    - Folate and vitamin B12 levels
    - CBC
    - Serum chemistry and eGFR
    - Iron indices

9.3.2 Baseline Visit (Day 1)

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

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

- Review of study inclusion and exclusion criteria
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- Recording of any concomitant medication use since screening visit
- Laboratory procedures:
    - Urine pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The urine sample will be analyzed by the local lab. The baseline results must be available and must be negative before the subject takes the first dose of study drug.
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
    - C-reactive protein
    - VEGF
- Dispense blinded study drug
- Review dosing instructions

9.3.3 Week 1 Visit

At the Week 1 visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue
- CBC
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.4 Week 2 Visit

At the Week 2 visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
- Subjects should be questioned regarding dosing compliance
- Dispense blinded study drug (as necessary)
- Review dosing instructions and 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

9.3.5 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 (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
    - Pre-dose PK sample

- Record date and time of the last dose of the study that was taken prior to the pre-dose PK sample
- Subjects should be questioned regarding dosing compliance
- Dispense blinded study drug (as necessary)
- Review dosing instructions

9.3.6 Week 6 Visit

Individual subject data (up to Week 6) will be cleaned and locked after the Week 6 visit. Following data lock, individual subject's randomized treatment assignment will be unblinded and the subject will be informed at the Week 10 visit.

At the Week 6 visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
  - CBC
  - Serum chemistry and eGFR
  - Iron indices
  - C-reactive protein
  - VEGF
- Subjects should be questioned regarding dosing compliance
- Dispense blinded study drug (as necessary)
- Review dosing instructions

9.3.7 Week 10 Visit (End-of-treatment visit for the blinded period and early withdrawals)

All enrolled subjects who receive at least 1 dose of blinded study drug should complete the Week 10 assessments.

Subjects who withdraw early from the study prior to the Week 6 visit or permanently discontinue study medication prior to the Week 6 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 9.3.10).

Individual subject data (up to Week 6) will be locked after the Week 6. Following data lock, individual subject's randomized treatment assignment will be unblinded and the subject will be informed at the Week 10 visit. Subjects who were assigned to receive placebo will discontinue from the study at the end of the Week 10 visit, and subjects who were assigned to receive vadadustat will continue to the open-label extension period.

At the Week 10 visit, 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)
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)

- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Hb using HemoCue for dose adjustment (not for subjects who discontinue prior to the Week 6 visit)
- Laboratory procedures:
    - Serum pregnancy test for females of childbearing potential (to be analyzed by the central lab)
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
    - C-reactive protein
    - VEGF
- Subjects should be questioned regarding dosing compliance
- Dispense open-label vadadustat (as necessary) and review dosing instructions (only applicable to subjects who are continuing to the open-label extension period)

9.3.8 Week 14 Visit

At this visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue for dose adjustment
- CBC
- Serum chemistry and eGFR
- Subjects should be questioned regarding dosing compliance
- Dispense vadadustat (as necessary)
- Review dosing instructions

9.3.9 Week 16 Visit (End-of-treatment visit for the open-label period and early withdrawal visit for withdrawals after Week 10 but before Week 16)

All subjects who received at least 1 dose of open-label vadadustat should complete the Week 16 assessments.

Subjects who withdraw early from the open-label period 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 9.3.10).

At the Week 16 visit, 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)
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)

- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
    - Serum pregnancy test for females of childbearing potential (to be analyzed by the central lab)
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
    - C-reactive protein
    - VEGF
- Subjects should be questioned regarding dosing compliance

9.3.10 Week 18 Safety Follow-Up Visit (Or 2 Weeks after End-of-Treatment Safety Follow-Up Visit)

For subjects randomized to vadadustat who complete the open-label extension period, the safety visit will be conducted 2 weeks after their end-of-treatment visit (Week 16).

For subjects who discontinue the study early during the primary efficacy period or the blinded dose adjustment and data cleaning period, the safety visit will be conducted 2 weeks after their end-of-treatment visit (Week 10).

At the follow-up visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
    - CBC
    - Serum chemistry and eGFR

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.

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 AE reporting period for a subject begins upon receiving the first dose of study medication and ends at the final protocol-required visit. In addition, SAEs that occur after the protocol-defined AE reporting period that are considered to be related to the study medication should be recorded and reported to the sponsor's medical monitor or CRO designee.

10.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the AE 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, or the investigator should call the CRO SAE hotline within 24 hours of being made aware of the pregnancy (reference the site manual for contact information).

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

The 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.
- 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

11.1 Primary Endpoint and Sample Size Determination

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 NDD-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 EOT visit minus the mean pre-treatment Hb. Pre-treatment Hb is defined as the average of 2 Hb values obtained prior to treatment based on the qualifying screening Hb value and the Hb value at the baseline visit. Linear regression analysis will be used to calculate the relationship between vadadustat dose and change in Hb.

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

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 reasonable to assume that 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.

11.2 Study Populations

11.2.1 Analysis Population 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.

11.2.2 Analysis Populations for the Efficacy Analyses

The modified intent-to-treat (MITT) population will include all subjects assigned to study medication who receive at least 1 dose of study medication and have a pre-treatment average and at least one post-baseline measurement. All efficacy endpoints will be analyzed using the MITT population.

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.

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

11.3 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.

11.4 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.

11.5 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

For purposes of analysis, a pre-treatment average (defined as the average of 2 samples obtained prior to treatment [ie, the qualifying screening value and baseline value]) will be used as the

baseline value for Hb and RBC count, and last observation before the first dose of study medication will be used as baseline for other parameters.

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 assess the vadadustat dose-response relationship. 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.

11.6 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, components of the CBC, and VEGF.

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.

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.

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 course of 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.

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Appendix A: Schedule of Activities

Please refer to Section 9.2 for detailed information regarding the study procedures and evaluations, and please refer to Section 9.3 for detailed information regarding the activities to be performed at each study visit.

	Screening	Primary efficacy period (blinded, fixed-dose treatment) (Day 1-Week 6)					Blinded dose adjustment, data cleaning period (Week 7-10)	Open-label extension period (Week 11-16)		Safety Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**1**	**2**	**4**	**6**	**10 (EOT, Blinded Period)**	**14**	**16 (EOT, Open-Label Period)**	**18**
Study Day	**-28 to -4**	**1**	**8**	**15**	**29**	**43**	**81**	**109**	**123**	**137**
Visit Window (Days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X									
Review inclusion/exclusion criteria	X	X								
Individual subject data lock (for subjects who complete Week 6)						X				
Individual subject unblinding (for subjects who complete Week 6)							X			
Demographics, medical history, physical exam, and weight	X									
Vital signs	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram	X						X		X	
Adverse event review			X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X						X		X	
Urine pregnancy test		X								
Coagulation tests	X									

	Screening	Primary efficacy period (blinded, fixed-dose treatment) (Day 1-Week 6)					Blinded dose adjustment, data cleaning period (Week 7-10)	Open-label extension period (Week 11-16)		Safety Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**1**	**2**	**4**	**6**	**10 (EOT, Blinded Period)**	**14**	**16 (EOT, Open-Label Period)**	**18**
Study Day	**-28 to -4**	**1**	**8**	**15**	**29**	**43**	**81**	**109**	**123**	**137**
Visit Window (Days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Folate and vitamin B12	X									
Hb using HemoCue® (Week 10 assessment is not for subjects who discontinue prior to Week 6)			X	X	X	X	X	X		
Complete blood count, including Hb [a]	X	X	X	X	X	X	X	X	X	X
Serum chemistry and eGFR	X	X		X	X	X	X	X	X	X
Iron indices	X	X		X	X	X	X		X	
C-reactive protein		X				X	X		X	
VEGF		X				X	X		X	
PK pre-dose sample (study drug to be administered after sample collection)					X					
Blinded study drug dispensation, as necessary		X		X	X	X				
Blinded study drug dosing		Blinded study drug dosing								
Vadadustat dispensation, as necessary [b]							X	X		
Vadadustat dosing [b]								Open-label vadadustat dosing		
Study drug compliance check			X	X	X	X	X	X	X	

Abbreviations: eGFR, estimated glomerular filtration rate; EOT, end of treatment; Hb, hemoglobin; PK, pharmacokinetics; VEGF, vascular endothelial growth factor

[a] For subjects who discontinue study drug due to an excess Hb response, blood samples will be collected weekly to monitor Hb until the subject no longer exhibits an excess Hb response. The blood samples will be analyzed in a lab. Point-of-care Hb assessment will not be used for such evaluations.

[b] Subjects who were randomized to receive vadadustat treatment during the primary efficacy period and complete the Week 10 visit will continue to the open-label extension period.

Appendix B: Japanese Society of Nephrology 2009 Equation to Calculate eGFR

The estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine using the 2009 Japanese Society of Nephrology Equation (3-variables; Matsuo 2009).

eGFR (mL/min/1.73 m^2) = **194** x (S_{cr} in mg/dL)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female)

1 GLOBAL SPONSOR

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Role: Overall management of clinical study in Japan

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7 MONITOR LEADER

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8 CENTRALLABORATORY

8.1 Central Laboratory Service Provider

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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 NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0021
Phase:	Phase 2
Status / Date:	Original protocol (Version 1; 23 May 2016) Original protocol (Version 1.1; 22 June 2016)
Sponsor:	Akebia Therapeutics, Inc. 245 First Street, Suite 1100 Cambridge, MA 02142, United States of America

1 SIGNATURE PAGES

1.1 Protocol Approval

[redacted] Medical Research
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 also 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)

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Investigator's Title

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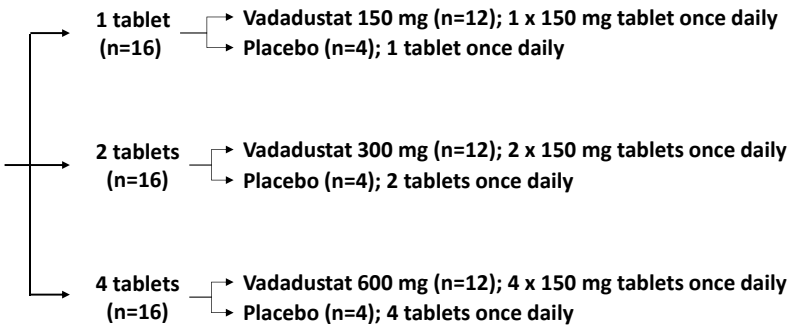
2 PROTOCOL SYNOPSIS

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 Non-Dialysis Dependent Chronic Kidney Disease
Protocol Number	AKB-6548-CI-0021
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 non-dialysis dependent chronic kidney disease (NDD-CKD) who are not currently being treated with an erythropoiesis-stimulating agent (ESA)
Investigative Sites	Approximately 25 sites in Japan
Planned Number of Subjects	Approximately 48 subjects will be enrolled in the study, with 36 subjects receiving one of the 3 doses of vadadustat and 12 subjects receiving placebo: • 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 (QD) dosing for 6 weeks and the change in hemoglobin (Hb) in Japanese subjects with anemia secondary to NDD-CKD; in order 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 QD dosing in Japanese subjects with anemia secondary to NDD-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 maintenance period
Study Design Overview	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 NDD-CKD. The study will include the following periods: • Eligibility screening period (up to 4 weeks) • Primary efficacy period (6 weeks; Weeks 1 to 6) • Dose adjustment and maintenance period (10 weeks), including the following: – Blinded dose adjustment and data cleaning period (4 weeks; Weeks 7 to 10): Individual subject data (from screening to Week 6) will be locked and individual subject unblinding will take place at the Week 10 visit – Open-label extension period (6 weeks; Weeks 11 to 16): Subjects randomized to receive vadadustat treatment during the blinded period will continue into this period • Safety follow-up period (2 weeks; Weeks 17 and 18): Subjects who complete

	participation in the open-label extension period and subjects who discontinue early during the blinded study periods will complete the safety follow-up period. Subjects identified as having received placebo during the Week 10 unblinding visit will not participate in this safety follow-up period. Following the screening period, eligible subjects will be randomized to receive blinded study drug treatment during a 6-week primary efficacy period, with subjects randomized at a 3:1 ratio to receive vadadustat (150, 300, or 600 mg vadadustat) or placebo. See "Dosage and Regimen" in the synopsis for additional information regarding the randomization scheme. Fixed-dose treatment during the blinded primary efficacy period will allow a dose-response relationship to be established. However, if Hb levels increase too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose can be decreased or discontinued (see "Dosage and Regimen" for additional information). After completing the primary efficacy period, subjects will continue to a 10-week dose adjustable maintenance period which will include a 4-week, blinded dose adjustment and data cleaning period and a 6-week, open-label extension period. Dose can be adjusted during the open-label period to achieve a target Hb of 10-12 g/dL, and the dose adjustment guidelines are listed under "Dosage and Regimen" (see below). Individual subject's study data (from screening to Week 6) will be cleaned and locked during the 4-week, blinded, dose adjustment and data cleaning period. At the Week 10 visit, treatment assignment will be unblinded on an individual subject basis. Subjects who were randomized to receive placebo will end study participation after unblinding at the Week 10 visit. Subjects who were randomized to receive 1 of the 3 vadadustat doses will continue receiving vadadustat during the open-label extension period. Vadadustat treatment will stop after the extension period has been completed (Week 16) and subjects will continue in a 2-week follow-up safety period (Week 17-18).
Study Duration	Up to 22 weeks, including the eligibility screening period (up to 4 weeks), primary efficacy period (6 weeks), blinded dose adjustment and data cleaning period (4 weeks), open-label extension period (6 weeks), and safety follow-up period (2 weeks). Only subjects who are randomized to receive vadadustat will continue in the maintenance period and the safety follow-up period.
Key Inclusion Criteria (the complete list is provided in the protocol)	• Male and female Japanese subjects (20 years or older) • Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009) • Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening • Hb ≤10.5 g/dL • Serum ferritin ≥50 ng/mL • Transferrin saturation (TSAT) ≥20% • Folate and vitamin B12 ≥lower limit of normal
Key Exclusion Criteria (the complete list is provided in the	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

protocol)	aplasia; red blood cell (RBC) transfusion within 4 weeks prior to or during screening; intravenous iron within 4 weeks prior to or during screening; and any ESA use within 6 weeks prior to or during screening.
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 or eGFR 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 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 Endpoints	Note that a pre-treatment value for Hb and RBC count is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value and the baseline value. Last observation before the first dose of study medication will be used as baseline for other parameters. **Primary Endpoint:** • Mean change in Hb levels from pre-treatment to the end of the primary efficacy period (Week 6) **Secondary Endpoints:** • Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the open-label extension period (Week 16) • Mean change in Hb between pre-treatment and the end of the open-label extension period (Week 16) • Mean change in hematocrit, RBC count, and reticulocyte count from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, and ferritin) and hepcidin from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Proportion of subjects with confirmed Hb values <10.0 or >12.0 g/dL from pre-treatment to the end of the open-label extension 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 open-label extension 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 open-label extension period (Week 16) • Number of dose adjustments from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Plasma concentration profile of vadadustat and its metabolites using pre-dose sample from Week 4
Safety Endpoints	Safety and tolerability assessments, including adverse events, vital signs, electrocardiograms (ECGs), and other laboratory assay results (eg, serum 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 other oral beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food. Note: Hb will be assessed at the central laboratory and also monitored using point-of-care HemoCue®. Note that the point-of-care HemoCue Hb value will be used to determine if the dose of study medication will be adjusted or discontinued. **Primary efficacy period (Day 1 to Week 6)** 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.  The primary efficacy period includes a fixed-dose treatment to establish a dose-response relationship. However, if Hb level increases too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose will be decreased or discontinued as presented below. • Subjects who meet the following criteria for excess Hb response will undergo a dose reduction by 1 tablet: – Hb increase >1 g/dL within any 2-week period, OR – Hb increase >2 g/dL within any 4-week period, OR – Hb level >13 g/dL • Subjects who meet the following criteria will discontinue study drug: – Excess Hb response as defined by any of the aforementioned criteria, AND – Current dose 1 tablet OR subject had previously decreased study drug dose due to excess Hb response **Blinded dose adjustment and data cleaning period (Week 7 to 10)** During this period, data from screening through the Week 6 visit will be cleaned and locked in preparation for the Week 10 unblinding visit. Blinded study drug dosage will be adjusted to achieve a target Hb 10-12 g/dL. Starting at the Week 6 visit,

	adjustments to doses will be based on the dose adjustment guidelines listed below. **Open-label extension period (Weeks 11 to 16):** Subjects who were randomized to receive vadadustat will enter this open-label extension period, and vadadustat dosage will continue to be adjusted to achieve a target Hb 10-12 g/dL. Dose adjustments will continue to be based on the dose adjustment guidelines listed below. **Dose adjustment guidelines from Week 7 to Week 16** The dose adjustment for blinded study drug (from Week 7 to 10) and open-label vadadustat (from Week 11 to 16) will follow the dose adjustment guidelines listed below to achieve a target Hb of 10-12 g/dL. The point-of-care HemoCue Hb value will be used to determine if the dose of study drug will be adjusted. • Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased at Week 10 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 14. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range.
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**: 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 – Exhibits Hb level <9.0 g/dL • **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.
Oral Iron Supplementation	Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be considered a reason for subject discontinuation. Subjects who are not taking oral iron supplementation at baseline should not start

	oral iron during their study participation. **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.
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. The target enrollment will be approximately 48 subjects for the study with 12 subjects enrolled in each of the 4 treatment groups. 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.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
CV	cardiovascular
dL	deciliter
DVT	deep venous thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
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
GFR	glomerular filtration rate
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
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)
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.

A number of 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.

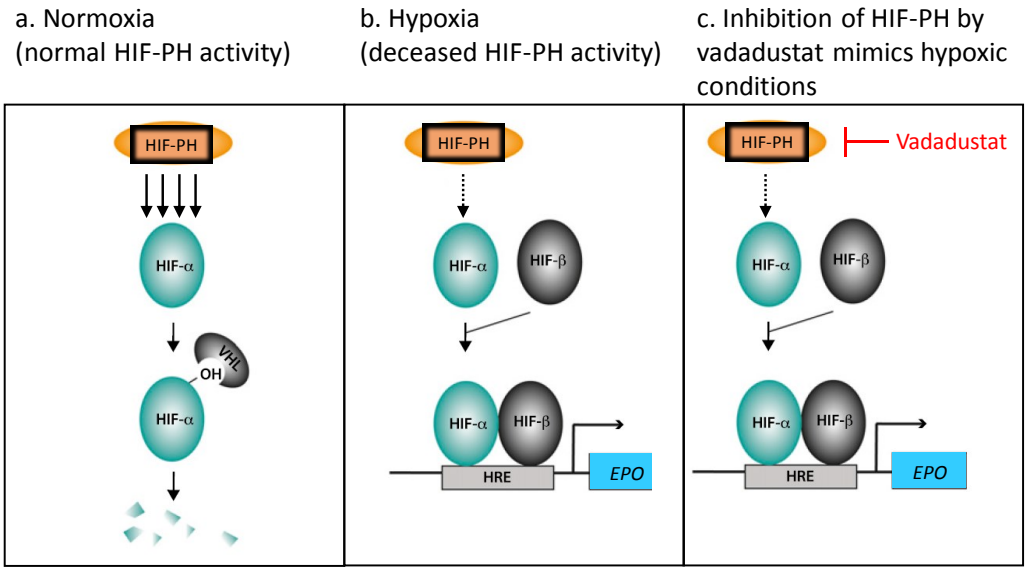
4.3 Hypoxia-Inducible Factor

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 patients with DD-CKD 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. As a result, 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 recently 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.

