AKB-6548-CI-0015

This Supplement Contains:

AKB-6548-CI-0015 (ClinicalTrials.gov Identifier: NCT02680574; EudraCT Number: 2015-004774-14)

1. Original Protocol
2. Final Protocol
3. Rationale for Change for Protocol Amendments

Date: 26 Feb 2019

CLINICAL PROTOCOL

PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE MAINTENANCE TREATMENT OF ANEMIA IN SUBJECTS WITH NON-DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD) (PRO$_2$TECT - CONVERSION)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0015
US IND Number:	102,465
EudraCT Number	2015-004774-14
Phase:	Phase 3
Status/Date:	Version 1.0/[redacted]
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Suite 1100 Cambridge, MA 02142 United States of America

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title:	Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD) (PRO_2TECT – Conversion)
Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0015
Status/Date:	Version 1.0/10 November 2015

Sponsor Approval:

By signing this form, I confirm that I have read and that I approve this protocol and that this document has been prepared in accordance with the principles of Good Clinical Practices, as outlined by the International Conference on Harmonization, and applicable regional regulations.

Signature:

[redacted]

[redacted] Date

[redacted]
Akebia Therapeutics, Inc.

1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the Investigator 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 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD) (PRO_2TECT - CONVERSION)
Protocol Number	AKB-6548-CI-0015
Study Phase	Phase 3
Investigational Product	Vadadustat; 150 mg tablets
Reference Medicinal Product	Darbepoetin alfa (Aranesp™); Amgen Inc.
Study Population	The study population will consist of subjects ≥18 years of age with NDD-CKD, estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2, and hemoglobin (HGB) between 8.0 and 11.0 g/dL (inclusive) in the United States (US) and between 9.0 and 12.0 g/dL (inclusive) outside of the US, who are currently treated with an erythropoiesis-stimulating agent (ESA) for anemia.
Investigative Sites	Approximately 450 investigative sites in North America, Latin America, Europe, and Asia Pacific.
Planned Number of Subjects	Approximately 2100 subjects.
Primary Objective	Demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with NDD-CKD after conversion from current ESA therapy.
Study Design Overview	Phase 3, randomized, open-label, active-controlled study of the efficacy and safety of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia after conversion from current ESA therapy. Following a Screening period of up to 4 weeks, subjects who meet all inclusion and no exclusion criteria will be randomized 1:1 to vadadustat or darbepoetin alfa. Randomization will be stratified by: • Geographic region (US versus European Union [EU] versus Rest of World [ROW]) • New York Heart Association congestive heart failure (CHF) Class 0 or I versus II or III • Study entry HGB (<10.0 versus ≥10.0 g/dL). Following randomization, there will be 3 periods during the study: • **Conversion and Maintenance Period (Weeks 0-52):** conversion to study treatment for maintaining HGB (Weeks 0-23), primary efficacy evaluation (Weeks 24-36), and secondary efficacy evaluation (Weeks 40-52) • **Long-Term Treatment Period (Weeks 53-End of Treatment [EOT])**: continued study medication to assess long-term safety • **Follow-Up Period (EOT + 4 weeks):** post-treatment visit (either in person or via telephone) for safety.