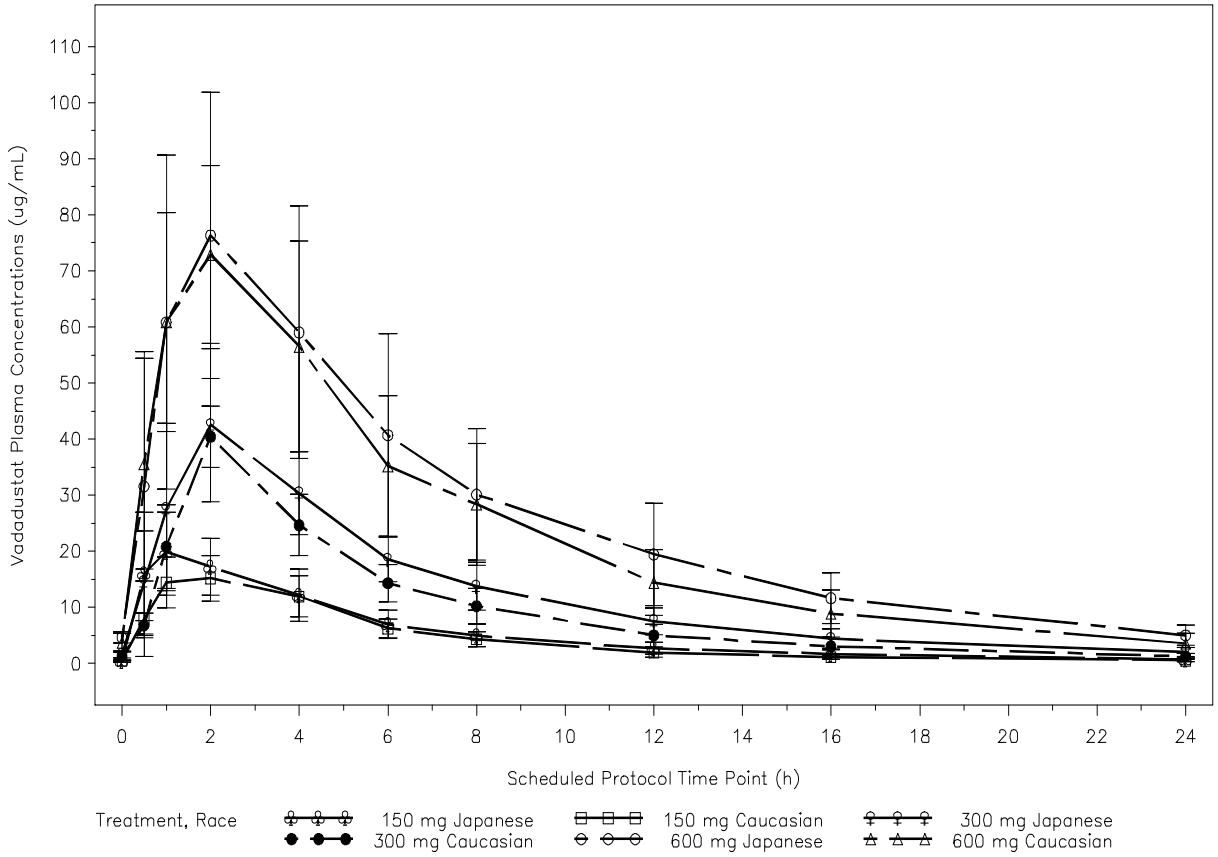
Eligible subjects were enrolled into one of 3 dose cohorts: 150, 300, or 600 mg daily oral doses of vadadustat (or placebo). Subjects received daily doses of study drug (either vadadustat or placebo) for 10 days. Each of the 3 dose cohorts enrolled 8 Japanese and 8 Caucasian subjects.

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.

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 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 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, all of 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 HIFPH 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 value for Hb, hematocrit, RBC count, reticulocyte count, and iron metabolism markers is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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 Hb in Japanese subjects with anemia secondary to NDD-CKD; in order 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 NDD-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 maintenance period

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

- Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the open-label extension period (Week 16)
- Mean change in Hb between pre-treatment and the end of the open-label extension period (Week 16)
- Mean change in hematocrit, RBC count, and reticulocyte count from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, and ferritin) and hepcidin from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Proportion of subjects with confirmed Hb values <10.0 or >12.0 g/dL from pre-treatment to the end of the open-label extension 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 open-label extension 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 open-label extension period (Week 16)
- Number of dose adjustments from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension 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, serum chemistry, components of the complete blood count [CBC] other than the ones noted above, and vascular endothelial growth factor [VEGF])

6 STUDY DESIGN

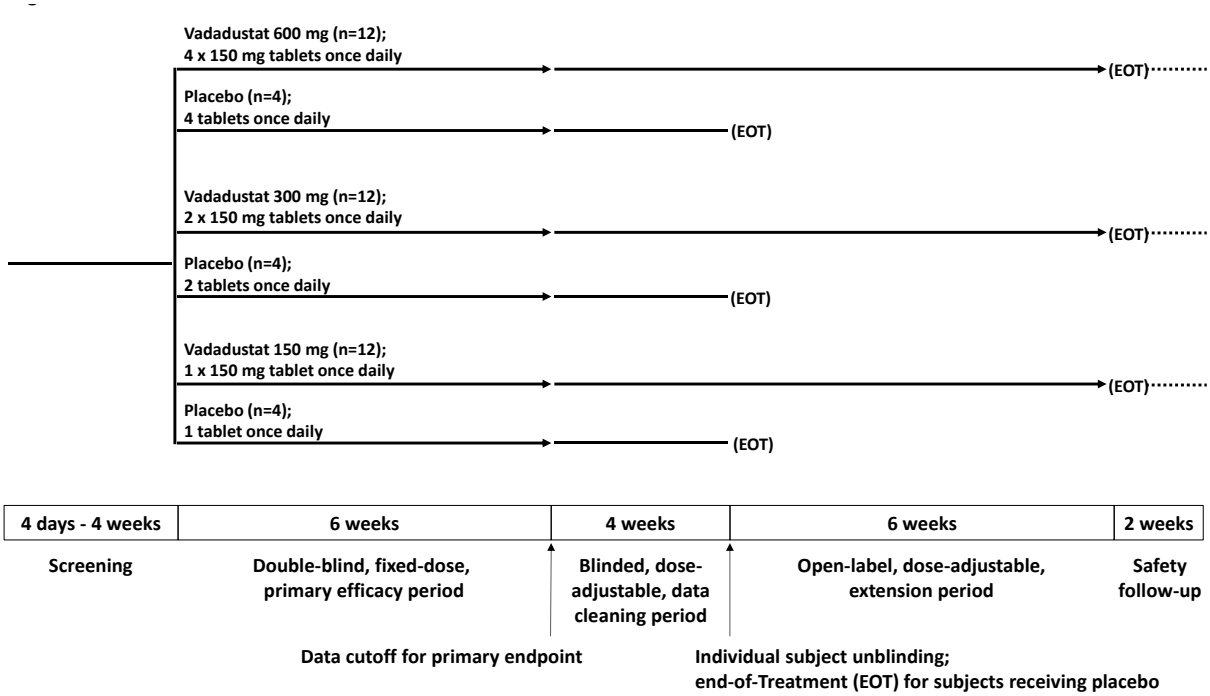
6.1 Study Design

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 subjects with anemia secondary to NDD-CKD.

The study has a planned enrollment of 48 subjects to be enrolled at approximately 25 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



The study will include the following periods:

- Eligibility screening period (up to 4 weeks)
- Primary efficacy period (6 weeks; Weeks 1 to 6)
- Dose adjustment and maintenance period (10 weeks) include the following:
  - Blinded dose adjustment and data cleaning period (4 weeks; Weeks 7 to 10): Individual subject data (from screening to Week 6) will be cleaned and locked and individual subject unblinding will take place at the Week 10 visit
  - Open-label extension period (6 weeks; Weeks 11 to 16): Subjects randomized to receive vadadustat treatment during the blinded period will continue into this period
- Safety follow-up period (2 weeks; Weeks 17 and 18): Subjects who complete participation in the open-label extension period and subjects who discontinue early during the blinded study periods will complete the safety follow-up period. Subjects identified as having received placebo during the Week 10 unblinding visit will not participate in this safety follow-up period.

Subjects will participate in a screening period (4 days to 4 weeks) to determine study eligibility, and 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.

Blinded 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 levels increase too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose can be decreased or discontinued (see Section 8.2.4).

After completing the primary efficacy period, subjects will continue to a 10-week dose adjustment and maintenance period including a 4-week, blinded dose adjustment and data cleaning period and a 6-week, open-label extension period (see Sections 8.2.5 and 8.2.6). Dose will be adjusted to achieve a target Hb of 10-12 g/dL, and dose adjustments will be based on dose adjustment guidelines (see Section 8.2.7).

Individual subject's study data (from screening to Week 6) will be cleaned and locked during the 4-week, blinded, dose adjustment period.

At the Week 10 visit, treatment assignment will be unblinded on an individual subject basis. Subjects who were randomized to receive placebo will end study participation after unblinding at the Week 10 visit. Subjects who were randomized to receive 1 of the 3 vadadustat doses will continue receiving vadadustat during the 6-week, open-label extension period.

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

The clinical and safety assessments will be performed as described in Section 9.3 and as listed in Appendix A.

6.2 Study Duration

Individual subjects will participate in the study for up to 22 weeks, including the eligibility screening period (up to 4 weeks), primary efficacy period (6 weeks), blinded dose adjustment and data cleaning period (4 weeks), open-label extension period (6 weeks), and safety follow-up period (2 weeks).

Only subjects who are randomized to receive vadadustat will continue in the open-label extension period and the safety follow-up period. Subjects who are randomized to receive placebo during the blinded treatment period will discontinue from the study after unblinding at Week 10.

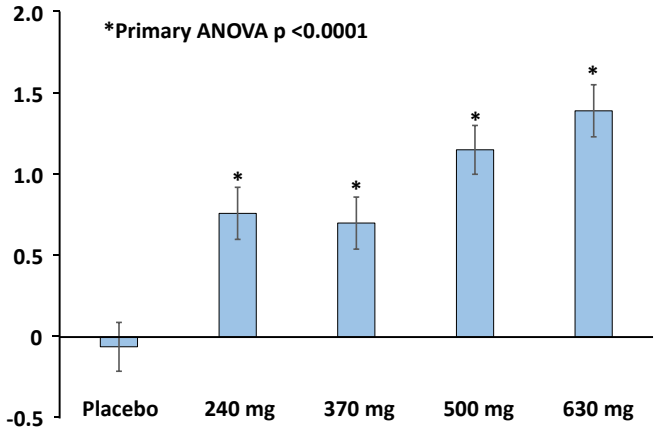
6.3 Rationale for Study Design

The study design of this randomized, double-blind, placebo-controlled, dose-finding study in Japanese subjects with anemia secondary to NDD-CKD is modeled on a previously completed dose-finding study in Caucasian subjects with anemia secondary to NDD-CKD (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 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 safe and 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 safe, 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 according to 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

The study population will consist of male and female Japanese adults aged 20 years or older with anemia secondary to NDD-CKD who are not currently being treated with an ESA.

To be eligible for this study, a subject or their legally acceptable representative must have provided valid informed consent and must meet all of 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 all of the following inclusion criteria to be eligible for study participation:

1. Male and female Japanese subjects, aged 20 years or older
2. Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009)
3. Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening
4. Hemoglobin (Hb) ≤10.5 g/dL during screening
5. Serum ferritin ≥50 ng/mL during screening
6. TSAT ≥20% during screening
7. Folate and vitamin B12 greater than or equal to the lower limit of normal during screening
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. RBC transfusion within 4 weeks prior to or during screening
4. Intravenous iron within 4 weeks prior to or during screening

5. Any ESA use within 6 weeks prior to or during screening (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta)

6. 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.

7. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mm Hg or systolic blood pressure >180 mm Hg) during screening

8. Body mass index (BMI) >42.0 kg/m^2

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

10. 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

11. 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

12. 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

13. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) requiring active treatment within 8 weeks prior to or during screening

14. History of hemosiderosis or hemochromatosis

15. History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list are not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis are not excluded)

16. 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

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

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

19. Females who are pregnant or breast-feeding

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

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

22. 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.

The screening period can last up to 4 weeks long, with a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1), ie, the screening period window is from Day -28 to Day -4.

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 or eGFR 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 B12 values may be considered for rescreening after receiving replacement therapy.

If intravenous (IV) iron is used to replete iron stores, the last dose of IV iron must be administered at least 4 weeks prior to rescreening.

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 randomized to receive placebo will be considered as having completed the study after completing participation in the Week 10 (unblinding) visit.

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

Note that for subjects who discontinue study drug due to an excess Hb response during the primary efficacy period, Hb levels will be monitored weekly via lab evaluation until the subject no longer exhibits an excess Hb response.

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 will discontinue study medication for any of the following conditions:

- Completion of the protocol-defined dosing period (see Appendix A)
- Meets discontinuation criteria related to excess Hb response during the primary efficacy period (defined in Section 8.2.4)
- Major toxicity considered to be related to study medication
- Worsening of anemia requiring ESA rescue or blood transfusion
- Administrative reasons, such as, subject non-compliance or a major protocol violation
- Upon request of the sponsor or regulatory agency
- If, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject
- Study termination (see Section 14)

Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be considered a reason for subject discontinuation.

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

7.6.3 Individual Subject Discontinuation during the Primary Efficacy Period or Blinded Dose Adjustment and Data Cleaning Period

Subjects discontinuing study medication or withdrawing early from the study during the blinded periods should undergo the Week 10 (EOT for blinded period) clinical and laboratory assessments within 1 day of stopping study medication, if possible. Such subjects should also complete the 2-week safety follow-up period (see Appendix A). 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.

7.6.4 Individual Subject Discontinuation during the Open-Label Extension Period

Only subjects randomized to vadadustat will continue to the open-label extension period. Subjects discontinuing vadadustat or withdrawing from the study during the open-label period should complete the Week 16 (EOT for open-label period) clinical and laboratory assessments within 1 day of stopping study medication, if possible. Such subjects should also complete the 2-week safety follow-up period and complete the Week 18 visit assessments (see Appendix A). 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 according to 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 at the baseline visit. Each bottle will contain 100 tablets of study drug. Subjects will be instructed to finish 1 bottle before opening a new bottle.

Resupply of additional study drug at subsequent 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.

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 at all times.

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 according to 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 other oral beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food.

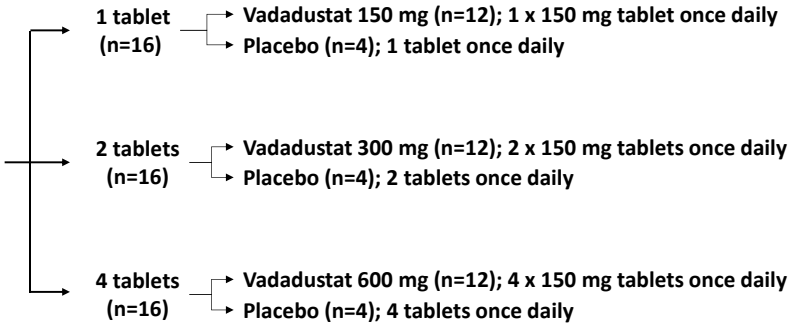
Subjects should be instructed to take the study medication at approximately the same time each day, preferably between 7 am and 2 pm, with the exception of the Week 4 visit. On the day of the Week 4 visit, the dose of study medication should be held until after the pre-dose PK sample has been obtained.

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 Primary Efficacy Period and Breaking the Blind

During the blinded periods, all subjects and personnel involved with the conduct and interpretation of the study will be blinded to the study drug treatment, including investigators, site personnel, site pharmacist, and sponsor's staff and designees.

The study blind should be broken for individual subjects after a subject completes the Week 6 visit and the subject's data (from screening to Week 6) is cleaned and locked.

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.

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. The applicable standard operating procedure will be followed for blind-breaking procedures. After each subject's data is cleaned and locked, their individual randomization code will be broken to determine eligibility for continuation to the open-label extension period.

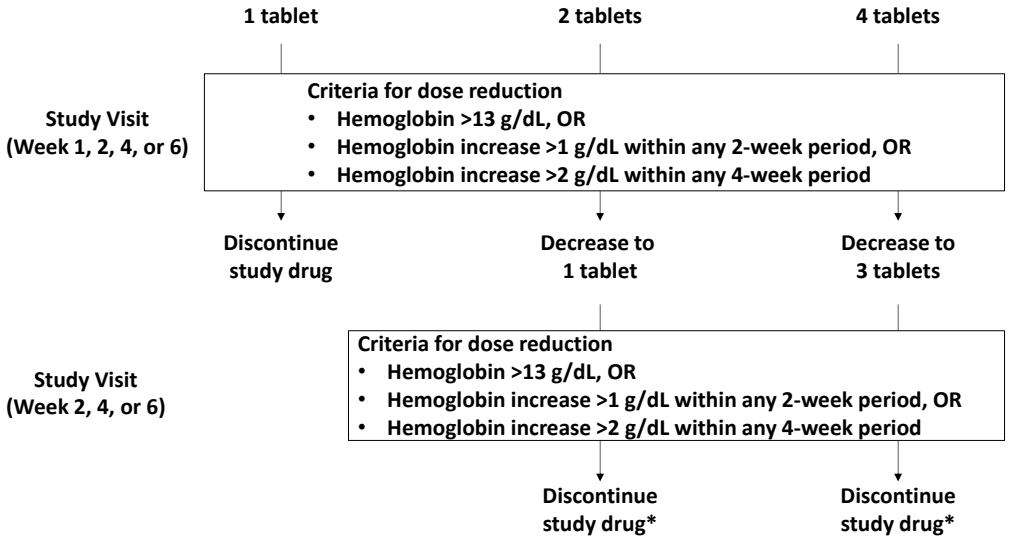
8.2.4 Study Drug Administration during the Primary Efficacy Period

To establish a dose-response relationship, the primary efficacy period includes a blinded fixed-dose treatment regimen. However, if Hb levels increase too rapidly or if the Hb levels exceed the desired range, the dose will be decreased or discontinued as presented below (and as depicted in Figure 6).

- Subjects who meet the following criteria for excess Hb response will undergo a dose reduction by 1 tablet:
  - Hb level >13 g/dL, OR
  - Hb increase >1 g/dL within any 2-week period, OR
  - Hb increase >2 g/dL within any 4-week period
- Subjects who meet the following criteria will discontinue study drug:
  - Excess Hb response as defined by any of the aforementioned criteria, AND
  - Current dose of 1 tablet daily OR subject had previously decreased study drug dose due to excess Hb response

Hb will be assessed at the central laboratory and also monitored using point-of-care HemoCue® (as listed in Appendix A). Note that the point-of-care HemoCue Hb value will be used to determine if the dose of study medication will be adjusted or discontinued.

Figure 6: Guidelines for Dose Reduction or Discontinuation of Study Drug During the Primary Efficacy Period



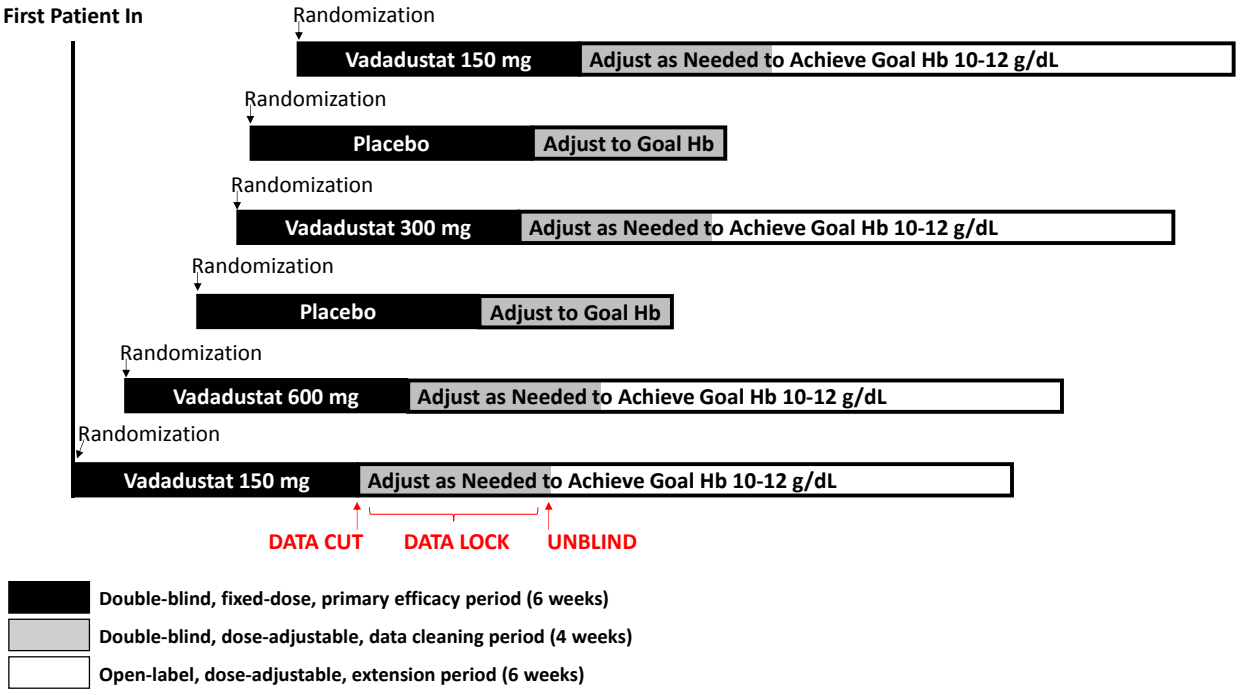
***Note: A subject who had previously decreased study drug dose due to an excess Hb response and meets the criteria for excess Hb response at a subsequent visit during the primary efficacy period (Week 2, 4, or 6) will discontinue study drug**

8.2.5 Study Drug Administration during the Blinded Dose Adjustment and Data Cleaning Period

After completing the Week 6 visit, subjects will continue blinded study treatment for an additional 4 weeks during which time their data from screening through the Week 6 visit will be cleaned and locked. Individual subjects will be unblinded at their Week 10 visit. Potential scenarios for individual subject unblinding is shown in Figure 7.

Point-of-care Hb levels will be monitored via HemoCue to determine if the dose of study medication will be adjusted (as listed in Appendix A). Dose adjustments will be based on dose adjustment guidelines (see Section 8.2.7).

Figure 7: Potential Scenarios for Individual Subject Unblinding



8.2.6 Vadadustat Administration during the Open-Label Extension Period

During the 6-week, open-label extension period, vadadustat dosage will be adjusted to achieve a target Hb level of 10-12 g/dL. Point-of-care Hb will be monitored via HemoCue to determine if the dose of study medication will be adjusted (see Appendix A). Dose adjustments will be based on dose adjustment guidelines (see Section 8.2.7).

8.2.7 Dose Adjustment Guidelines

Dose adjustment of blinded study drug (from Week 7 to 10) and open-label vadadustat (from Week 11 to 16) will follow the dose adjustment guidelines listed below to achieve a target Hb of 10-12 g/dL. The point-of-care HemoCue Hb value will be used to determine if the dose of study drug will be adjusted.

- Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased at Week 10 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 14. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range.

8.2.8 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**: 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
  - Exhibits Hb level <9.0 g/dL
- **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.

8.2.9 Oral Iron Supplementation (Information on Allowed Use)

Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be considered a reason for subject discontinuation.

Subjects who are not taking oral iron supplementation at baseline should not start oral iron during their study participation (see Section 8.4.3).

Important: Because of the potential for oral iron to reduce the bioavailability of vadadustat, the 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.

8.2.10 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.

Subjects should be questioned regarding dosing compliance and the information should be recorded.

8.2.11 Treatment Compliance

Subjects will be questioned regarding dosing compliance at all study visits from Week 1 through Week 18, 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.

8.2.12 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 through the course of 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, Intravenous Iron, and Blood Transfusion

Subjects may not receive any ESA treatment within 6 weeks prior to the screening period and through the safety follow-up period (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta). See Section 8.2.8 for the rescue therapy guidelines.

Subjects may not receive intravenous iron or blood transfusion within 4 weeks prior to the screening period and through the safety follow-up period. Use of intravenous iron supplementation after Day 1 will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.8 for the rescue therapy guidelines. Note that subjects who initiate rescue therapy will be required to stop study drug treatment and will be discontinued from the study.

8.4.3 Oral Iron Supplementation (Information on Prohibition)

Subjects who are not taking oral iron supplementation at baseline should not start oral iron during study participation. Use of oral iron supplementation by such subjects will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

See Section 8.2.9 for information on circumstances allowing use of oral iron supplementation.

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

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

- Eligibility screening period (Day -28 to Day -4)
- Baseline visit (Day 1)
- Primary efficacy period (Week 1 ± 1 day, Week 2 ± 1 day, Week 4 ± 3 days, and Week 6 ± 3 days)
- Blinded dose adjustment and data cleaning period (Week 10 ± 3 days)
- Open-label extension period (Week 14 ± 3 days and Week 16 ± 3 days)
- Safety follow-up period (Week 18 ± 3 days)

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same investigator or site personnel whenever possible.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.2 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.

9.1.3 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 9.1.3.1.

9.1.3.1 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) and at baseline (assessed using urine 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

9.2 Study Procedures and Evaluations

9.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study. Detailed information regarding the timing of the assessments is presented in Section 9.3 and summarized in Appendix A:

- Demographics and medical history: Relevant medical history (with particular 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
- Weight assessment
- 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.
- 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.

  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.

9.2.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis, with the exception of the urine pregnancy test at baseline which will be performed locally. 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 course of the study:

- Serum and urine 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) and urine pregnancy tests (to be analyzed by the local lab). The screening and baseline pregnancy test results must be available and must be negative for a subject to initiate or continue study drug.
- 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.
- HemoCue®: Hb will be monitored via HemoCue point-of-care device to determine if the dose of study drug will be adjusted.
- 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).

For subjects who discontinue study drug due to an excess Hb response during the primary efficacy period, Hb will be assessed weekly via lab evaluation until the subject no longer exhibits an excess Hb response.

- Serum chemistry and eGFR: The serum chemistry will include the following assays: 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. eGFR will be calculated from serum creatinine as described in Appendix B.
- 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.

9.3 Schedule of Activities

The Schedule of Events in 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.

9.3.1 Screening Visit

The screening visit must be performed within 28 days prior to dosing and there must be a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1).

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo a number of screening activities. The investigator will maintain a log of subjects and indicate who was enrolled or excluded and the reason for exclusion (see Section 9.1.2).

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

- Review of study inclusion and exclusion criteria

- Demographics, medical history, and physical examination
- Weight assessment
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- Prior and current medication use
- 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.
    - Folate and vitamin B12 levels
    - CBC
    - Serum chemistry and eGFR
    - Iron indices

9.3.2 Baseline Visit (Day 1)

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

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

- Review of study inclusion and exclusion criteria
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)
- Recording of any concomitant medication use since screening visit
- Laboratory procedures:
    - Urine pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The urine sample will be analyzed by the local lab. The baseline results must be available and must be negative before the subject takes the first dose of study drug.
    - Coagulation tests (including prothrombin time, partial thromboplastin time, and international normalized ratio)
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
    - Hepcidin
    - C-reactive protein
    - VEGF
- Dispense blinded study drug
- Review dosing instructions

9.3.3 Week 1 Visit

At the Week 1 visit, 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)

- AE review
- Concomitant medication review
- Hb using HemoCue
- CBC
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.4 Week 2 Visit

At the Week 2 visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
- Dispense blinded study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and 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

9.3.5 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 (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
    - CBC
    - Serum chemistry and eGFR
    - Iron indices
    - Pre-dose PK sample
- Record date and time of the last dose of the study that was taken prior to the pre-dose PK sample
- Dispense blinded study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.6 Week 6 Visit

Individual subject data (up to Week 6) will be cleaned and locked after the Week 6 visit. Following data lock, individual subject's randomized treatment assignment will be unblinded and the subject will be informed at the Week 10 visit.

At the Week 6 visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
  - CBC
  - Serum chemistry and eGFR
  - Iron indices
  - Hepcidin
  - C-reactive protein
  - VEGF
- Dispense blinded study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.7 Week 10 Visit (End-of-treatment visit for the blinded period and early withdrawals)

All enrolled subjects who receive at least 1 dose of blinded study drug should complete the Week 10 assessments.

Subjects who withdraw early from the study prior to the Week 6 visit or permanently discontinue study medication prior to the Week 6 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 9.3.10).

Individual subject data (up to Week 6) will be locked after the Week 6. Following data lock, individual subject's randomized treatment assignment will be unblinded and the subject will be informed at the Week 10 visit. Subjects who were assigned to receive placebo will discontinue from the study at the end of the Week 10 visit, and subjects who were assigned to receive vadadustat will continue to the open-label extension period.

At the Week 10 visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
  - Hb using HemoCue for dose adjustment (not for subjects who discontinue prior to the Week 6 visit)
  - CBC
  - Serum chemistry and eGFR

  - Iron indices
  - Hepcidin
  - C-reactive protein
  - VEGF
- Dispense open-label vadadustat (as necessary; only applicable to subjects who are continuing to the open-label extension period)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions (only applicable to subjects who are continuing to the open-label extension period)

9.3.8 Week 14 Visit

At this visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue for dose adjustment
- CBC
- Serum chemistry and eGFR
- Dispense vadadustat (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.9 Week 16 Visit (End-of-treatment visit for the open-label period and early withdrawal visit for withdrawals after Week 10 but before Week 16)

All subjects who received at least 1 dose of open-label vadadustat should complete the Week 16 assessments.

Subjects who withdraw early from the open-label period 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 9.3.10).

At the Week 16 visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
  - Serum pregnancy test for females of childbearing potential (to be analyzed by the central lab)
  - CBC
  - Serum chemistry and eGFR
  - Iron indices
  - Hepcidin

  - C-reactive protein
  - VEGF
- Subjects should be questioned regarding dosing compliance

9.3.10 Week 18 Safety Follow-Up Visit (Or 2 Weeks after End-of-Treatment Safety Follow-Up Visit)

For subjects randomized to vadadustat who complete the open-label extension period, the safety visit will be conducted 2 weeks after their end-of-treatment visit (Week 16).

For subjects who discontinue the study early during the primary efficacy period or the blinded dose adjustment and data cleaning period, the safety visit will be conducted 2 weeks after their end-of-treatment visit (Week 10).

At the follow-up visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Serum chemistry and eGFR

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.

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 AE reporting period for a subject begins upon receiving the first dose of study medication and ends at the final protocol-required visit. In addition, SAEs that occur after the protocol-defined AE reporting period that are considered to be related to the study medication should be recorded and reported to the sponsor's medical monitor or CRO designee.

10.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the AE 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, or the investigator should call the CRO SAE hotline within 24 hours of being made aware of the pregnancy (reference the site manual for contact information).

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

The 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.
- 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

11.1 Primary Endpoint and Sample Size Determination

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 NDD-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 EOT visit minus the mean pre-treatment Hb. Pre-treatment Hb is defined as the average of 2 Hb values obtained prior to treatment based on the qualifying screening Hb value and the Hb value at the baseline visit. Linear regression analysis will be used to calculate the relationship between vadadustat dose and change in Hb.

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

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 reasonable to assume that 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.

11.2 Study Populations

11.2.1 Analysis Population 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.

11.2.2 Analysis Populations for the Efficacy Analyses

The modified intent-to-treat (MITT) population for Hb or RBC count will include subjects who receive at least 1 dose of study medication, have a pre-treatment average defined as the average of the qualifying screening value and the baseline value, and at least one post-baseline measurement. The MITT population for other parameters will include subjects who receive at least 1 dose of study medication, have at least one pre-treatment value, and at least one post-baseline 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.

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

11.3 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.

11.4 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.

11.5 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

For purposes of analysis, a pre-treatment average (defined as the average of 2 samples obtained prior to treatment [ie, the qualifying screening value and baseline value]) will be used as the baseline value for Hb and RBC count, and last observation before the first dose of study medication will be used as baseline for other parameters.

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 assess the vadadustat dose-response relationship. 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.

11.6 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, components of the CBC, and VEGF.

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.

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.

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 course of 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.

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Appendix A: Schedule of Activities

Please refer to Section 9.2 for detailed information regarding the study procedures and evaluations, and please refer to Section 9.3 for detailed information regarding the activities to be performed at each study visit.

	Screening	**Primary efficacy period (blinded, fixed-dose treatment) (Day 1-Week 6)**					**Blinded dose adjustment, data cleaning period (Week 7-10)**	**Open-label extension period (Week 11-16)**		**Safety Follow-up (Week 17-18)**
Study Week	**-4 to 0**	**Base line**	**1**	**2**	**4**	**6**	**10 (EOT, Blinded Period)**	**14**	**16 (EOT, Open-Label Period)**	**18**
Study Day	**-28 to -4**	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X									
Review inclusion/exclusion criteria	X	X								
Individual subject data lock (for subjects who complete Week 6)						X				
Individual subject unblinding (for subjects who complete Week 6)							X			
Demographics, medical history, physical exam, and weight	X									
Vital signs	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X								
Adverse event review			X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X								X	
Urine pregnancy test		X								
Coagulation tests		X								

	Screening	Primary efficacy period (blinded, fixed-dose treatment) (Day 1-Week 6)					Blinded dose adjustment, data cleaning period (Week 7-10)	Open-label extension period (Week 11-16)		Safety Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**1**	**2**	**4**	**6**	**10 (EOT, Blinded Period)**	**14**	**16 (EOT, Open-Label Period)**	**18**
Study Day	**-28 to -4**	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Folate and vitamin B12	X									
Hb using HemoCue® (Week 10 assessment is not for subjects who discontinue prior to Week 6)			X	X	X	X	X	X		
Complete blood count, including Hb [a]	X	X	X	X	X	X	X	X	X	X
Serum chemistry and eGFR	X	X		X	X	X	X	X	X	X
Iron indices	X	X		X	X	X	X		X	
Hepcidin		X				X	X		X	
C-reactive protein		X				X	X		X	
VEGF		X				X	X		X	
PK pre-dose sample (study drug to be administered after sample collection)					X					
Blinded study drug dispensation, as necessary		X		X	X	X				
Blinded study drug dosing		Blinded study drug dosing								
Vadadustat dispensation, as necessary [b]							X	X		
Vadadustat dosing [b]								Open-label vadadustat dosing		
Study drug compliance check			X	X	X	X	X	X	X	

Abbreviations: eGFR, estimated glomerular filtration rate; EOT, end of treatment; Hb, hemoglobin; PK, pharmacokinetics; VEGF, vascular endothelial growth factor

[a] For subjects who discontinue study drug due to an excess Hb response, blood samples will be collected weekly to monitor Hb until the subject no longer exhibits an excess Hb response. The blood samples will be analyzed in a lab. Point-of-care Hb assessment will not be used for such evaluations.

[b] Subjects who were randomized to receive vadadustat treatment during the primary efficacy period and complete the Week 10 visit will continue to the open-label extension period.

Appendix B: Japanese Society of Nephrology 2009 Equation to Calculate eGFR

The estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine using the 2009 Japanese Society of Nephrology Equation (3-variables; Matsuo 2009).

eGFR (mL/min/1.73 m^2) = **194** x (S_{cr} in mg/dL)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female)

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 NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0021
Phase:	Phase 2
Status / Date:	Original protocol (Version 1; 23 May 2016) Original protocol (Version 1.1; 22 June 2016) Original protocol (Version 2; 19 July 2016)
Sponsor:	Akebia Therapeutics, Inc. 245 First Street, Suite 1100 Cambridge, MA 02142, United States of America

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 also 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

_____

_____

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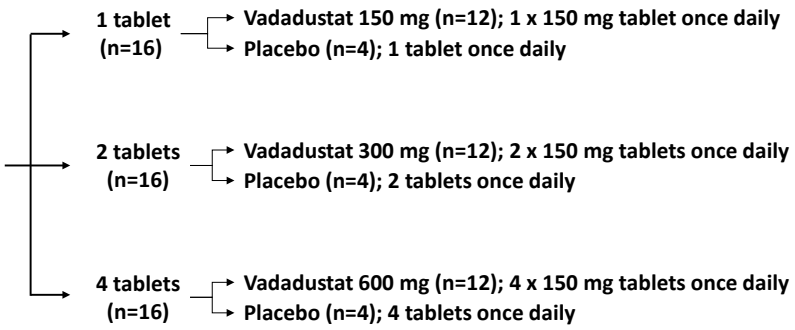
2 PROTOCOL SYNOPSIS

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 Non-Dialysis Dependent Chronic Kidney Disease
Protocol Number	AKB-6548-CI-0021
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 non-dialysis dependent chronic kidney disease (NDD-CKD) who are not currently being treated with an erythropoiesis-stimulating agent (ESA)
Investigative Sites	Approximately 25 sites in Japan
Planned Number of Subjects	Approximately 48 subjects will be enrolled in the study, with 36 subjects receiving one of the 3 doses of vadadustat and 12 subjects receiving placebo: • 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 (QD) dosing for 6 weeks and the change in hemoglobin (Hb) in Japanese subjects with anemia secondary to NDD-CKD; in order 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 QD dosing in Japanese subjects with anemia secondary to NDD-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 maintenance period
Study Design Overview	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 NDD-CKD. The study will include the following periods: • Eligibility screening period (up to 4 weeks) • Primary efficacy period (6 weeks; Weeks 1 to 6) • Dose adjustment and maintenance period (10 weeks), including the following: – Blinded dose adjustment and data cleaning period (4 weeks; Weeks 7 to 10): Individual subject data (from screening to Week 6) will be locked and individual subject unblinding will take place at the Week 10 visit – Open-label extension period (6 weeks; Weeks 11 to 16): Subjects randomized to receive vadadustat treatment during the blinded period will continue into this period • Safety follow-up period (2 weeks; Weeks 17 and 18): Subjects who complete

	participation in the open-label extension period and subjects who discontinue early during the blinded study periods will complete the safety follow-up period. Subjects identified as having received placebo during the Week 10 unblinding visit will not participate in this safety follow-up period. Following the screening period, eligible subjects will be randomized to receive blinded study drug treatment during a 6-week primary efficacy period, with subjects randomized at a 3:1 ratio to receive vadadustat (150, 300, or 600 mg vadadustat) or placebo. See "Dosage and Regimen" in the synopsis for additional information regarding the randomization scheme. Fixed-dose treatment during the blinded primary efficacy period will allow a dose-response relationship to be established. However, if Hb levels increase too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose can be decreased or discontinued (see "Dosage and Regimen" for additional information). After completing the primary efficacy period, subjects will continue to a 10-week dose adjustable maintenance period which will include a 4-week, blinded dose adjustment and data cleaning period and a 6-week, open-label extension period. Dose can be adjusted during the open-label period to achieve a target Hb of 10-12 g/dL, and the dose adjustment guidelines are listed under "Dosage and Regimen" (see below). Individual subject's study data (from screening to Week 6) will be cleaned and locked during the 4-week, blinded, dose adjustment and data cleaning period. At the Week 10 visit, treatment assignment will be unblinded on an individual subject basis. Subjects who were randomized to receive placebo will end study participation after unblinding at the Week 10 visit. Subjects who were randomized to receive 1 of the 3 vadadustat doses will continue receiving vadadustat during the open-label extension period. Vadadustat treatment will stop after the extension period has been completed (Week 16) and subjects will continue in a 2-week follow-up safety period (Week 17-18).
Study Duration	Up to 22 weeks, including the eligibility screening period (up to 4 weeks), primary efficacy period (6 weeks), blinded dose adjustment and data cleaning period (4 weeks), open-label extension period (6 weeks), and safety follow-up period (2 weeks). Only subjects who are randomized to receive vadadustat will continue in the maintenance period and the safety follow-up period.
Key Inclusion Criteria (the complete list is provided in the protocol)	• Male and female Japanese subjects (20 years or older) • Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009) • Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening • Hb ≤10.5 g/dL • Serum ferritin ≥50 ng/mL • Transferrin saturation (TSAT) ≥20% • Folate and vitamin B12 ≥lower limit of normal
Key Exclusion Criteria (the complete list is provided in the	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