Study Duration	Estimated time to full enrollment of approximately 2100 randomized subjects is 20 months, and average follow-up duration is expected to be 1.8 years. All subjects will remain in the study until approximately 631 major adverse cardiovascular events (MACE) occur across 2 separate NDD-CKD studies, at which time subjects will be scheduled for a final visit and the study will close. Sites will be notified of the global study end date approximately 3 months prior to study closure (based on accrual of MACE across the 2 studies) and should inform active subjects of the global study end date thereafter.
Inclusion Criteria	1. ≥18 years of age 2. Diagnosis of CKD with an eGFR ≤60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation at Screening and not expected to start dialysis within 6 months of Screening 3. Currently maintained on ESA therapy, with the last dose received within 8 weeks prior to Screening 4. Mean Screening HGB between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) outside of the US, as determined by the average of 2 HGB values measured by the central laboratory during Screening 5. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% at Screening 6. Folate and vitamin B_{12} measurements ≥lower limit of normal at Screening 7. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.
Exclusion Criteria	1. Anemia due to a cause other than CKD or subjects with active bleeding or recent blood loss 2. Subjects with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia 3. Red blood cell (RBC) transfusion within 4 weeks prior to or during Screening 4. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2.0 x upper limit of normal (ULN) at Screening. Subjects with a history of Gilbert's syndrome are not excluded. 5. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mmHg or systolic blood pressure >180 mmHg) at Screening 6. Severe heart failure at Screening (New York Heart Association Class IV) 7. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), urgent coronary revascularization, hospitalization for CHF, or stroke within 12 weeks prior to Screening 8. History of active malignancy within 2 years prior to Screening, except for curatively resected basal cell carcinoma of skin, squamous cell carcinoma of skin, cervical carcinoma in situ, or resected benign colonic polyps 9. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) requiring active treatment within 8 weeks prior to Screening 10. History of hemosiderosis or hemochromatosis 11. History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list are not excluded), or prior stem cell or bone marrow transplant (corneal transplants are not excluded) 12. 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 the Screening visit 13. Previous participation in this study, receipt of vadadustat in another study, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) 14. Females who are pregnant or breast-feeding. Women of childbearing potential who are unable or unwilling to use an acceptable method of contraception 15. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception 16. Any other reason that in the opinion of the Investigator would make the subject not suitable for participation in the study.
Retesting/Rescreening	Subjects who initially fail to qualify for the study based on laboratory test results may be retested once within the 28-day Screening period, per Investigator discretion. Subjects who fail to meet the qualifying criteria for HGB or eGFR during a Screening period may be considered for rescreening at the discretion of the Investigator if it is felt that the subject's status has progressed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} 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	**Primary** • Mean change in HGB between Baseline (mean pretreatment HGB) and the primary evaluation period (mean HGB from Weeks 24-36) **Key Secondary** • Mean change in HGB value between Baseline (mean pretreatment HGB) and the secondary evaluation period (Weeks 40-52) • Proportion of subjects with mean HGB within the target range during the primary evaluation period (Weeks 24-36) • Mean weekly dose of intravenous (IV) elemental iron administered from Baseline to Week 52 • Proportion of subjects receiving RBC transfusion(s) from Baseline to Week 52. **Other Secondary** • Progression of CKD • Proportion of HGB values within the target range during the maintenance period (Weeks 24-52) • Confirmed HGB values <10.0 or >12.0 g/dL • ESA rescue • Dose adjustments • Maintenance of iron sufficiency (defined as ferritin ≥100 ng/mL and TSAT ≥20%) • Receiving IV iron therapy.

Safety Endpoints	• MACE, defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke
	• Individual components of MACE:
	  o All-cause mortality
	  o Non-fatal myocardial infarction
	  o Non-fatal stroke
	• Thromboembolic events: arterial thrombosis, DVT, PE, or vascular access thrombosis
	• HGB >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
	• HGB increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
	• Adverse events (AEs) and serious adverse events (SAEs)
	• Vital signs and clinical laboratory values.

Study Procedures and Assessments	See Appendix A: Schedule of Activities.
Dosage and Regimens	Subjects will be randomized 1:1 to either: Vadadustat starting dose: 2 tablets once daily (300 mg/day) Darbepoetin alfa subcutaneous (SC): initial dose as follows • For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen. • For subjects taking other ESAs, the initial dose of darbepoetin should be based on the approved local product label. For all subjects, it is recommended that no additional ESA doses be administered after Screening visit 2 (SV2) and prior to the Randomization visit. **Dose Adjustment Guidelines – All Treatment Groups** Dosing will be initiated at the Baseline visit, and the first dose of study medication (vadadustat or darbepoetin alfa) will be administered at the investigative site after other Baseline procedures have been completed. For all subjects, it is recommended that no additional ESA doses be administered after SV2 and prior to the Randomization visit. Hemoglobin will be monitored via HemoCue® point of care device throughout the study to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be adjusted or suspended. From Weeks 0 to 12, HGB will be measured via HemoCue® every 2 weeks for monitoring for dose adjustment. From Week 12 to Week 52, HGB via HemoCue® will be monitored every 4 weeks. From Week 53 through the end of the study, HGB will continue to be monitored via HemoCue® to determine if the dose of study medication will be adjusted or suspended. Hemoglobin will also be assessed with a complete blood count (CBC) through the central laboratory for efficacy and safety evaluations; however, dose adjustments should be based on the local HemoCue® HGB value. The aim is to maintain a HGB level of 10-11 g/dL in the US and 10-12 g/dL outside the US throughout the study. Adjustments to doses will be guided by an interactive web response (IWR) system based on HGB concentration and programmed Dose Adjustment Algorithms. The programmed Dose Adjustment Algorithm for vadadustat will follow the Dose Adjustment Guidelines (see below). The programmed Dose Adjustment Algorithm for darbepoetin alfa will be based on the local product label. When adjusting therapy, consider HGB rate of rise, rate of decline, and variability as well as the subject's clinical condition (ie, recent illness, volume depletion, volume overload, etc). In cases of extenuating clinical circumstances, the Investigator may