protocol)	aplasia; red blood cell (RBC) transfusion within 4 weeks prior to or during screening; intravenous iron within 4 weeks prior to or during screening; and any ESA use within 6 weeks prior to or during screening.
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 or eGFR 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 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 Endpoints	Note that a pre-treatment value for Hb and RBC count is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value and the baseline value. Last observation before the first dose of study medication will be used as baseline for other parameters. **Primary Endpoint:** • Mean change in Hb levels from pre-treatment to the end of the primary efficacy period (Week 6) **Secondary Endpoints:** • Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the open-label extension period (Week 16) • Mean change in Hb between pre-treatment and the end of the open-label extension period (Week 16) • Mean change in hematocrit, RBC count, and reticulocyte count from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, and ferritin) and hepcidin from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Proportion of subjects with confirmed Hb values <10.0 or >12.0 g/dL from pre-treatment to the end of the open-label extension 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 open-label extension 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 open-label extension period (Week 16) • Number of dose adjustments from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16) • Plasma concentration profile of vadadustat and its metabolites using pre-dose sample from Week 4
Safety Endpoints	Safety and tolerability 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 other oral beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food. Note: Hb will be assessed at the central laboratory and also monitored using point-of-care HemoCue®. Note that the point-of-care HemoCue Hb value will be used to determine if the dose of study medication will be adjusted or discontinued. **<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.  The primary efficacy period includes a fixed-dose treatment to establish a dose-response relationship. However, if Hb level increases too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose will be decreased or discontinued as presented below. • Subjects who meet the following criteria for excess Hb response will undergo a dose reduction by 1 tablet: – Hb increase >1 g/dL within any 2-week period, OR – Hb increase >2 g/dL within any 4-week period, OR – Hb level >13 g/dL • Subjects who meet the following criteria will discontinue study drug: – Excess Hb response as defined by any of the aforementioned criteria, AND – Current dose 1 tablet OR subject had previously decreased study drug dose due to excess Hb response **<u>Blinded dose adjustment and data cleaning period (Week 7 to 10)</u>** During this period, data from screening through the Week 6 visit will be cleaned and locked in preparation for the Week 10 unblinding visit. Blinded study drug dosage will be adjusted to achieve a target Hb 10-12 g/dL. Starting at the Week 6 visit,

	adjustments to doses will be based on the dose adjustment guidelines listed below. **Open-label extension period (Weeks 11 to 16):** Subjects who were randomized to receive vadadustat will enter this open-label extension period, and vadadustat dosage will continue to be adjusted to achieve a target Hb 10-12 g/dL. Dose adjustments will continue to be based on the dose adjustment guidelines listed below. **Dose adjustment guidelines from Week 7 to Week 16** The dose adjustment for blinded study drug (from Week 7 to 10) and open-label vadadustat (from Week 11 to 16) will follow the dose adjustment guidelines listed below to achieve a target Hb of 10-12 g/dL. The point-of-care HemoCue Hb value will be used to determine if the dose of study drug will be adjusted. • Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased at Week 10 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 14. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range.
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**: 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 – Exhibits Hb level <9.0 g/dL • **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.
Oral Iron Supplementation	Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be considered a reason for subject discontinuation. Subjects who are not taking oral iron supplementation at baseline should not start

	oral iron during their study participation. **<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	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. The target enrollment will be approximately 48 subjects for the study with 12 subjects enrolled in each of the 4 treatment groups. 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.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
CV	cardiovascular
dL	deciliter
DVT	deep venous thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
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
GFR	glomerular filtration rate
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
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)
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.

A number of 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.

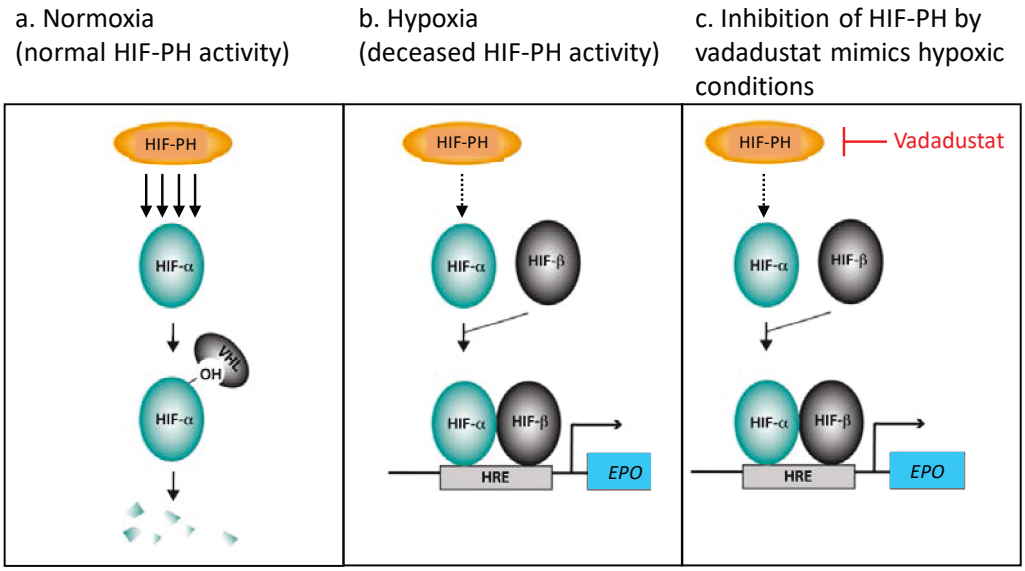
4.3 Hypoxia-Inducible Factor

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 patients with DD-CKD 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. As a result, 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 recently 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.

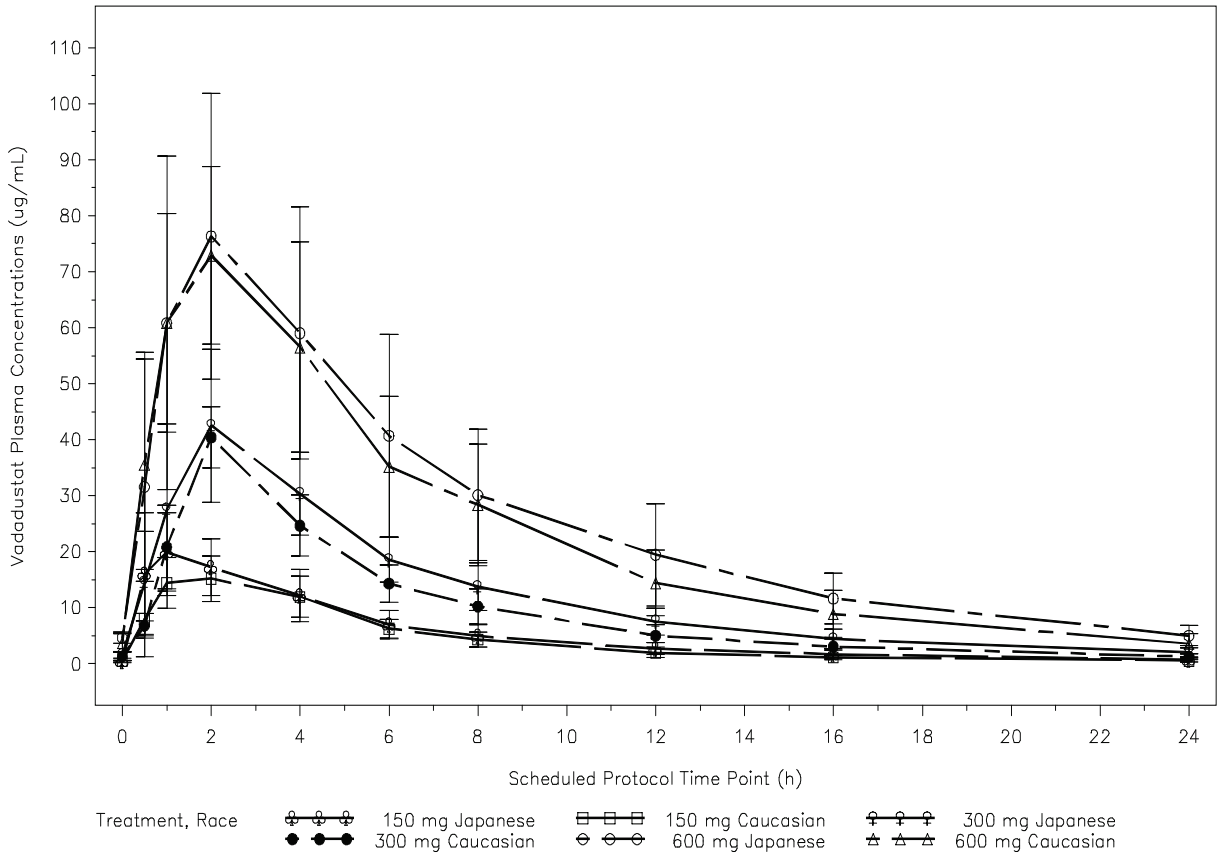
Eligible subjects were enrolled into one of 3 dose cohorts: 150, 300, or 600 mg daily oral doses of vadadustat (or placebo). Subjects received daily doses of study drug (either vadadustat or placebo) for 10 days. Each of the 3 dose cohorts enrolled 8 Japanese and 8 Caucasian subjects.

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.

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 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 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, all of 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 HIFPH 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 value for Hb, hematocrit, RBC count, reticulocyte count, and iron metabolism markers is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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 Hb in Japanese subjects with anemia secondary to NDD-CKD; in order 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 NDD-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 maintenance period

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

- Proportion of subjects who achieve target Hb 10-12 g/dL at the end of the open-label extension period (Week 16)
- Mean change in Hb between pre-treatment and the end of the open-label extension period (Week 16)
- Mean change in hematocrit, RBC count, and reticulocyte count from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Mean change in iron indices (ie, iron, total iron-binding capacity [TIBC], TSAT, and ferritin) and hepcidin from pre-treatment to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Proportion of subjects with confirmed Hb values <10.0 or >12.0 g/dL from pre-treatment to the end of the open-label extension 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 open-label extension 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 open-label extension period (Week 16)
- Number of dose adjustments from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension period (Week 16)
- Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and the end of the open-label extension 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

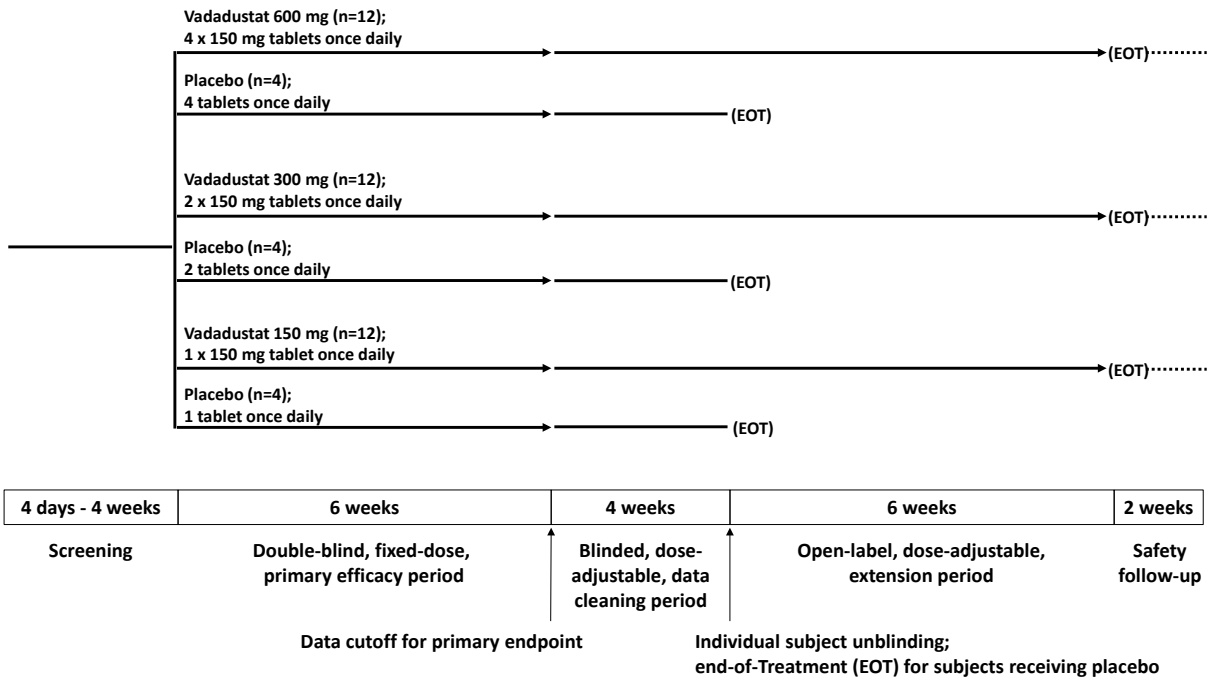
6.1 Study Design

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 subjects with anemia secondary to NDD-CKD.

The study has a planned enrollment of 48 subjects to be enrolled at approximately 25 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



The study will include the following periods:

- Eligibility screening period (up to 4 weeks)
- Primary efficacy period (6 weeks; Weeks 1 to 6)
- Dose adjustment and maintenance period (10 weeks) include the following:
  - Blinded dose adjustment and data cleaning period (4 weeks; Weeks 7 to 10): Individual subject data (from screening to Week 6) will be cleaned and locked and individual subject unblinding will take place at the Week 10 visit
  - Open-label extension period (6 weeks; Weeks 11 to 16): Subjects randomized to receive vadadustat treatment during the blinded period will continue into this period
- Safety follow-up period (2 weeks; Weeks 17 and 18): Subjects who complete participation in the open-label extension period and subjects who discontinue early during the blinded study periods will complete the safety follow-up period. Subjects identified as having received placebo during the Week 10 unblinding visit will not participate in this safety follow-up period.

Subjects will participate in a screening period (4 days to 4 weeks) to determine study eligibility, and 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.

Blinded 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 levels increase too rapidly or if the Hb levels exceed the desired range, the blinded study drug dose can be decreased or discontinued (see Section 8.2.4).

After completing the primary efficacy period, subjects will continue to a 10-week dose adjustment and maintenance period including a 4-week, blinded dose adjustment and data cleaning period and a 6-week, open-label extension period (see Sections 8.2.5 and 8.2.6). Dose will be adjusted to achieve a target Hb of 10-12 g/dL, and dose adjustments will be based on dose adjustment guidelines (see Section 8.2.7).

Individual subject's study data (from screening to Week 6) will be cleaned and locked during the 4-week, blinded, dose adjustment period.

At the Week 10 visit, treatment assignment will be unblinded on an individual subject basis. Subjects who were randomized to receive placebo will end study participation after unblinding at the Week 10 visit. Subjects who were randomized to receive 1 of the 3 vadadustat doses will continue receiving vadadustat during the 6-week, open-label extension period.

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

The clinical and safety assessments will be performed as described in Section 9.3 and as listed in Appendix A.

6.2 Study Duration

Individual subjects will participate in the study for up to 22 weeks, including the eligibility screening period (up to 4 weeks), primary efficacy period (6 weeks), blinded dose adjustment and data cleaning period (4 weeks), open-label extension period (6 weeks), and safety follow-up period (2 weeks).

Only subjects who are randomized to receive vadadustat will continue in the open-label extension period and the safety follow-up period. Subjects who are randomized to receive placebo during the blinded treatment period will discontinue from the study after unblinding at Week 10.

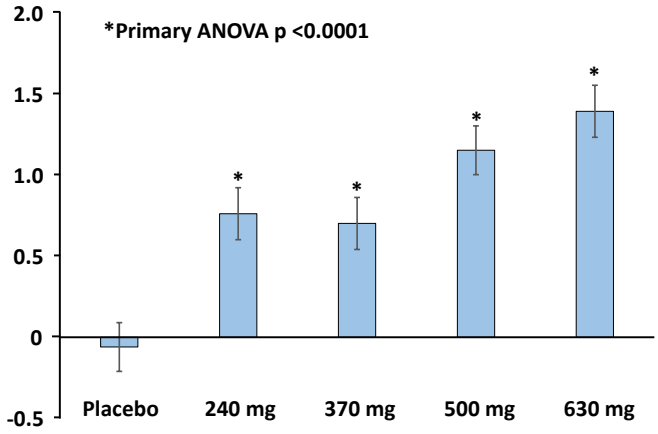
6.3 Rationale for Study Design

The study design of this randomized, double-blind, placebo-controlled, dose-finding study in Japanese subjects with anemia secondary to NDD-CKD is modeled on a previously completed dose-finding study in Caucasian subjects with anemia secondary to NDD-CKD (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 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 safe and 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 safe, 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 according to 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

The study population will consist of male and female Japanese adults aged 20 years or older with anemia secondary to NDD-CKD who are not currently being treated with an ESA.

To be eligible for this study, a subject or their legally acceptable representative must have provided valid informed consent and must meet all of 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 all of the following inclusion criteria to be eligible for study participation:

1. Male and female Japanese subjects, aged 20 years or older
2. Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009)
3. Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening
4. Hemoglobin (Hb) ≤10.5 g/dL during screening
5. Serum ferritin ≥50 ng/mL during screening
6. TSAT ≥20% during screening
7. Folate and vitamin B12 greater than or equal to the lower limit of normal during screening
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. RBC transfusion within 4 weeks prior to or during screening
4. Intravenous iron within 4 weeks prior to or during screening

5. Any ESA use within 6 weeks prior to or during screening (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta)

6. 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.

7. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mm Hg or systolic blood pressure >180 mm Hg) during screening

8. Body mass index (BMI) >42.0 kg/m^2

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

10. 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

11. 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

12. 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

13. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) requiring active treatment within 8 weeks prior to or during screening

14. History of hemosiderosis or hemochromatosis

15. History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list are not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis are not excluded)

16. 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

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

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

19. Females who are pregnant or breast-feeding

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

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

22. 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.

The screening period can last up to 4 weeks long, with a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1), ie, the screening period window is from Day -28 to Day -4.

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 or eGFR 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 B12 values may be considered for rescreening after receiving replacement therapy.

If intravenous (IV) iron is used to replete iron stores, the last dose of IV iron must be administered at least 4 weeks prior to rescreening.

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 randomized to receive placebo will be considered as having completed the study after completing participation in the Week 10 (unblinding) visit.

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

Note that for subjects who discontinue study drug due to an excess Hb response during the primary efficacy period, Hb levels will be monitored weekly via lab evaluation until the subject no longer exhibits an excess Hb response.

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 will discontinue study medication for any of the following conditions:

- Completion of the protocol-defined dosing period (see Appendix A)
- Meets discontinuation criteria related to excess Hb response during the primary efficacy period (defined in Section 8.2.4)
- Major toxicity considered to be related to study medication
- Worsening of anemia requiring ESA rescue or blood transfusion
- Administrative reasons, such as, subject non-compliance or a major protocol violation
- Upon request of the sponsor or regulatory agency
- If, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject
- Study termination (see Section 14)

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

7.6.3 Individual Subject Discontinuation during the Primary Efficacy Period or Blinded Dose Adjustment and Data Cleaning Period

Subjects discontinuing study medication or withdrawing early from the study during the blinded periods should undergo the Week 10 (EOT for blinded period) clinical and laboratory assessments within 1 day of stopping study medication, if possible. Such subjects should also complete the 2-week safety follow-up period (see Appendix A). 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.

7.6.4 Individual Subject Discontinuation during the Open-Label Extension Period

Only subjects randomized to vadadustat will continue to the open-label extension period. Subjects discontinuing vadadustat or withdrawing from the study during the open-label period should complete the Week 16 (EOT for open-label period) clinical and laboratory assessments within 1 day of stopping study medication, if possible. Such subjects should also complete the 2-week safety follow-up period and complete the Week 18 visit assessments (see Appendix A). 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 according to 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 at the baseline visit. Each bottle will contain 100 tablets of study drug. Subjects will be instructed to finish 1 bottle before opening a new bottle.

Resupply of additional study drug at subsequent 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.

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 at all times.

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 according to 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 other oral beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food.