elect to dose outside the IWR system dosing recommendation to maintain the HGB within the target range. In such cases, the clinical circumstances must be documented in the subject's record and collected in the case report form (CRF).

Vadadustat

Vadadustat should be dosed according to the following Dose Adjustment Guidelines.

US

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If a dose adjustment is required to maintain HGB at the desired level, the vadadustat dose is adjusted by 1 tablet (minimum dose of vadadustat is 150 mg/day [1 tablet]; maximum dose of vadadustat is 600 mg/day [4 tablets]).
- If the HGB rises rapidly (eg, >1 g/dL in any 2-week period), reduce the dose of vadadustat by 1 tablet.
- If the HGB falls below 10.0 g/dL, increase the dose of vadadustat by 1 tablet.
- If the HGB exceeds 11.0 g/dL, interrupt vadadustat until HGB decreases to 10.5 g/dL or less then resume dosing of vadadustat with 1 fewer tablet.

Non-US

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If a dose adjustment is required to maintain HGB at the desired level, the vadadustat dose is adjusted by 1 tablet (minimum dose of vadadustat is 150 mg/day [1 tablet]; maximum dose of vadadustat is 600 mg/day [4 tablets]).
- If the HGB rises rapidly (eg, >1 g/dL in any 2-week period), reduce the dose of vadadustat by 1 tablet.
- If the HGB falls below 10.0 g/dL, increase the dose of vadadustat by 1 tablet.
- If the HGB level exceeds 12.0 g/dL, reduce the dose of vadadustat by 1 tablet. If the HGB level exceeds 13.0 g/dL, interrupt vadadustat until HGB decreases to 12.5 g/dL or less then resume dosing of vadadustat with 1 fewer tablet.

Darbepoetin alfa

For subjects randomized to darbepoetin alfa, the initial dose will be determined as follows:

- For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen.
- For subjects taking other ESAs, the initial dose of darbepoetin should be based on the approved local product label.

Following the dose conversion, darbepoetin alfa will be dosed SC, with dose adjustments guided by an IWR system implementing a Dose Adjustment Algorithm based on the approved darbepoetin alfa local product label. Darbepoetin alfa dosing is independent of the visit schedule, and the dosing schedule may shift per local standard of care and country-specific darbepoetin dosing guidelines.

Dosing Instructions	**Vadadustat** All subjects will start with 2 tablets daily (300 mg/day). Dose levels of vadadustat include 150, 300, 450, and 600 mg (available tablet strength is 150 mg). Each subject will take his/her first dose of vadadustat at the investigative site at the Baseline visit. Thereafter, vadadustat will be taken once daily on an outpatient basis. Subjects may take vadadustat with or without food. The dose should be taken at approximately the same time each day, preferably between 7 AM and 2 PM. The subject should be instructed to take any oral iron supplements at least 2 hours before or 2 hours after the dose of vadadustat. **Darbepoetin alfa** Darbepoetin alfa will be administered, stored, and dispensed according to the approved local product label.
Iron Supplementation	Investigators should prescribe iron supplementation as needed during the study to maintain ferritin ≥100 ng/mL and TSAT ≥20%. In general, only oral iron should be used for therapy. Intravenous iron use is restricted and should only be administered to subjects who have documented intolerance to oral iron and iron deficiency (eg, ferritin <100 ng/mL and/or TSAT <20%). Discontinuation of IV iron is required once the subject is no longer iron deficient (ferritin ≥100 ng/mL and TSAT ≥20%). **Important:** Because of the potential for oral iron to reduce the bioavailability of vadadustat, the study medication should not be administered concurrently with an oral iron supplement (including multivitamins containing iron). The subject should be instructed to take any oral iron supplements at least 2 hours before or 2 hours after the dose of vadadustat.
Rescue Therapy Guidelines	To ensure the safety of study subjects and to standardize the use of rescue in the study, rescue therapy guidelines are provided. 1. **ESA Rescue:** Starting at Week 6, subjects in both treatment arms will be allowed (although will not be required) to have their HGB rescued with ESA therapy, per the local standard of care. When possible, a subject on vadadustat should be on the maximum dose of vadadustat for 2 weeks prior to ESA rescue. A subject on darbepoetin alfa may rescue with another ESA per the standard of care. To qualify for ESA rescue, a subject must fulfill ALL of the following: • The subject has experienced a clinically significant worsening of their anemia or symptoms of anemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared with Baseline • The subject's HGB is <9.0 g/dL • Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal. The ESA rescue therapy should be administered as per the local institution's guidelines and per the approved local product label. While receiving ESA rescue therapy, subjects must temporarily discontinue taking study medication (vadadustat or darbepoetin alfa). Hemoglobin will be monitored throughout the study at scheduled visits as defined in the Schedule of Activities using a HemoCue® point of care device, and ESA rescue treatment should be stopped when HGB is ≥9.0 g/dL. A minimum interval must be observed prior to restarting vadadustat after the last dose of rescue medication, and treatment may be resumed after the following intervals: • 2 days after last dose of epoetin rescue • 7 days after last dose of darbepoetin alfa rescue • 14 days after last dose of methoxy polyethylene glycol-epoetin beta rescue. Following ESA rescue, the study medication should be resumed and adjusted according to the Dose Adjustment Guidelines.

	2. **RBC Transfusion:** Investigators should use their local institution's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, a RBC transfusion should be administered as clinically indicated. In less severe instances but where there may be worsening of anemia or moderate to severe symptoms of anemia, RBC transfusions are permitted at the discretion of the Investigator given the medical necessity. Study medication (vadadustat or darbepoetin alfa) may be continued during the transfusion period.
Phlebotomy	If a subject's HGB exceeds 14.0 g/dL or the rate of rise of HGB raises concern to the Investigator, the subject may be phlebotomized based on the Investigator's judgment. The method of phlebotomy will be in accordance with the investigative site's standard clinical practice.
Subject Completion, Premature Termination of Study Medication, or Withdrawal from the Study	**Subject Completion** A subject will be considered as having completed the study, regardless of whether the subject is on or off study medication, if the subject is followed until the global study end date as determined by the accrual of MACE. Subjects who continue on the study medication up to the global study end date will continue receiving vadadustat or darbepoetin alfa until the EOT visit. A post-treatment follow-up either in person or via telephone will occur approximately 4 weeks after the EOT visit. The need for rescue therapy or the occurrence of safety endpoints do not constitute study completion and are not criteria for subject withdrawal from the study or study medication (vadadustat or darbepoetin alfa). **Discontinuation of Study Medication Treatment** During the course of this long-term study, it is anticipated that subjects may temporarily interrupt or permanently discontinue study medication (vadadustat or darbepoetin alfa) for any of the following reasons: • Unacceptable toxicity or drug intolerability • Investigator discretion • Subject withdrawal of consent • Subject becomes pregnant • Development of end-stage kidney disease and initiation of ongoing chronic hemodialysis or peritoneal dialysis or receipt of a kidney transplant. (Note that a subject who receives *transient acute* dialysis may still continue study medication per Investigator discretion.) • Other reasons. **Subjects who either temporarily interrupt or permanently discontinue study medication (vadadustat or darbepoetin alfa) after randomization and prior to completion of the study should continue with study visits and assessments through Week 52 and should be followed for safety assessments after Week 52 (see "Procedures to Avoid Withdrawal or Lost to Follow-Up" below).** Unless contraindicated, treatment should be resumed wherever possible and routinely considered at every visit following study medication interruption/discontinuation. Receipt of rescue therapy is not a reason for permanent study medication discontinuation. While receiving ESA rescue, subjects must temporarily discontinue study medication, but should resume study medication following the end of rescue therapy. **Complete Withdrawal from Study Visits/Assessments** Subjects may request to be withdrawn or may be withdrawn from the study prior to completion only for the following reasons: • Death