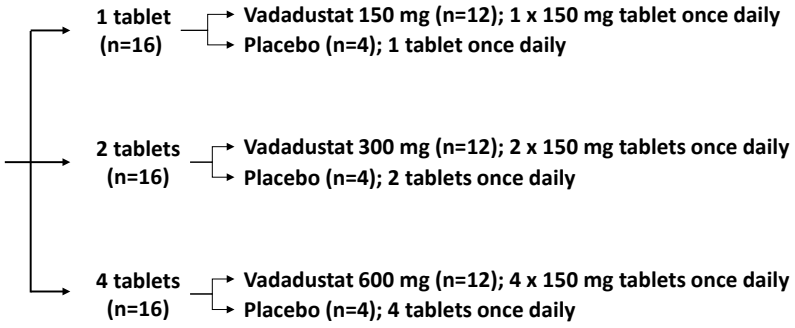
Subjects should be instructed to take the study medication at approximately the same time each day, preferably between 7 am and 2 pm, with the exception of the Week 4 visit. On the day of the Week 4 visit, the dose of study medication should be held until after the pre-dose PK sample has been obtained.

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 Primary Efficacy Period and Breaking the Blind

During the blinded periods, all subjects and personnel involved with the conduct and interpretation of the study will be blinded to the study drug treatment, including investigators, site personnel, site pharmacist, and sponsor's staff and designees.

The study blind should be broken for individual subjects after a subject completes the Week 6 visit and the subject's data (from screening to Week 6) is cleaned and locked.

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.

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. The applicable standard operating procedure will be followed for blind-breaking procedures. After each subject's data is cleaned and locked, their individual randomization code will be broken to determine eligibility for continuation to the open-label extension period.

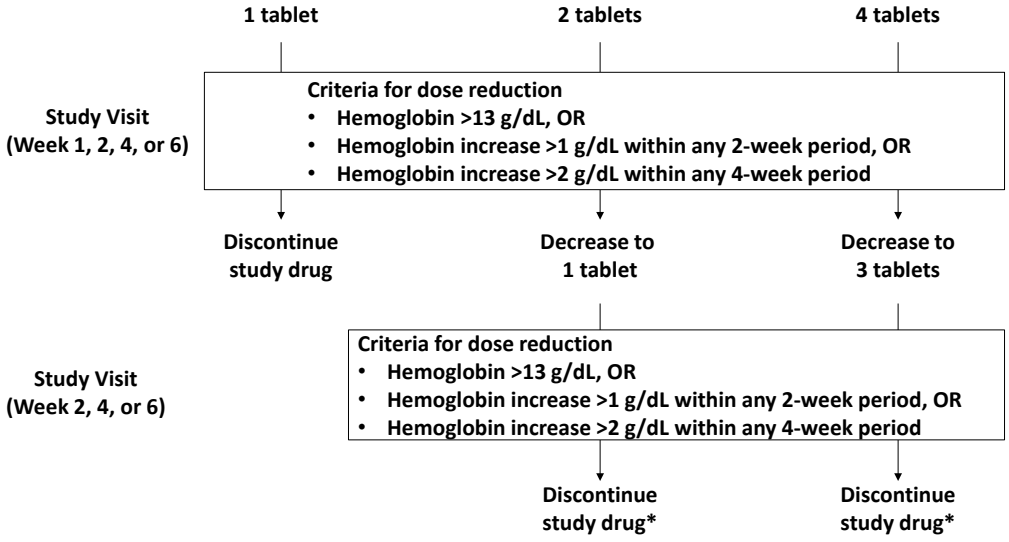
8.2.4 Study Drug Administration during the Primary Efficacy Period

To establish a dose-response relationship, the primary efficacy period includes a blinded fixed-dose treatment regimen. However, if Hb levels increase too rapidly or if the Hb levels exceed the desired range, the dose will be decreased or discontinued as presented below (and as depicted in Figure 6).

- Subjects who meet the following criteria for excess Hb response will undergo a dose reduction by 1 tablet:
  - Hb level >13 g/dL, OR
  - Hb increase >1 g/dL within any 2-week period, OR
  - Hb increase >2 g/dL within any 4-week period
- Subjects who meet the following criteria will discontinue study drug:
  - Excess Hb response as defined by any of the aforementioned criteria, AND
  - Current dose of 1 tablet daily OR subject had previously decreased study drug dose due to excess Hb response

Hb will be assessed at the central laboratory and also monitored using point-of-care HemoCue® (as listed in Appendix A). Note that the point-of-care HemoCue Hb value will be used to determine if the dose of study medication will be adjusted or discontinued.

Figure 6: Guidelines for Dose Reduction or Discontinuation of Study Drug During the Primary Efficacy Period



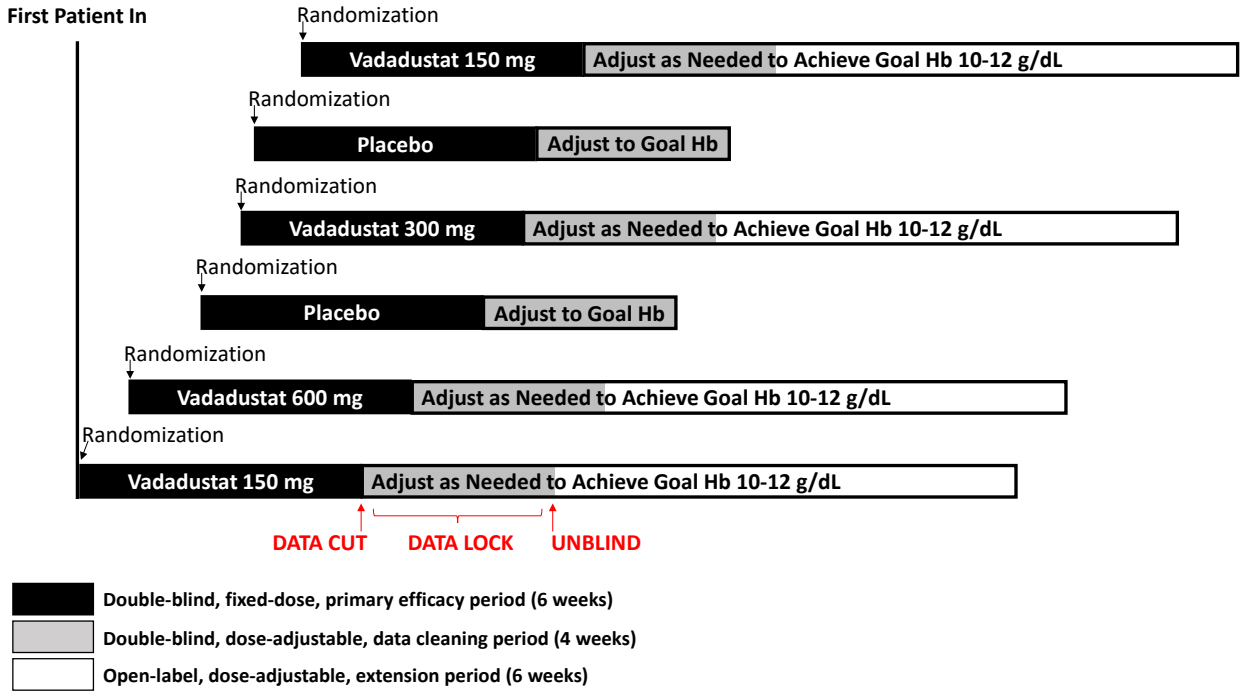
***Note: A subject who had previously decreased study drug dose due to an excess Hb response and meets the criteria for excess Hb response at a subsequent visit during the primary efficacy period (Week 2, 4, or 6) will discontinue study drug**

8.2.5 Study Drug Administration during the Blinded Dose Adjustment and Data Cleaning Period

After completing the Week 6 visit, subjects will continue blinded study treatment for an additional 4 weeks during which time their data from screening through the Week 6 visit will be cleaned and locked. Individual subjects will be unblinded at their Week 10 visit. Potential scenarios for individual subject unblinding is shown in Figure 7.

Point-of-care Hb levels will be monitored via HemoCue to determine if the dose of study medication will be adjusted (as listed in Appendix A). Dose adjustments will be based on dose adjustment guidelines (see Section 8.2.7).

Figure 7: Potential Scenarios for Individual Subject Unblinding



8.2.6 Vadadustat Administration during the Open-Label Extension Period

During the 6-week, open-label extension period, vadadustat dosage will be adjusted to achieve a target Hb level of 10-12 g/dL. Point-of-care Hb will be monitored via HemoCue to determine if the dose of study medication will be adjusted (see Appendix A). Dose adjustments will be based on dose adjustment guidelines (see Section 8.2.7).

8.2.7 Dose Adjustment Guidelines

Dose adjustment of blinded study drug (from Week 7 to 10) and open-label vadadustat (from Week 11 to 16) will follow the dose adjustment guidelines listed below to achieve a target Hb of 10-12 g/dL. The point-of-care HemoCue Hb value will be used to determine if the dose of study drug will be adjusted.

- Do not increase the dose more frequently than once within any given 4-week interval. For example, if a subject's dose was increased at Week 10 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 14. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range.

8.2.8 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**: 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
  - Exhibits Hb level <9.0 g/dL
- **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.

8.2.9 Oral Iron Supplementation (Information on Allowed Use)

Subjects who are taking oral iron supplementation at baseline should continue their oral iron at the same dose throughout their study participation. Changes to oral iron supplementation dose will be considered protocol deviations but will not be considered a reason for subject discontinuation.

Subjects who are not taking oral iron supplementation at baseline should not start oral iron during their study participation (see Section 8.4.3).

Important: Because of the potential for oral iron to reduce the bioavailability of vadadustat, the 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.

8.2.10 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.

Subjects should be questioned regarding dosing compliance and the information should be recorded.

8.2.11 Treatment Compliance

Subjects will be questioned regarding dosing compliance at all study visits from Week 1 through Week 18, 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.

8.2.12 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 through the course of 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, Intravenous Iron, and Blood Transfusion

Subjects may not receive any ESA treatment within 6 weeks prior to the screening period and through the safety follow-up period (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta). See Section 8.2.8 for the rescue therapy guidelines.

Subjects may not receive intravenous iron or blood transfusion within 4 weeks prior to the screening period and through the safety follow-up period. Use of intravenous iron supplementation after Day 1 will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.8 for the rescue therapy guidelines. Note that subjects who initiate rescue therapy will be required to stop study drug treatment and will be discontinued from the study.

8.4.3 Oral Iron Supplementation (Information on Prohibition)

Subjects who are not taking oral iron supplementation at baseline should not start oral iron during study participation. Use of oral iron supplementation by such subjects will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

See Section 8.2.9 for information on circumstances allowing use of oral iron supplementation.

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

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

- Eligibility screening period (Day -28 to Day -4)
- Baseline visit (Day 1)
- Primary efficacy period (Week 1 ± 1 day, Week 2 ± 1 day, Week 4 ± 3 days, and Week 6 ± 3 days)
- Blinded dose adjustment and data cleaning period (Week 10 ± 3 days)
- Open-label extension period (Week 14 ± 3 days and Week 16 ± 3 days)
- Safety follow-up period (Week 18 ± 3 days)

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same investigator or site personnel whenever possible.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.2 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.

9.1.3 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 9.1.3.1.

9.1.3.1 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) and at baseline (assessed using urine 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

9.2 Study Procedures and Evaluations

9.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study. Detailed information regarding the timing of the assessments is presented in Section 9.3 and summarized in Appendix A:

- Demographics and medical history: Relevant medical history (with particular 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
- Weight assessment
- 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.
- 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.

  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.

9.2.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis, with the exception of the urine pregnancy test at baseline which will be performed locally. 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 course of the study:

- Serum and urine 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) and urine pregnancy tests (to be analyzed by the local lab). The screening and baseline pregnancy test results must be available and must be negative for a subject to initiate or continue study drug.
- 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.
- HemoCue®: Hb will be monitored via HemoCue point-of-care device to determine if the dose of study drug will be adjusted.
- 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).

For subjects who discontinue study drug due to an excess Hb response during the primary efficacy period, Hb will be assessed weekly via lab evaluation until the subject no longer exhibits an excess Hb response.

- Chemistry and eGFR: 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. eGFR will be calculated from serum creatinine as described in Appendix B. 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.

9.3 Schedule of Activities

The Schedule of Events in 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.

9.3.1 Screening Visit

The screening visit must be performed within 28 days prior to dosing and there must be a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1).

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo a number of screening activities. The investigator will maintain a log of subjects and indicate who was enrolled or excluded and the reason for exclusion (see Section 9.1.2).

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

- Review of study inclusion and exclusion criteria

- Demographics, medical history, and physical examination
- Weight assessment
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- Prior and current medication use
- 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.
    - Folate and vitamin B12 levels
    - CBC
    - Chemistry and eGFR
    - Iron indices

9.3.2 Baseline Visit (Day 1)

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

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

- Review of study inclusion and exclusion criteria
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)
- Recording of any concomitant medication use since screening visit
- Laboratory procedures:
    - Urine pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The urine sample will be analyzed by the local lab. The baseline results must be available and must be negative before the subject takes the first dose of study drug.
    - Coagulation tests (including prothrombin time, partial thromboplastin time, and international normalized ratio)
    - CBC
    - Chemistry and eGFR
    - Iron indices
    - Hepcidin
    - C-reactive protein
    - VEGF
- Dispense blinded study drug
- Review dosing instructions

9.3.3 Week 1 Visit

At the Week 1 visit, 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)

- AE review
- Concomitant medication review
- Hb using HemoCue
- CBC
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.4 Week 2 Visit

At the Week 2 visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
    - CBC
    - Chemistry and eGFR
    - Iron indices
- Dispense blinded study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and 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

9.3.5 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 (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
    - CBC
    - Chemistry and eGFR
    - Iron indices
    - Pre-dose PK sample
- Record date and time of the last dose of the study that was taken prior to the pre-dose PK sample
- Dispense blinded study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.6 Week 6 Visit

Individual subject data (up to Week 6) will be cleaned and locked after the Week 6 visit. Following data lock, individual subject's randomized treatment assignment will be unblinded and the subject will be informed at the Week 10 visit.

At the Week 6 visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR
  - Iron indices
  - Hepcidin
  - C-reactive protein
  - VEGF
- Dispense blinded study drug (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.7 Week 10 Visit (End-of-treatment visit for the blinded period and early withdrawals)

All enrolled subjects who receive at least 1 dose of blinded study drug should complete the Week 10 assessments.

Subjects who withdraw early from the study prior to the Week 6 visit or permanently discontinue study medication prior to the Week 6 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 9.3.10).

Individual subject data (up to Week 6) will be locked after the Week 6. Following data lock, individual subject's randomized treatment assignment will be unblinded and the subject will be informed at the Week 10 visit. Subjects who were assigned to receive placebo will discontinue from the study at the end of the Week 10 visit, and subjects who were assigned to receive vadadustat will continue to the open-label extension period.

At the Week 10 visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
  - Hb using HemoCue for dose adjustment (not for subjects who discontinue prior to the Week 6 visit)
  - CBC
  - Chemistry and eGFR

  - Iron indices
  - Hepcidin
  - C-reactive protein
  - VEGF
- Dispense open-label vadadustat (as necessary; only applicable to subjects who are continuing to the open-label extension period)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions (only applicable to subjects who are continuing to the open-label extension period)

9.3.8 Week 14 Visit

At this visit, 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)
- AE review
- Concomitant medication review
- Hb using HemoCue for dose adjustment
- CBC
- Chemistry and eGFR
- Dispense vadadustat (as necessary)
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions

9.3.9 Week 16 Visit (End-of-treatment visit for the open-label period and early withdrawal visit for withdrawals after Week 10 but before Week 16)

All subjects who received at least 1 dose of open-label vadadustat should complete the Week 16 assessments.

Subjects who withdraw early from the open-label period 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 9.3.10).

At the Week 16 visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
  - Serum pregnancy test for females of childbearing potential (to be analyzed by the central lab)
  - CBC
  - Chemistry and eGFR
  - Iron indices
  - Hepcidin

  - C-reactive protein
  - VEGF
- Subjects should be questioned regarding dosing compliance

9.3.10 Week 18 Safety Follow-Up Visit (Or 2 Weeks after End-of-Treatment Safety Follow-Up Visit)

For subjects randomized to vadadustat who complete the open-label extension period, the safety visit will be conducted 2 weeks after their end-of-treatment visit (Week 16).

For subjects who discontinue the study early during the primary efficacy period or the blinded dose adjustment and data cleaning period, the safety visit will be conducted 2 weeks after their end-of-treatment visit (Week 10).

At the follow-up visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR

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.

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 AE reporting period for a subject begins upon receiving the first dose of study medication and ends at the final protocol-required visit. In addition, SAEs that occur after the protocol-defined AE reporting period that are considered to be related to the study medication should be recorded and reported to the sponsor's medical monitor or CRO designee.

10.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the AE 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, or the investigator should call the CRO SAE hotline within 24 hours of being made aware of the pregnancy (reference the site manual for contact information).

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

The 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.
- 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

11.1 Primary Endpoint and Sample Size Determination

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 NDD-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 EOT visit minus the mean pre-treatment Hb. Pre-treatment Hb is defined as the average of 2 Hb values obtained prior to treatment based on the qualifying screening Hb value and the Hb value at the baseline visit. Linear regression analysis will be used to calculate the relationship between vadadustat dose and change in Hb.

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

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 reasonable to assume that 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.

11.2 Study Populations

11.2.1 Analysis Population 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.

11.2.2 Analysis Populations for the Efficacy Analyses

The modified intent-to-treat (MITT) population for Hb or RBC count will include subjects who receive at least 1 dose of study medication, have a pre-treatment average defined as the average of the qualifying screening value and the baseline value, and at least one post-baseline measurement. The MITT population for other parameters will include subjects who receive at least 1 dose of study medication, have at least one pre-treatment value, and at least one post-baseline 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.

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

11.3 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.

11.4 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.

11.5 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

For purposes of analysis, a pre-treatment average (defined as the average of 2 samples obtained prior to treatment [ie, the qualifying screening value and baseline value]) will be used as the baseline value for Hb and RBC count, and last observation before the first dose of study medication will be used as baseline for other parameters.

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 assess the vadadustat dose-response relationship. 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.

11.6 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, components of the CBC, and VEGF.

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.

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.

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 course of 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.

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Appendix A: Schedule of Activities

Please refer to Section 9.2 for detailed information regarding the study procedures and evaluations, and please refer to Section 9.3 for detailed information regarding the activities to be performed at each study visit.

	Screening	Primary efficacy period (blinded, fixed-dose treatment) (Day 1-Week 6)					Blinded dose adjustment, data cleaning period (Week 7-10)	Open-label extension period (Week 11-16)		Safety Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**1**	**2**	**4**	**6**	**10 (EOT, Blinded Period)**	**14**	**16 (EOT, Open-Label Period)**	**18**
Study Day	**-28 to -4**	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X									
Review inclusion/exclusion criteria	X	X								
Individual subject data lock (for subjects who complete Week 6)						X				
Individual subject unblinding (for subjects who complete Week 6)							X			
Demographics, medical history, physical exam, and weight	X									
Vital signs	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X								
Adverse event review			X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X								X	
Urine pregnancy test		X								
Coagulation tests		X								

	Screening	Primary efficacy period (blinded, fixed-dose treatment) (Day 1-Week 6)					Blinded dose adjustment, data cleaning period (Week 7-10)	Open-label extension period (Week 11-16)		Safety Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**1**	**2**	**4**	**6**	**10 (EOT, Blinded Period)**	**14**	**16 (EOT, Open-Label Period)**	**18**
Study Day	**-28 to -4**	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Folate and vitamin B12	X									
Hb using HemoCue® (Week 10 assessment is not for subjects who discontinue prior to Week 6)			X	X	X	X	X	X		
Complete blood count, including Hb [a]	X	X	X	X	X	X	X	X	X	X
Chemistry and eGFR	X	X		X	X	X	X	X	X	X
Iron indices	X	X		X	X	X	X		X	
Hepcidin		X				X	X		X	
C-reactive protein		X				X	X		X	
VEGF		X				X	X		X	
PK pre-dose sample (study drug to be administered after sample collection)					X					
Blinded study drug dispensation, as necessary		X		X	X	X				
Blinded study drug dosing		Blinded study drug dosing								
Vadadustat dispensation, as necessary [b]							X	X		
Vadadustat dosing [b]								Open-label vadadustat dosing		
Study drug compliance check			X	X	X	X	X	X	X	

Abbreviations: eGFR, estimated glomerular filtration rate; EOT, end of treatment; Hb, hemoglobin; PK, pharmacokinetics; VEGF, vascular endothelial growth factor

[a] For subjects who discontinue study drug due to an excess Hb response, blood samples will be collected weekly to monitor Hb until the subject no longer exhibits an excess Hb response. The blood samples will be analyzed in a lab. Point-of-care Hb assessment will not be used for such evaluations.