	• Withdrawal of informed consent (complete withdrawal of consent requires a subject's refusal of ALL methods of follow-up noted in the informed consent form: procedures, participation in reduced procedures/study visits, telephone contact only or alternative contact only, source document or designated alternative contact, or access to medical records from alternative sources) • Lost to follow-up (detailed procedures to prevent subjects from becoming "lost to follow-up" are provided below and these procedures must be followed by the Investigators, their staff, and all designated study personnel).
Procedures to Avoid Withdrawal or Lost to Follow-Up	**Avoiding Study Discontinuation** As part of the informed consent process, only subjects who fully understand and agree to full participation and long-term follow-up should be consented to participate. In all cases of impending study medication discontinuation, subject request for withdrawal from study visits, or consent withdrawal, Investigators should discuss with the subject their options of continuing in the study. The Investigator should ensure understanding and documentation of the reasons for a subject's desire to stop study procedures or stop study medication. **Minimizing Lost to Follow-Up** The Investigator must make every effort to contact subjects who fail to return for scheduled visits so that they will not be declared "lost to follow-up." These actions must include, but are not limited to, the following: 1. Contact all telephone numbers for the subject and his/her listed contacts (to be collected in the source at the subject's entry into the study), as applicable. This includes making phone calls after normal business hours or on holidays or weekends. 2. Contact the subject's primary care physician, referring specialist, pharmacist, or other healthcare professional, as applicable. 3. Send email, text, and postal mail with certified letters to all of the subject's addresses and contacts, as applicable. 4. Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the subject, as applicable. 5. Utilize the internet to search for additional contact information, as applicable. 6. Check local, regional, and national public records to locate the subject or search for mortality status as allowed by law, as applicable. Once all of these actions have been exhausted and documented then the Sponsor or Sponsor representative should be contacted for additional guidance.
Study Termination/ Individual Study Site Termination	The entire study may be suspended or terminated by the Sponsor for safety or other unanticipated reasons or upon request of regulatory agencies. If this occurs, prompt notification will be given to Investigators, Institutional Review Boards (IRBs)/Institutional Ethics Committees (IECs), and regulatory authorities in accordance with regulatory requirements. The Investigator must notify the Sponsor if the study is terminated by the Investigator or the IRB/IEC at the investigative site. If the Investigator, IRB/IEC, or Sponsor decides to terminate or suspend the study conducted at a particular investigative site for safety, non-enrollment, non-compliance with the protocol, or other unanticipated reasons, the above parties will be promptly notified.

Statistical Considerations	**Primary Efficacy Endpoint Analysis** The primary efficacy endpoint is defined as the mean HGB change from Baseline (mean pretreatment HGB) to the mean HGB from Weeks 24-36 (inclusive). The primary analysis will use an analysis of variance (ANOVA), stratified by the randomization strata with strata weighted by the stratum size. A 2-sided, 95% confidence interval will be calculated for the difference between the vadadustat group and control group. Noninferiority of vadadustat will be established if the lower limit of this confidence interval is ≥-0.5 g/dL. **MACE Analysis** The MACE endpoint (adjudicated result) will be analyzed as the time from first dose of study medication to first MACE. Subjects who have not experienced an adjudicated MACE by study closure will be censored as of their last assessment time. Major adverse cardiovascular events will be analyzed using a stratified Cox proportional hazards model with a model containing treatment group. The randomization strata will be used in this analysis. The primary MACE analysis will take place at study conclusion and will be based upon all subjects in the safety population. The hazard ratio (vadadustat/control) will be estimated, together with its 95% confidence interval. As this individual study has not been powered to provide a stand-alone estimate of the hazard ratio for MACE, this interval will be considered as descriptive. The time to first MACE will also be graphically presented using Kaplan-Meier curves. The primary analysis for MACE will be performed using the safety population. These analyses will be repeated with censoring occurring 4 weeks following early discontinuation of study medication. An independent statistical analysis center will perform analyses in support of the Independent Data Monitoring Committee (IDMC).
Sample Size Estimation	For the primary efficacy analysis in this study, it will be assumed that the difference in mean change in HGB for vadadustat will be the same as the active control, darbepoetin alfa, and the common standard deviation for the mean change will be assumed to be 1.5 g/dL. The noninferiority margin of -0.5 g/dL will be used. With these assumptions and approximately 1050 subjects per treatment group, the noninferiority evaluation will have >99% power. The primary MACE analysis will be based upon all events that accrue over 2 separately planned NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015). It has been calculated that 631 events will be required overall to have 80% power to establish noninferiority with a margin of 1.25, and >90% power to establish noninferiority with a margin of 1.3, evaluated with a 2-sided 95% confidence interval assuming no difference between the treatments. The power is >90% to establish a noninferiority margin of 1.25 if the hazard ratio is 0.95 favoring vadadustat. A MACE rate of 10% annually is anticipated in both treatment arms based on a comprehensive review of available epidemiology and prospective clinical studies in the field. With 1050 subjects per treatment group enrolled in this study, approximately 20 months for accrual, and up to 36 months of follow-up, approximately 68% of the needed MACE (429) would be captured.
Independent Data Monitoring Committee	An IDMC will be established to review and discuss the available study safety data as subjects are enrolled and followed. The team will meet approximately twice per year throughout the course of the study. The IDMC will be unblinded and will include, at a minimum, a nephrologist, a cardiologist, and a biostatistician. The discussions of the IDMC will include a review of key safety data (ie, AEs, vital signs measurements, and laboratory assessments).

Endpoint Adjudication Committee (EAC)	An independent safety EAC, blinded to treatment group, will be formed prior to study commencement to adjudicate the components of the primary safety endpoints (eg, death, myocardial infarction, and stroke). Thromboembolic events will also be adjudicated by the EAC.

3 LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AST	aspartate aminotransferase (SGOT)
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CHF	congestive heart failure
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CS	clinically significant
CV	cardiovascular
CVD	cardiovascular disease
dL	deciliter
DVT	deep venous thrombosis
EAC	Endpoint Adjudication Committee
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GMP	Good Manufacturing Practice
HA	health authority
HDL	high-density lipoprotein
HGB	hemoglobin
HIF	hypoxia-inducible factor
HIFPH	hypoxia-inducible factor prolyl-hydroxylase
HIF-PHI	hypoxia-inducible factor prolyl-hydroxylase inhibitor
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization

IDMC	Independent Data Monitoring Committee
IDMS	isotope dilution mass spectrometry
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous(ly)
IWR	interactive web response
JSDT	Japanese Society for Dialysis Therapy
JSN	Japanese Society of Nephrology
KDIGO	Kidney Disease: Improving Global Outcomes
kg	kilogram
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
MACE	major adverse cardiovascular events
MCH	mean corpuscular (cell) hemoglobin
MCHC	mean corpuscular (cell) hemoglobin concentration
MCV	mean corpuscular (cell) volume
MedDRA	Medical Dictionary for Regulatory Activities
µM	micromolar
mg	milligram
mL	milliliter
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NDD-CKD	non-dialysis dependent chronic kidney disease
ng	nanogram
PD	pharmacodynamics(s)
PE	pulmonary embolism
PHD	prolyl 4-hydroxylase domain
PK	pharmacokinetic(s)
PP	per protocol
PT	prothrombin time
PTT	partial thromboplastin time
QA	quality assurance
QC	quality control
RBC	red blood cell
RDW	red cell distribution width
ROW	rest of world
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SmPC	summary of product characteristics
SV	Screening visit
TIBC	total iron binding capacity

TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	transferrin saturation
uACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHO	World Health Organization

4 BACKGROUND INFORMATION

Chronic kidney disease (CKD), defined as the presence of kidney damage or a decreased level of kidney function, is a major public health problem worldwide. Globally, CKD is estimated to affect between 8-16% of the population (Jha et al. 2013; KDIGO 2013). At the most advanced stages of CKD, end-stage renal disease (ESRD), patients require chronic dialysis or kidney transplantation to sustain life. Chronic kidney disease is not only a cause of ESRD, but is also a significant risk factor for cardiovascular disease (CVD), infection, cancer, and mortality (Iseki and Kohagura 2007).

Renal anemia often develops during the progression of CKD and is present in almost all patients with ESRD. Anemia is defined as a decrease in circulating red blood cell (RBC) mass that is usually detected by low hemoglobin (HGB) concentration. The causes of anemia in CKD include blood loss, shortened RBC lifespan, iron deficiency, erythropoietin (EPO) deficiency, and inflammation (Nurko 2006). Although many factors contribute to anemia in CKD, it occurs primarily due to an inadequate synthesis of EPO by the kidneys, leading to a deficiency in the production of RBC progenitor cells by the bone marrow. Also contributing to anemia in CKD are impaired iron homeostasis and iron loss, which often necessitate iron supplementation (Nurko 2006). Anemia in CKD patients usually occurs when the glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m^2, and is present in >90% of the patients undergoing dialysis (CKD Stage 5) (Goodkin et al. 2011).