[b] Subjects who were randomized to receive vadadustat treatment during the primary efficacy period and complete the Week 10 visit will continue to the open-label extension period.

Appendix B: Japanese Society of Nephrology 2009 Equation to Calculate eGFR

The estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine using the 2009 Japanese Society of Nephrology Equation (3-variables; Matsuo 2009).

eGFR (mL/min/1.73 m^2) = **194** x (S_{cr} in mg/dL)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female)

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 NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0021
Phase:	Phase 2
Status / Date:	Original protocol (Version 1; 23 May 2016) Original protocol (Version 1.1; 22 June 2016) Original protocol (Version 2; 19 July 2016) Original protocol (Version 3; 05 August 2016)
Sponsor:	Akebia Therapeutics, Inc. 245 First Street, Suite 1100 Cambridge, MA 02142 United States of America

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 also 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

_____

_____

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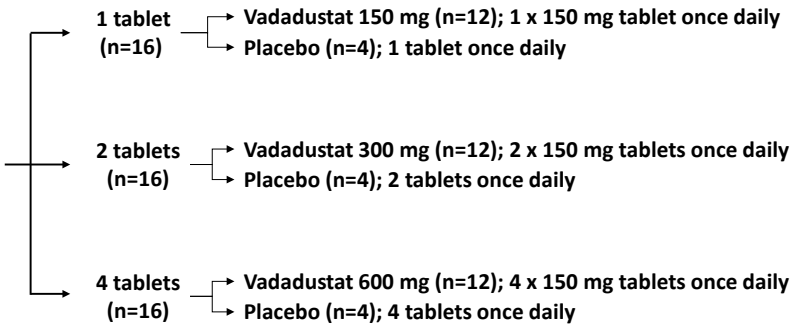
2 PROTOCOL SYNOPSIS

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 Non-Dialysis Dependent Chronic Kidney Disease
Protocol Number	AKB-6548-CI-0021
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 non-dialysis dependent chronic kidney disease (NDD-CKD) who are not currently being treated with an erythropoiesis-stimulating agent (ESA)
Investigative Sites	Approximately 25 sites in Japan
Planned Number of Subjects	Approximately 48 subjects will be enrolled in the study, with 36 subjects receiving one of the 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 (QD) dosing for 6 weeks and the change in hemoglobin (Hb) in Japanese subjects with anemia secondary to NDD-CKD; in order 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 QD dosing in Japanese subjects with anemia secondary to NDD-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
Study Design Overview	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 NDD-CKD. The study will include the following periods: • Eligibility screening period (up to 4 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). Following the screening period, eligible subjects will be randomized to receive blinded study drug treatment during a 6-week primary efficacy period, with subjects randomized at a 3:1 ratio to receive vadadustat (150, 300, or 600 mg vadadustat) or

	placebo. See "Dosage and Regimen" in the synopsis 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 levels increase too rapidly or if the Hb levels exceed the desired range, the study drug dose can be decreased or interrupted (see "Dosage and Regimen" for additional information). 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	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). 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. In addition, 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.
Key Inclusion Criteria (the complete list is provided in the protocol)	• Male and female Japanese subjects (20 years or older) • Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009) • Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening • Hb ≤10.5 g/dL • Serum ferritin ≥50 ng/mL • Transferrin saturation (TSAT) ≥20% • Folate and vitamin B12 ≥ lower limit of normal • For subjects who are receiving oral iron supplementation, the dose of oral iron supplementation must be stable for at least 28 days prior to the screening period. For subjects who are not receiving oral iron supplementation, no iron supplementation may have been ingested 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; intravenous iron within 4 weeks prior to or during screening; and any ESA use within 6 weeks prior to or during screening.
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 or eGFR 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 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 value for Hb is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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 10.0-12.0 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) • Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and 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 and tolerability 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 other oral 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.



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.

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. 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.

Dose adjustment and maintenance period (Weeks 7 to 16):

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 at Week 6 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 10. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range. 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	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**: 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 • **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.
Oral Iron Supplementation	Subjects who are receiving a stable dose of oral iron supplementation for at least 28 days prior to the screening period should continue their oral iron supplementation at the same dose through the primary efficacy period (through Week 6). Changes to oral 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 adjust oral iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT <20%, and the iron dose will be selected at the investigator's discretion. Subjects who are not receiving oral iron supplementation at the beginning of the screening period should not start oral iron supplementation through the primary efficacy period (through Week 6). Initiation of oral 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 oral iron supplementation for subjects with ferritin <100 ng/mL and TSAT <20%, and the iron dose 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.
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. The target enrollment will be approximately 48 subjects for the study with 12 subjects enrolled in each of the 4 treatment groups. 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. 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. 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. 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.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
CV	cardiovascular
dL	deciliter
DVT	deep venous thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
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
GFR	glomerular filtration rate
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
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)
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.

A number of 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.

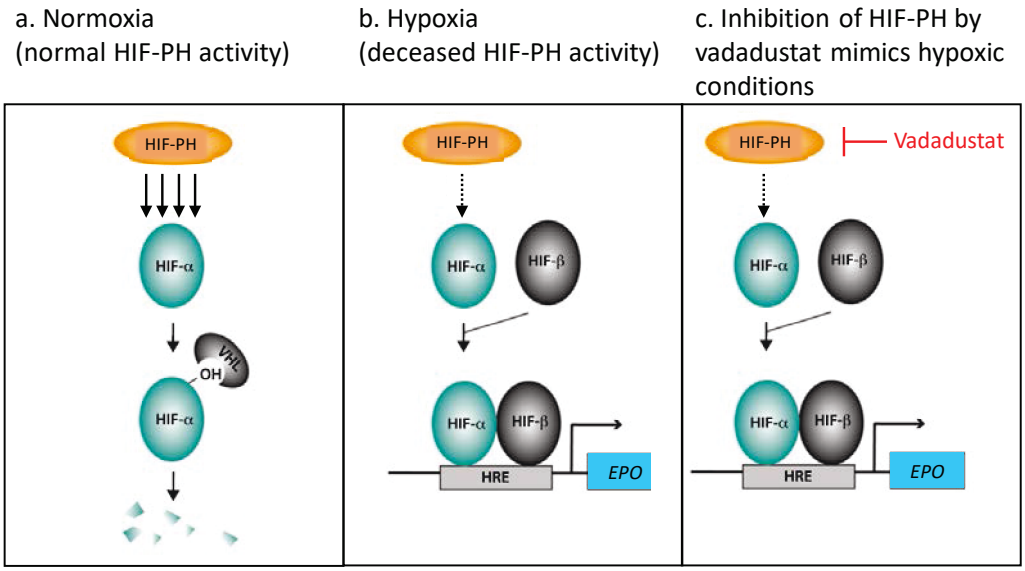
4.3 Hypoxia-Inducible Factor

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. As a result, 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 recently 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.

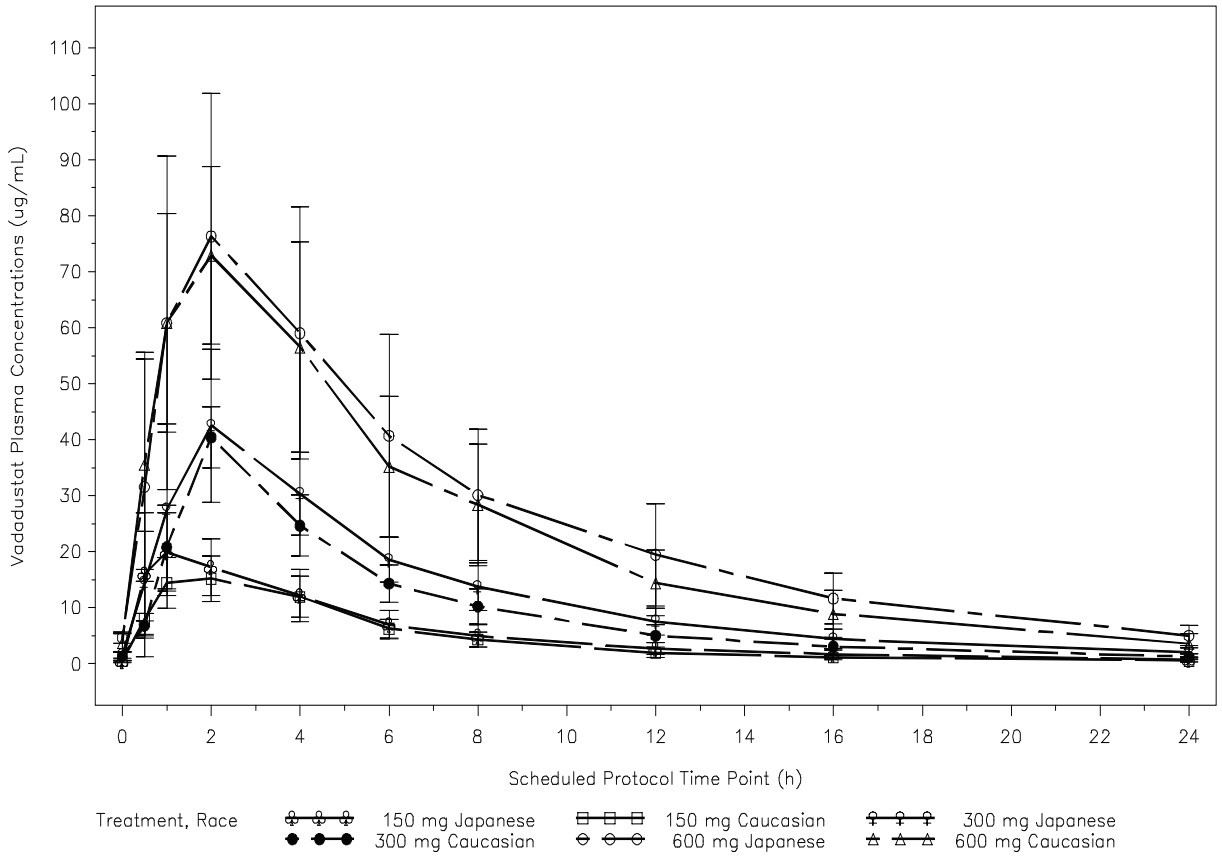
Eligible subjects were enrolled into one of 3 dose cohorts: 150, 300, or 600 mg daily oral doses of vadadustat (or placebo). Subjects received daily doses of study drug (either vadadustat or placebo) for 10 days. Each of the 3 dose cohorts enrolled 8 Japanese and 8 Caucasian subjects.

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.

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 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 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, all of 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 HIFPH 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 value for Hb is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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 Hb in Japanese subjects with anemia secondary to NDD-CKD; in order 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 NDD-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)
- Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and 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

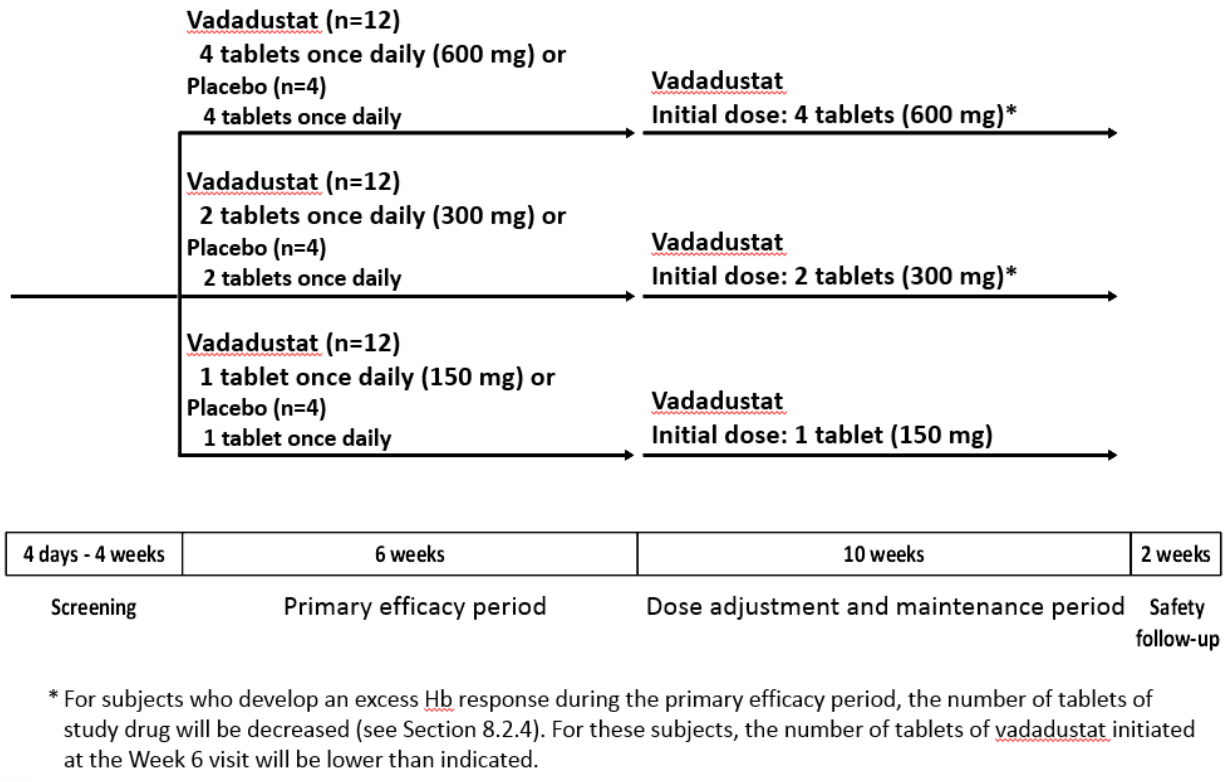
6.1 Study Design

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 subjects with anemia secondary to NDD-CKD.

The study has a planned enrollment of 48 subjects to be enrolled at approximately 25 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 (up to 4 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)

Subjects will participate in a screening period (4 days to 4 weeks) to determine study eligibility, and 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 levels increase too rapidly or if the Hb levels exceed the desired range, 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).

The clinical and safety assessments will be performed as described in Section 9.3 and as listed in Appendix A.

6.2 Study Duration

Individual subjects will participate in the study for 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).

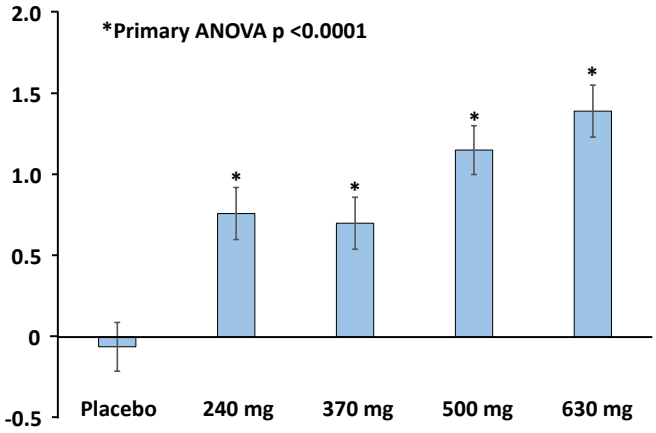
Note: Subjects who discontinue prematurely from the study will complete the end-of-treatment Week 16 visit followed in two weeks by the Week 18 visit. In addition, for subjects with Hb>13.0 g/dL at the follow-up visit, Hb will be assessed every 2 weeks until the Hb<13.0 g/dL.

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 NDD-CKD is modeled on a previously completed dose-finding study in Caucasian subjects with anemia secondary to NDD-CKD (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 safe and 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 safe, 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 according to 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

The study population will consist of male and female Japanese adults aged 20 years or older with anemia secondary to NDD-CKD who are not currently being treated with an ESA.

To be eligible for this study, a subject or their legally acceptable representative must have provided valid informed consent and must meet all of 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 all of the following inclusion criteria to be eligible for study participation:

1. Male and female Japanese subjects, aged 20 years or older
2. Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009)
3. Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening
4. Hemoglobin (Hb) ≤10.5 g/dL during screening
5. Serum ferritin ≥50 ng/mL during screening
6. TSAT ≥20% during screening
7. Folate and vitamin B12 greater than or equal to the lower limit of normal during screening
8. For subjects who are receiving oral iron supplementation, the dose of oral iron supplementation must be stable for at least 28 days prior to the screening period. For subjects who are not receiving oral iron supplementation, no iron supplementation may have been ingested for at least 28 days prior to the screening period.
9. 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. RBC transfusion within 4 weeks prior to or during screening
4. Intravenous iron within 4 weeks prior to or during screening

5. Any ESA use within 6 weeks prior to or during screening (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta)

6. 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.

7. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mm Hg or systolic blood pressure >180 mm Hg) during screening

8. Body mass index (BMI) >42.0 kg/m^2

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

10. 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

11. 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

12. 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

13. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) requiring active treatment within 8 weeks prior to or during screening

14. History of hemosiderosis or hemochromatosis

15. History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list are not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis are not excluded)

16. 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

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

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

19. Females who are pregnant or breast-feeding

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

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

22. 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.

The screening period can last up to 4 weeks long, with a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1), ie, the screening period window is from Day -28 to Day -4.

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 or eGFR 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 B12 values may be considered for rescreening after receiving replacement therapy.

If intravenous (IV) iron is used to replete iron stores, the last dose of IV iron must be administered at least 4 weeks prior to rescreening.

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: 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. In addition, 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.

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 will discontinue study medication for any of the following conditions:

- Completion of the protocol-defined dosing period (see Appendix A)
- Worsening of anemia requiring ESA rescue or blood transfusion
- Unacceptable toxicity or drug intolerability
- Investigator discretion
- Subject withdrawal of consent
- Subject becomes pregnant
- 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 discontinuing study medication or withdrawing from the study 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 Appendix A). 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 according to 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. 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 from each subject the study drug bottle 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.

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 at all times.

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 according to 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 other oral beverage and should be instructed to swallow the intact tablet(s). Subjects may take the study medication with or without food.

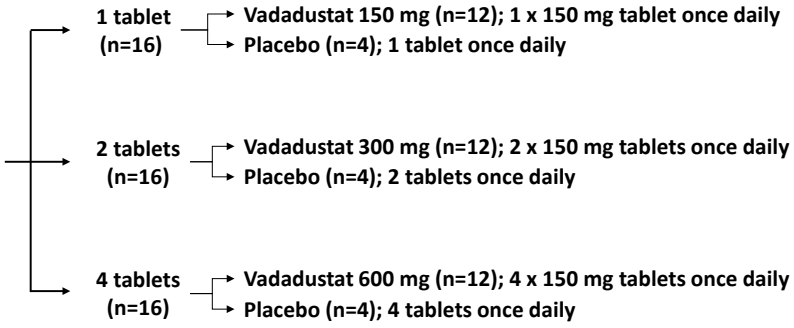
Subjects should be instructed to take the study medication at approximately the same time each day, preferably between 7 am and 2 pm, with the exception of the Week 4 visit. On the day of the Week 4 visit, the dose of study medication should be held until after the pre-dose PK sample has been obtained.

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 (Section 11.1). Sponsor and CRO study team personnel involved in 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.

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. The applicable standard operating procedure will be followed for blind-breaking procedures.

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, 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.

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. 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 Week 16)

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 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 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 at Week 6 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 10. 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 rises 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range.

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 "Rescue Therapy Guidelines" below).

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**: 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.