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 and Fan 2014). In patients with anemia related to CKD, compensatory changes occur in cardiac structure and function, including an increase in cardiac output, the development of left ventricular hypertrophy, and, eventually, the development of heart failure (Metivier et al. 2000). Risk of stroke also increases with anemia, which may be an underlying mechanism leading to stroke in CKD (Abramson et al., 2003; Iseki and Kohagura 2007). 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 these patients (Iseki and Kohagura 2007; NICE 2011). Overall, anemia contributes to a poorer prognosis in patients with CKD (Nurko 2006; Iseki and Kohagura 2007).

Erythropoiesis-stimulating agents (ESAs) administered either intravenously (IV) or subcutaneously (SC), along with oral or IV iron therapy, are currently the cornerstones for treating anemia in patients with CKD. Treatment with exogenous recombinant ESAs can raise HGB levels, relieve symptoms, and reduce the complications of anemia, including RBC transfusions which carry the risks of infection, iron overload, and impact candidacy for kidney transplantation.

Clinical practice guidelines and prescribing information for approved ESAs and guidelines provided by the United States (US) Food and Drug Administration (FDA), the European Union (EU), the Japanese Society of Nephrology, and the Japanese Society for Dialysis Therapy Guideline Committee differ slightly in their recommendations for treatment of renal anemia, as summarized in Table 1.

Table 1 Treatment Guidelines and Prescribing Information for Renal Anemia in NDD-CKD

KDIGO guidelines	Treatment should occur in symptomatic patients and when HGB generally falls below 10 g/dL (Kidney Disease: Improving Global Outcomes [KDIGO] 2012).
US darbepoetin alfa label	Same as other approved ESAs, but also recommend that if HGB exceeds 10 g/dL in adults not on dialysis, the dose of ESA should be reduced or interrupted (Aranesp® US Package Insert 2015).
EU practice guidelines	Recommend that in high-risk patients with NDD-CKD, treatment with ESAs should be initiated when the HGB levels are between 9 g/dL and 10 g/dL, although in low-risk patients and those in whom a clear benefit of quality of life can be foreseen, the initiation of ESA therapy could be considered at higher HGB levels (Locatelli 2013).
Japan practice guidelines	JSDT recommends that ESA treatment be initiated when HGB is below 11 g/dL following a diagnosis of renal anemia in NDD-CKD. JSN 2013 does not provide a clear recommendation or maintenance range for HGB. Both guidelines recommend that if the HGB exceeds 13 g/dL, the dose of ESA should be reduced or interrupted. In patients with CVD or complications, ESA treatment should be reduced or interrupted if the HGB exceeds 12 g/dL (Tsubakihara 2010; Japanese Society of Nephrology 2014).

Abbreviations: CVD = cardiovascular disease; ESA = erythropoietin stimulating agent; EU = European Union; HGB = hemoglobin; JSDT = Japanese Society for Dialysis Therapy; JSN = Japanese Society of Nephrology; KDIGO = Kidney Disease Improving Global Outcomes; NDD-CKD = non-dialysis dependent chronic kidney disease; US = United States.

The majority of patients with CKD currently receives interventional therapy in the form of iron therapy, and may initiate therapy with an ESA if other interventions fail and HGB levels fall below 9 to 11 g/dL, dependent upon local clinical practice guidelines.

A number of large, prospective, randomized controlled trials in CKD (Stages 3 to 5) have explored the potential benefit of ESAs in patients with CKD with respect to overall mortality, cardiovascular (CV) events, and progression of CKD with higher HGB targets (≥13 g/dL) (Besarab et al. 1998; Drüeke et al. 2006; Singh et al. 2006; Pfeffer et al. 2009a; Pfeffer et al. 2009b). These trials did not demonstrate the expected beneficial effects of correcting anemia on these outcomes, but suggested an increased risk of death and CV events when targeting higher HGB levels (Besarab et al. 1998; Drüeke et al. 2006; Singh et al. 2006; Pfeffer et al. 2009a; Pfeffer et al. 2009b). Additional analyses from these trials suggest that the risk of death or CV events appears to be highest in CKD patients who fail to respond to ESAs, as indicated by lower achieved HGB levels and higher average ESA dose requirements (Szczech et al. 2008; Solomon et al. 2010). This suggests that in some subjects the ESAs themselves, and not the HGB level, may be causative of the increase in events. This is supported by studies in CKD patients on dialysis with naturally high HGB levels and no increase in CV events (Goodkin et al. 2011).