8.2.7 Oral Iron Supplementation (Information on Allowed Use)

Subjects who are receiving a stable dose of oral iron supplementation for at least 28 days prior to the screening period should continue their oral iron supplementation at the same dose through the primary efficacy period (through Week 6). Changes to oral 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 adjust oral iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT is <20%, and the iron dose will be selected at the investigator's discretion.

Subjects who are not receiving oral iron supplementation at the beginning of the screening period should not start oral iron supplementation through the primary efficacy period (through Week 6) (see Section 8.4.3). Initiation of oral 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 oral iron supplementation for subjects with ferritin is <100 ng/mL and TSAT is <20%, and the iron dose 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.

Subjects should be questioned regarding dosing compliance and the information should be recorded.

8.2.9 Treatment Compliance

Subjects will be questioned regarding dosing compliance at all study visits 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.

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 through the course of 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, Intravenous Iron, and Blood Transfusion

Subjects may not receive any ESA treatment within 6 weeks prior to the screening period and through the follow-up period (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta). See Section 8.2.6 for the rescue therapy guidelines.

Subjects may not receive intravenous iron or blood transfusion within 4 weeks prior to the screening period and through the follow-up period. Use of intravenous iron supplementation after Day 1 will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.6 for the rescue therapy guidelines. Note that subjects who initiate rescue therapy will be required to stop study drug treatment and will be discontinued from the study.

8.4.3 Oral 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 oral iron supplementation through 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

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

- Eligibility screening period (Day -28 to Day -4)
- Primary efficacy period (from Day 1 to the Week 6 visit)
  - Baseline visit (Day 1)
  - Week 2 ± 1 day
  - Week 4 ± 3 days
  - Week 6 ± 3 days
- Dose adjustment and maintenance period (after the Week 6 visit to the Week 16 visit)
  - Week 8 visit ± 3 days
  - Week 10 visit ± 3 days

  - Week 12 visit ± 3 days
  - Week 14 ± 3 days
  - Week 16 ± 3 days
- Follow-up period (after the Week 16 visit to the Week 18 visit)
  - Week 18 ± 3 days

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same investigator or site personnel whenever possible.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

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

9.1.2 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.

9.1.3 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 9.1.3.1.

9.1.3.1 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) and at baseline (assessed using urine 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

9.2 Study Procedures and Evaluations

9.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study. Detailed information regarding the timing of the assessments is presented in Section 9.3 and summarized in Appendix A:

- Demographics and medical history: Relevant medical history (with particular 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
- Weight assessment
- 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.
- 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.

  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.

9.2.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis, with the exception of the urine pregnancy test at baseline which will be performed locally. 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 course of the study:

- Serum and urine 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) and urine pregnancy tests (to be analyzed by the local lab). The screening and baseline pregnancy test results must be available and must be negative for a subject to initiate or continue study drug.
- 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: 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).

  For subjects with Hb>13.0 g/dL at the follow-up visit, CBC will be assessed every 2 weeks until the Hb<13.0 g/dL.

- Chemistry and eGFR: 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. eGFR will be calculated from serum creatinine as described in Appendix B. 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.

9.3 Schedule of Activities

The Schedule of Events in 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.

9.3.1 Screening Visit

The screening visit must be performed within 28 days prior to dosing and there must be a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1).

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo a number of screening activities. The investigator will maintain a log of subjects and indicate who was enrolled or excluded and the reason for exclusion (see Section 9.1.2).

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

- Review of study inclusion and exclusion criteria
- Demographics, medical history, and physical examination
- Weight assessment
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)

- Prior and current medication use
- 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.
    - Folate and vitamin B12 levels
    - CBC
    - Chemistry and eGFR
    - Iron indices

9.3.2 Baseline Visit (Day 1)

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

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

- Review of study inclusion and exclusion criteria
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)
- Recording of any concomitant medication use since screening visit
- Laboratory procedures:
    - Urine pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The urine sample will be analyzed by the local lab. The baseline results must be available and must be negative before the subject takes the first dose of study drug.
    - Coagulation tests (including prothrombin time, partial thromboplastin time, and international normalized ratio)
    - CBC
    - Chemistry and eGFR
    - Iron indices
    - Hepcidin
    - C-reactive protein
    - VEGF
- Dispense one bottle of study drug
- Review dosing instructions

9.3.3 Week 2 Visit

At the Week 2 visit, 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)
- AE review
- Concomitant medication review
- Laboratory procedures:
    - CBC

  - Chemistry and eGFR
  - Iron indices
- 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 obtained from this visit demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.3.4 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 (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- AE review
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR
  - Iron indices
  - Pre-dose PK sample
- Record date and time of the last dose of the study that was taken prior to the pre-dose PK sample
- 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 obtained from this visit demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.3.5 Week 6 Visit

At the Week 6 visit, 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)
- AE review
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR
  - Iron indices

  - Hepcidin
  - C-reactive protein
  - VEGF
- Collect study bottle and all remaining study drug tablets remaining from the primary efficacy period
- Dispense one bottle of vadadustat
- 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)

9.3.6 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)
- AE review
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR
  - 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)

9.3.7 Week 16 Visit (end-of-treatment visit for subjects who complete the dose adjustment and maintenance period or for subjects who withdraw prematurely from the study prior to Week 16)

All subjects should complete the Week 16 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 9.3.8).

At the Week 16 visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:

  - Serum pregnancy test for females of childbearing potential (to be analyzed by the central lab)
  - CBC
  - Chemistry and eGFR
  - Iron indices
  - Hepcidin
  - C-reactive protein
  - VEGF
- Subjects should be questioned regarding dosing compliance

9.3.8 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, 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 (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR
- 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.

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.

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 AE reporting period for a subject begins upon receiving the first dose of study medication and ends at the final protocol-required visit. In addition, SAEs that occur after the protocol-defined AE reporting period that are considered to be related to the study medication should be recorded and reported to the sponsor's medical monitor or CRO designee.

10.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the AE 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, or the investigator should call the CRO SAE hotline within 24 hours of being made aware of the pregnancy (reference the site manual for contact information).

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

The 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.
- 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

11.1 Primary Endpoint and Sample Size Determination

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 NDD-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 EOT visit minus the mean pre-treatment Hb. Pre-treatment Hb is defined as the average of 2 Hb values obtained prior to treatment based on the qualifying screening Hb value and the Hb value at the baseline visit. Linear regression analysis will be used to calculate the relationship between vadadustat dose and change in Hb.

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

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 reasonable to assume that 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.

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. 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. 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.

11.2 Study Populations

11.2.1 Analysis Population 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.

11.2.2 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 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.

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

11.3 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.

11.4 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.

11.5 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

For purposes of analysis, a pre-treatment average (defined as the average of 2 samples obtained prior to treatment [ie, the qualifying screening value and baseline value]) will be used as the baseline value for Hb, and last observation before the first dose of study medication will be used as baseline for other parameters.

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 assess the vadadustat dose-response relationship. 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.

11.6 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, components of the CBC, and VEGF.

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.

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.

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 course of 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.

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Appendix A: Schedule of Activities

Please refer to Section 9.2 for detailed information regarding the study procedures and evaluations, and please refer to Section 9.3 for detailed information regarding the activities to be performed at each study visit.

	Screening	Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18
Study Week	**-4 to 0**	**Base line**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**-28 to -4**	**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										
Demographics, medical history, physical exam, and weight	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X									
Adverse event review			X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X									X	
Urine pregnancy test		X									
Coagulation tests		X									
Folate and vitamin B12	X										
Complete blood count, including Hb [a]	X	X	X	X	X	X	X	X	X	X	X
Chemistry and eGFR	X	X	X	X	X	X	X	X	X	X	X

	Screening	Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18
Study Week	**-4 to 0**	**Base line**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**-28 to -4**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Iron indices	X	X	X	X	X	X		X		X	
Hepcidin		X			X					X	
C-reactive protein		X			X					X	
VEGF		X			X					X	
PK pre-dose sample (study drug to be administered after sample collection)				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	
Based on Hb results from the visits noted, dose reduction for excess Hb response as needed according to guidelines (Section 8.2.4)			X	X							

	Screening	Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18
Study Week	**-4 to 0**	**Base line**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**-28 to -4**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Based on Hb results from the visits noted, dose adjustment to achieve target Hb 10.0-12.0 g/dL as needed according to guidelines (Section 8.2.5)					X	X	X	X	X		

Abbreviations: eGFR, estimated glomerular filtration rate; EOT, end of treatment; Hb, hemoglobin; PK, pharmacokinetics; VEGF, vascular endothelial growth factor

[a] 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.

Appendix B: Japanese Society of Nephrology 2009 Equation to Calculate eGFR

The estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine using the 2009 Japanese Society of Nephrology Equation (3-variables; Matsuo 2009).

eGFR (mL/min/1.73 m^2) = **194** x (S_{cr} in mg/dL)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female)

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 NON-DIALYSIS DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0021
Phase:	Phase 2
Status; Date:	Version 1.1; 22 June 2016 (Original Protocol) Version 2; 19 July 2016 Version 3; 5 August 2016 Version 4; 15 December 2016
Sponsor:	Akebia Therapeutics, Inc. 245 First Street, Suite 1100 Cambridge, MA 02142 United States of America

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 also 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.

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Signature of Investigator Date

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Investigator Name (print or type)

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Investigator's Title

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Full Address

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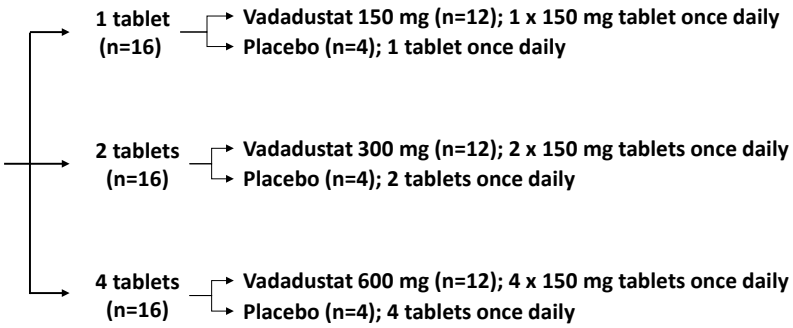
2 PROTOCOL SYNOPSIS

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 Non-Dialysis Dependent Chronic Kidney Disease
Protocol Number	AKB-6548-CI-0021
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 non-dialysis dependent chronic kidney disease (NDD-CKD) who are not currently being treated with an erythropoiesis-stimulating agent (ESA)
Investigative Sites	Approximately 25 sites in Japan
Planned Number of Subjects	Approximately 48 subjects will be enrolled in the study, with 36 subjects receiving one of the 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 (QD) dosing for 6 weeks and the change in hemoglobin (Hb) in Japanese subjects with anemia secondary to NDD-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 QD dosing in Japanese subjects with anemia secondary to NDD-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
Study Design Overview	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 NDD-CKD. The study will include the following periods: • Eligibility screening period (up to 4 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). Following the screening period, eligible subjects will be randomized to receive blinded study drug treatment during a 6-week primary efficacy period, with subjects randomized at a 3:1 ratio to receive vadadustat (150, 300, or 600 mg vadadustat) or placebo. See "Dosage and Regimen" in the synopsis 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 13.0 g/dL, the study drug dose can be decreased or interrupted (see "Dosage and Regimen" for additional information). 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	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). Note: Subjects who discontinue prematurely from the study or permanently discontinue study drug 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) • Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009) • Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening • Hb ≤10.5 g/dL • Serum ferritin ≥50 ng/mL • Transferrin saturation (TSAT) ≥20% • Folate and vitamin B12 ≥ lower limit of normal • For subjects who are receiving oral iron supplementation, the dose of oral iron supplementation must be stable for at least 28 days prior to the screening period. For subjects who are not receiving oral iron supplementation, no iron supplementation may have been ingested 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; intravenous iron within 4 weeks prior to or during screening; and any ESA use within 6 weeks prior to or during screening.
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 or eGFR 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 value for Hb is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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 10.0-12.0 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) • Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and 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 and tolerability 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.

Dose adjustment and maintenance period (Weeks 7 to 16):

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 at Week 6 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 10. 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). In cases of extenuating clinical circumstances, investigators may elect to dose outside the dosing guidelines to maintain the Hb within the target range. 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** To standardize the use of ESA rescue therapy 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 2 criteria listed above are met. **RBC Transfusion** Investigators should use their local institution's transfusion guidelines when determining whether to transfuse a study subject. Subjects who initiate rescue therapy (ESA rescue therapy or RBC transfusion), will be required to stop study drug treatment and will be discontinued from the study (see "Study Duration").
Oral Iron Supplementation	Subjects who are receiving a stable dose of oral iron supplementation for at least 28 days prior to the screening period should continue their oral iron supplementation at the same dose through the primary efficacy period (through Week 6). Changes to oral 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 adjust oral iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT <20%, and the iron dose will be selected at the investigator's discretion. Subjects who are not receiving oral iron supplementation at the beginning of the screening period should not start oral iron supplementation through the primary efficacy period (through Week 6). Initiation of oral 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 oral iron supplementation for subjects with ferritin <100 ng/mL and TSAT <20%, and the iron dose 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.
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. Therefore, no multiplicity adjustment will be needed for this analysis. 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), with a common standard deviation of 0.68 g/dL across treatment groups. With these assumptions, the study with n=12 subjects per group will have >95% 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 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.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
CV	cardiovascular
dL	deciliter
DVT	deep venous thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
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
GFR	glomerular filtration rate
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)
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.

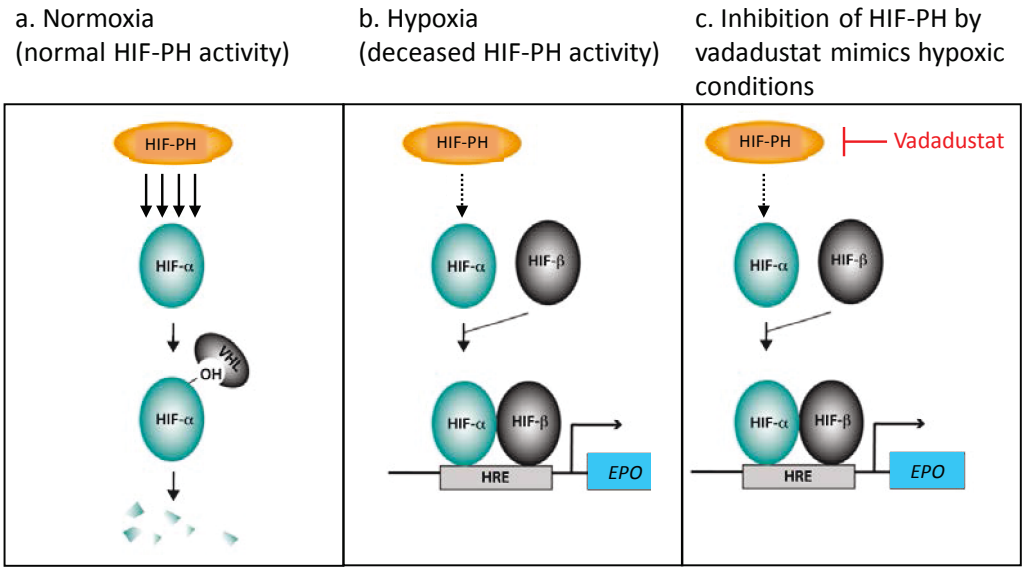
4.3 Hypoxia-Inducible Factor

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.

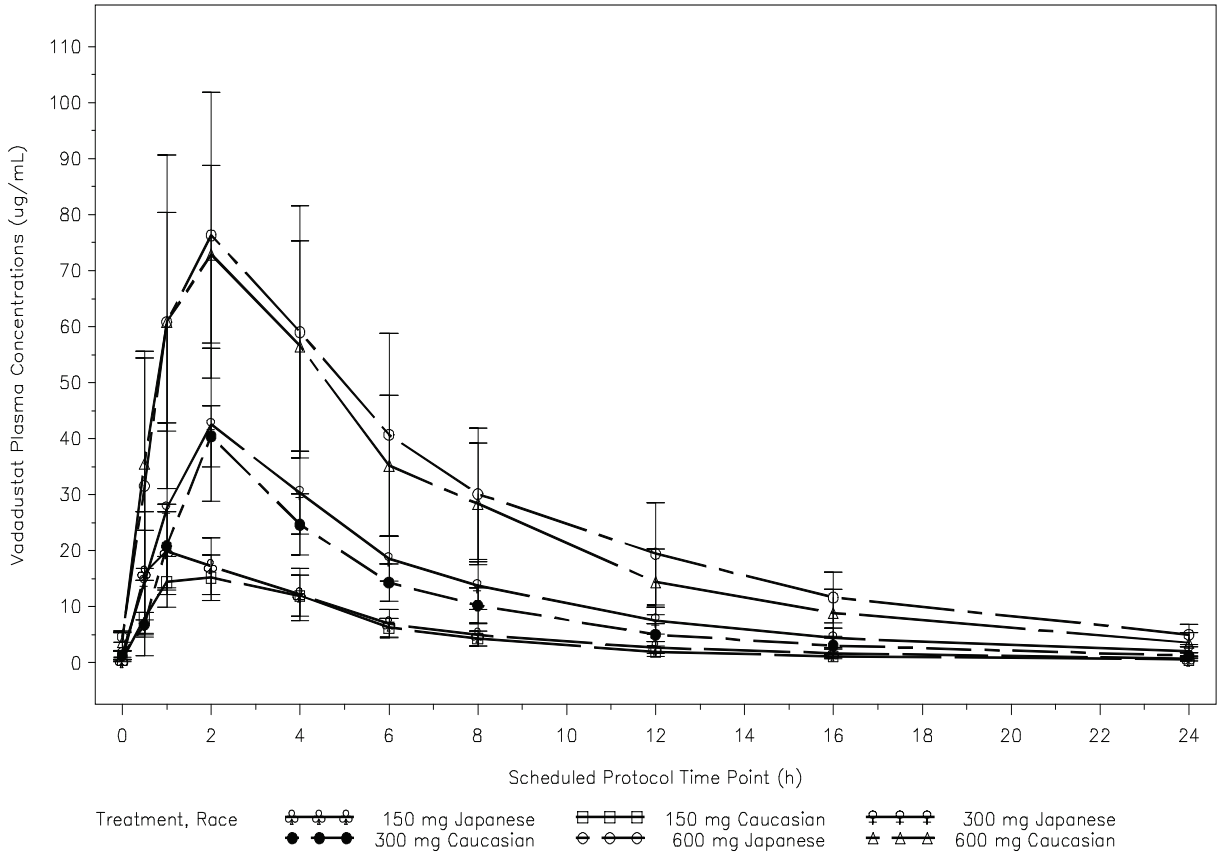
Eligible subjects were enrolled into one of 3 dose cohorts: 150, 300, or 600 mg daily oral doses of vadadustat (or placebo). Subjects received daily doses of study drug (either vadadustat or placebo) for 10 days. Each of the 3 dose cohorts enrolled 8 Japanese and 8 Caucasian subjects.

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 Hb 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 HIFPH 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 value for Hb is defined as the average of 2 values obtained prior to treatment, ie, the qualifying screening value 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 Hb in Japanese subjects with anemia secondary to NDD-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 NDD-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 range from baseline

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)
- Maintenance of iron sufficiency (defined as ferritin ≥50 ng/mL and TSAT ≥20%) from baseline to the end of the primary efficacy period (Week 6) and 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

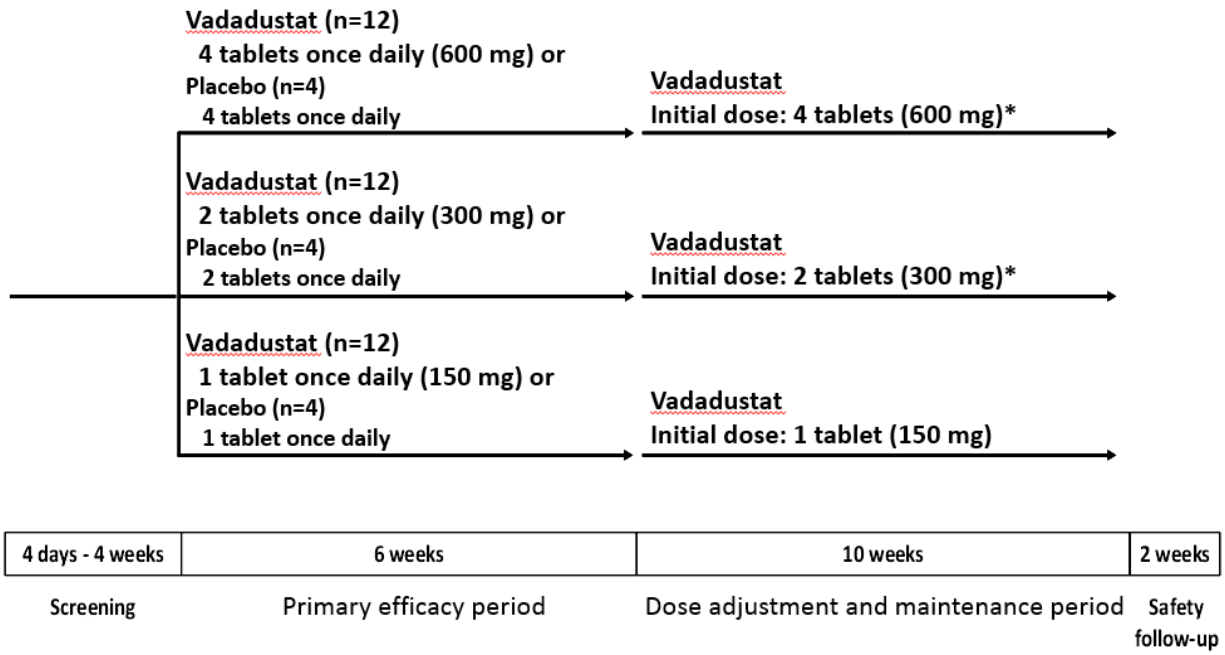
6.1 Study Design

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 subjects with anemia secondary to NDD-CKD.

The study has a planned enrollment of 48 subjects to be enrolled at approximately 25 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 (up to 4 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)

Subjects will participate in a screening period (4 days to 4 weeks) to determine study eligibility, and 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 level exceeds 13.0 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).

The clinical and safety assessments will be performed as described in Section 9.4 and as listed in Appendix A.

6.2 Study Duration

Individual subjects will participate in the study for 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).

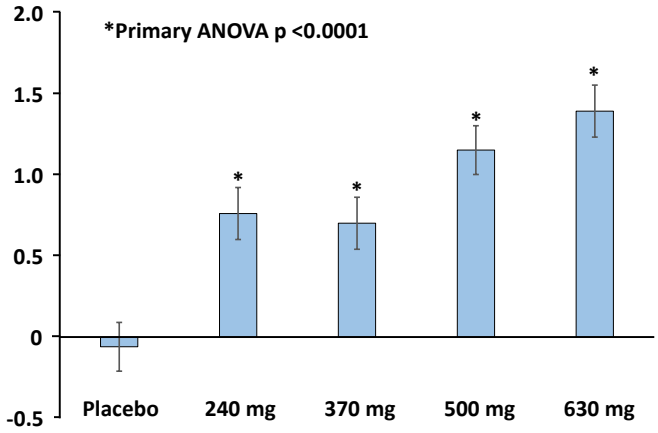
Note: Subjects who discontinue prematurely from the study or permanently discontinue study drug will complete the end-of-treatment (Week 16) visit followed in two weeks by the Week 18 visit (see Section 7.6.3).

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 NDD-CKD is modeled on a previously completed dose-finding study in subjects with anemia secondary to NDD-CKD that included mostly 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 according to 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

The study population will consist of male and female Japanese adults aged 20 years or older with anemia secondary to NDD-CKD who are not currently being treated with an ESA.

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, aged 20 years or older
2. Diagnosis of CKD based on an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73 m^2 (using the 2009 Japanese Society of Nephrology equation; Matsuo 2009)
3. Not currently being treated with dialysis and not expected to start dialysis within 3 months of screening
4. Hemoglobin (Hb) ≤10.5 g/dL during screening
5. Serum ferritin ≥50 ng/mL during screening
6. TSAT ≥20% during screening
7. Folate and vitamin B12 greater than or equal to the lower limit of normal during screening
8. For subjects who are receiving oral iron supplementation, the dose of oral iron supplementation must be stable for at least 28 days prior to the screening period. For subjects who are not receiving oral iron supplementation, no iron supplementation may have been ingested for at least 28 days prior to the screening period.
9. 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. RBC transfusion within 4 weeks prior to or during screening
4. Intravenous iron within 4 weeks prior to or during screening

5. Any ESA use within 6 weeks prior to or during screening (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta)

6. 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.

7. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mm Hg or systolic blood pressure >180 mm Hg) during screening

8. Body mass index (BMI) >42.0 kg/m^2

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

10. 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

11. 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

12. 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

13. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) requiring active treatment within 8 weeks prior to or during screening

14. History of hemosiderosis or hemochromatosis

15. History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list are not excluded), or prior hematopoietic stem cell or bone marrow transplant (corneal transplants and stem cell therapy for knee arthritis are not excluded)

16. 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

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

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

19. Females who are pregnant or breast-feeding

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

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

22. 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.

The screening period can last up to 4 weeks long, with a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1), ie, the screening period window is from Day -28 to Day -4.

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.

For eligibility purposes, if the Hb measured at the screening visit is >10.5 g/dL and <11.0 g/dL, Hb level can be retested once at the investigator's discretion. The subject should not be retested if the Hb level measured at the screening visit is ≥11.0 g/dL.

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

7.4.2 Rescreening

Subjects who fail to meet the qualifying criteria for Hb or eGFR 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.

If intravenous (IV) iron is used to replete iron stores, the last dose of IV iron must be administered at least 4 weeks prior to rescreening.

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: 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 (see Section 7.6.3).

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 will discontinue study medication for any of the following conditions:

- Completion of the protocol-defined dosing period (see Appendix A)
- Worsening of anemia requiring ESA rescue or blood transfusion
- Unacceptable toxicity or drug intolerability
- Investigator discretion
- Subject withdrawal of consent
- Subject becomes pregnant
- 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 medication or withdrawing early from the study prior to the Week 16 visit should complete the Week 16 (end-of-treatment) 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 Appendix A). 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 according to 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 according to 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.

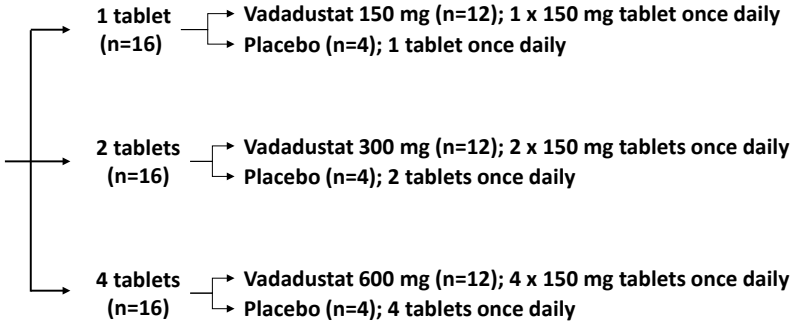
Subjects should be instructed to take the study medication at approximately the same time each day, preferably between 7 am and 2 pm, with the following exception. On the day of the Week 4 visit, the dose of study medication should be held until after the pre-dose PK sample has been obtained.

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 Week 16)

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 at Week 6 and the subject remains below the Hb target, the next opportunity to further increase the dose would be Week 10. 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 "Rescue Therapy Guidelines" below; Section 8.2.6).

8.2.6 Rescue Therapy Guidelines

- **ESA Rescue Therapy**

  To standardize the use of ESA rescue therapy 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 2 criteria listed above are met.

- **RBC Transfusion**

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

Subjects who initiate rescue therapy (either ESA rescue therapy or RBC transfusion) will be required to stop study drug treatment and will be discontinued from the study (see Section 7.6.3).

8.2.7 Oral Iron Supplementation (Information on Allowed Use)

Subjects who are receiving a stable dose of oral iron supplementation for at least 28 days prior to the screening period should continue their oral iron supplementation at the same dose through the primary efficacy period (through Week 6). Changes to oral 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 adjust oral iron supplementation as needed for subjects with ferritin <100 ng/mL and TSAT is <20%, and the iron dose will be selected at the investigator's discretion.

Subjects who are not receiving oral iron supplementation at the beginning of the screening period should not start oral iron supplementation through the primary efficacy period (through Week 6) (see Section 8.4.3). Initiation of oral 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 oral iron supplementation for subjects with ferritin is <100 ng/mL and TSAT is <20%, and the iron dose 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.

Subjects should be questioned regarding dosing compliance and the information should be recorded.

8.2.9 Treatment Compliance

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

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, Intravenous Iron, and Blood Transfusion

Subjects may not receive any ESA treatment within 6 weeks prior to the screening period and through the follow-up period (eg, recombinant human erythropoietin, darbepoetin alfa, or methoxy polyethylene glycol-epoetin beta). See Section 8.2.6 for the rescue therapy guidelines.

Subjects may not receive intravenous iron or blood transfusion within 4 weeks prior to the screening period and through the follow-up period. Use of intravenous iron supplementation after Day 1 will be considered a protocol deviation but will not be considered a reason for subject discontinuation.

ESAs and RBC transfusions are allowed as rescue therapies, please refer to Section 8.2.6 for the rescue therapy guidelines. Note that 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).

8.4.3 Oral 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 oral iron supplementation through 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 Activities

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

- Eligibility screening period (Day -28 to Day -4)
- Primary efficacy period (from Day 1 to the Week 6 visit)
  - Baseline visit (Day 1)

  - Week 2 ± 1 day
  - Week 4 ± 3 days
  - Week 6 ± 3 days
- Dose adjustment and maintenance period (after the Week 6 visit to the Week 16 visit)
  - Week 8 visit ± 3 days
  - Week 10 visit ± 3 days
  - Week 12 visit ± 3 days
  - Week 14 ± 3 days
  - Week 16 (or end-of-treatment) ± 3 days
- Follow-up period (after the Week 16 visit to the Week 18 visit)
  - Week 18 ± 3 days

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same investigator or site personnel whenever possible.

9.2 Administrative Procedures

9.2.1 Informed Consent Procedure

Informed consent must be obtained and legally signed prior to a subject entering into 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) and at baseline (assessed using urine 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. Detailed information regarding the timing of the assessments is presented in Section 9.4 and summarized in Appendix A:

- 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
- Weight assessment
- 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 the Day 1 visit) and through the follow-up visit, the investigator and study site 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.

  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, except for the baseline urine pregnancy test which will be analyzed locally. 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 and urine 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) and urine pregnancy tests (to be analyzed by the local lab). The screening and baseline pregnancy test results must be available and must be negative for a subject to initiate or continue study drug. Additional pregnancy tests may be conducted during the study to establish the absence of pregnancy based on the investigator's clinical judgment or as required by local regulations.
- 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.
- Urine albumin-to-creatinine ratio (uACR): A random urine spot sample will be collected to provide the uACR. Subjects should refrain from heavy exercise 24 hours before the test.
- 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).
- Chemistry and eGFR: 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. eGFR will be calculated from serum creatinine as described in Appendix B. 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

The Schedule of Events in 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.

9.4.1 Screening Visit

The screening visit must be performed within 28 days prior to dosing and there must be a minimum of 4 days between the last qualifying repeat measurement and the baseline visit (Day 1).

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo 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 the screening visit, the following activities/procedures will be performed:

- Signing of informed consent
- Review of study inclusion and exclusion criteria
- Demographics, medical history, and physical examination
- Weight assessment
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- Prior and current medication 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.
    - Folate and vitamin B12 levels
    - CBC
    - Chemistry and eGFR
    - Iron indices

9.4.2 Baseline Visit (Day 1)

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

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

- Review of study inclusion and exclusion criteria
- Vital signs (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- 12-lead ECG (prior to blood draws when possible and obtained after the subject has been resting supine comfortably for approximately 10 minutes)
- AE review
- Recording of any concomitant medication use since screening visit
- Laboratory procedures:
    - Urine pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method). The urine sample will be analyzed by the local lab. The baseline results must be available and must be negative before the subject takes the first dose of study drug.
    - Coagulation tests (including prothrombin time, partial thromboplastin time, and international normalized ratio)
    - Urine albumin-to-creatinine ratio (uACR through random urine spot sample)
    - CBC
    - Chemistry and eGFR
    - Iron indices
    - Hepcidin
    - C-reactive protein

  - VEGF
- Dispense one bottle of study drug
- Review dosing instructions

9.4.3 Week 2 Visit

At the Week 2 visit, 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)
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR
  - Iron indices
- 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 or interruption 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 obtained from this visit demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.4.4 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 (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
  - CBC
  - Chemistry and eGFR
  - 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)
- 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 or interruption if central lab Hb result demonstrates excess Hb response
- If central lab Hb result obtained from this visit demonstrates excess Hb response, contact subject for dose reduction (Section 8.2.4)

9.4.5 Week 6 Visit

At the Week 6 visit, 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)
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
    - CBC
    - Chemistry and eGFR
    - Iron indices
    - Hepcidin
    - C-reactive protein
    - VEGF
- Collect study bottle and all remaining study drug tablets remaining from the primary efficacy period
- Dispense one bottle of vadadustat
- Subjects should be questioned regarding dosing compliance
- Review dosing instructions and remind subjects that they may be contacted by telephone to discuss dose adjustment or interruption 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)

9.4.6 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)
- AE review
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
    - CBC
    - Chemistry and eGFR
    - 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)

9.4.7 Week 16 Visit (end-of-treatment visit for subjects who complete the dose adjustment and maintenance period or for subjects who withdraw prematurely from the study prior to Week 16)

All subjects should complete the Week 16 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 9.4.8).

At the Week 16 visit, 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)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
    - Serum pregnancy test for females of childbearing potential (to be analyzed by the central lab)
    - CBC
    - Chemistry and eGFR
    - Iron indices
    - Hepcidin
    - C-reactive protein
    - VEGF
- Subjects should be questioned regarding dosing compliance

9.4.8 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 (heart rate and blood pressure should be assessed in a seated position after 5 minutes of rest and prior to blood draws)
- AE review (see Section 10.3.6 for follow-up of unresolved events)
- Rescue therapy (ESA rescue and RBC transfusion) review
- Concomitant medication review
- Laboratory procedures:
    - CBC
    - Chemistry and eGFR

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.

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

Abnormal Test Findings – All laboratory test results will be reviewed by the investigator. 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.

Renal-Related Events – Some subjects will experience a progression of their CKD during the study as part of the natural course of the disease. In addition, the study population is prone to experience acute, transient loss of kidney function of different etiologies, sometimes concomitantly complicated by progression of CKD.

To ensure consistent reporting of renal events, the following guidelines are to be used when reporting a renal-related AE:

- The following situations **should always be reported as SAEs** with the respective seriousness criteria selected (see Section 10.1.2):
    - Progression of CKD leading to chronic dialysis: Subjects who undergo transition to chronic maintenance dialysis should be reported using the verbatim SAE term of "progression to end-stage renal disease" (ESRD) and the additional seriousness criterion "chronic dialysis"
    - Any medical event requiring transient acute dialysis: Subjects who undergo transient acute dialysis should be reported using the verbatim SAE term reflecting the indication for the dialysis. Examples of verbatim AE terms include hyperkalemia, volume overload, acute kidney injury, and uremia. The additional seriousness criterion "acute dialysis" should be selected.
    - Kidney transplantation: Subject receiving a kidney transplant should be reported using the verbatim SAE term "Progression to ESRD", with the additional serious criterion of "kidney transplant" selected.
- The following situations will be **reported as SAEs if they meet seriousness criteria** (see Section 10.1.2); otherwise, they should be reported as AEs:
    - Acute kidney injury not requiring dialysis – The reported AE term should reflect the etiology for the impairment of the renal function. Non-specific AE terms such as "Decreased eGFR" or "Increased creatinine" should be avoided whenever the underlying etiology is known.
        - Examples of verbatim AE terms for prerenal impairment include hypovolemia, hepatorenal syndrome, and heart failure
        - Examples of verbatim AE terms for intrarenal impairment include acute tubular necrosis, acute interstitial nephritis, and glomerulonephritis
        - Examples of verbatim AE terms for postrenal impairment include hydronephrosis, pelvicaliectasis, and urinary tract obstruction
    - Progression of CKD not requiring dialysis – If permanent loss of renal function due to underlying CKD has occurred, the reported AE term should reflect the underlying etiology. Non-specific terms such as "Decreased eGFR," "Increased creatinine," or "Worsening CKD" should be avoided whenever the underlying etiology is known. Examples of verbatim AE terms include worsening lupus nephritis, worsening diabetic kidney disease, and worsening glomerulonephritis.
    - Medical conditions related to CKD that occur without acute kidney injury or progression of CKD – If there is no decline in kidney function, the medical complication of CKD itself should be reported. AE terms such as "Progression of CKD" or "Acute Kidney Injury," should be avoided when there is no decline in kidney function. Examples of AE terms include edema and hyperkalemia.

10.1.2 Serious Adverse Events (SAEs)

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

- Death
- Life-threatening (see paragraph below on Life-threatening)
- In-patient hospitalization or prolongation of existing hospitalization (see paragraph below on Hospitalization)
- Persistent or significant disability/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. The following events are considered medically important events for this patient population:
    - Chronic dialysis
    - Acute dialysis
    - Kidney transplantation

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 AE reporting period for a subject begins upon receiving the first dose of study medication and ends at the final protocol-required visit. In addition, SAEs that occur after the protocol-defined AE reporting period that are considered to be related to the study medication should be recorded and reported to the sponsor's medical monitor or CRO designee.

10.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the AE 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).

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

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

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

Additional information about pregnancy outcomes follows:

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

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, 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 change in Hb in Japanese subjects with anemia secondary to NDD-CKD, 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 2 Hb values obtained prior to treatment based on the qualifying screening Hb value and the Hb value at the baseline visit.

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. Therefore, no multiplicity adjustment will be needed for this analysis.

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 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. With these assumptions, the study with n=12 subjects per group will have >95% 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 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 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.

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)

If 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 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.

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Appendix A: Schedule of Activities

Please refer to Section 9.3 for detailed information regarding the study procedures and evaluations, and please refer to Section 9.4 for detailed information regarding the activities to be performed at each study visit.

	Screening	Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**-28 to -4**	**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									
Demographics, medical history, physical exam, and weight	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram		X									
Adverse event review		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
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X									X	
Urine pregnancy test		X									
Coagulation tests		X									
Folate and vitamin B12	X										

	Screening	Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**-28 to -4**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Urine albumin to creatinine ratio		X									
Complete blood count, including Hb	X	X	X	X	X	X	X	X	X	X	X
Chemistry and eGFR	X	X	X	X	X	X	X	X	X	X	X
Iron indices	X	X	X	X	X	X		X		X	
Hepcidin		X			X					X	
C-reactive protein		X			X					X	
VEGF		X			X					X	
PK pre-dose sample (study drug to be administered after sample collection)				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	Primary efficacy period (Day 1-Week 6)				Dose adjustment and maintenance period (Week 7-16)					Follow-up (Week 17-18)
Study Week	**-4 to 0**	**Base line**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16 (EOT)**	**18**
Study Day	**-28 to -4**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**
Visit Window (Days)			**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Based on Hb results from the visits noted, dose reduction for excess Hb response as needed according to guidelines (Section 8.2.4)			X	X							
Based on Hb results from the visits noted, dose adjustment to achieve target Hb 10.0-12.0 g/dL as needed according to guidelines (Section 8.2.5)					X	X	X	X	X		

Abbreviations: eGFR, estimated glomerular filtration rate; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; PK, pharmacokinetics; RBC, red blood cells; VEGF, vascular endothelial growth factor

Appendix B: Japanese Society of Nephrology 2009 Equation to Calculate eGFR

The estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine using the 2009 Japanese Society of Nephrology Equation (3-variables; Matsuo 2009).

eGFR (mL/min/1.73 m^2) = **194** x (S_{cr} in mg/dL)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if female)