The risks identified with ESAs from these trials have led to changes in prescribing information and practice guidelines in the US, the EU, and Japan that guide clinicians toward more cautious use of ESAs and targeting lower HGB levels. In the US, the mortality and CV risks associated with ESAs are outlined in a black-box warning in the prescribing information of ESAs with a recommendation to use the lowest dose possible to avoid transfusions. While no similar major warnings exist in the EU Summary of Product Characteristics (SmPC) or on the approved labeling for ESAs in Japan, the EU SmPCs for ESAs do suggest caution with the use of these

drugs, with a recommendation to keep HGB levels below 12 g/dL, while the Japanese practice guidelines recommend ESA treatment be reduced or interrupted if the HGB exceeds 12 g/dL in patients with CVD or complications. Further, recent EU clinical practice guidelines (Locatelli et al. 2013) recommend 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 decisions to use ESAs for the treatment of anemia.

The risks associated with ESAs, including an increased risk of death and CV events, highlight the need for additional therapies that might minimize or avoid these risks when compared to currently available recombinant protein-based ESAs. Therefore, the unmet medical need for the treatment of anemia in non-dialysis dependent CKD (NDD-CKD) patients remains high, especially from a CV safety perspective. To fulfill this unmet need, the vadadustat clinical program is focused on developing an orally active therapeutic for the treatment of anemia in patients with CKD.

4.1 Hypoxia-Inducible Factor Prolyl-Hydroxylase Inhibitors

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

Vadadustat is a novel, synthetic, orally bioavailable, small molecule being developed as an inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIFPHs) for the treatment of anemia associated with CKD. Hypoxia-inducible factor prolyl-hydroxylase enzymes are also referred to as prolyl 4-hydroxylase domains (PHDs), of which the 2 most commonly expressed are PHD2 and PHD3. Vadadustat is a slightly more potent inhibitor of PHD3 (50% inhibitory concentration [IC_{50}] = 0.08 μM) than of PHD2 (IC_{50} = 0.19 μM). The inhibition of PHD3 and PHD2 stabilizes hypoxia-inducible factor (HIF)-2α and HIF-1α, which in turn stimulates the production of EPO. In vivo animal efficacy and messenger ribonucleic acid (mRNA) data indicate that vadadustat induces the production of EPO from both renal and extra-renal sites (liver and brain), and this increase in EPO results in an increase in RBC production in the bone marrow. In clinical trials, vadadustat has been shown to facilitate iron homeostasis by decreasing hepcidin and increasing transferrin levels in healthy adult male volunteers and male and female CKD patients. This enables iron transport mechanisms that should enhance the terminal steps of erythropoiesis. Vadadustat offers the potential of flexible oral dosing that provides a more gradual and reliable means of titration than injectable hormones. Therefore, vadadustat is being developed as an alternative to the existing protein hormone ESAs.

4.2 Summary of Clinical Experience

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

To date, the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of vadadustat have been characterized in 6 completed Phase 1 studies in healthy volunteers, 1 completed Phase 1 study in subjects undergoing chronic hemodialysis, 3 completed Phase 2a studies in NDD-CKD subjects, and 1 completed Phase 2b study in NDD-CKD subjects. The Phase 2a studies evaluated Stages 3, 4, and 5 CKD (not on dialysis) subjects in a single-dose PK study, a multi-dose, 28-day, open-label, dose escalation pilot study, and a randomized, placebo-controlled study with 5 different dose groups dosed for 42 days. The Phase 2b study evaluated Stages 3, 4, and 5 CKD (pre-dialysis). A total of 379 subjects have received

vadadustat, including 125 healthy volunteers and 254 subjects with CKD (242 subjects with Stage 3, 4, or 5 not on dialysis and 12 subjects with ESRD or Stage 5 on dialysis). An additional 94 subjects have been dosed with vadadustat in a recently completed open-label, dose range finding efficacy study in subjects with ESRD on dialysis for 16 weeks of dosing.

Overall, vadadustat has been well-tolerated and has demonstrated consistent, dose proportionate PK and PD. Vadadustat has demonstrated the desired and anticipated effects of raising EPO concentrations in a dose-dependent manner in Phase 1 and Phase 2a 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 have stimulated an increase in reticulocytes and HGB. Vadadustat has generally been well-tolerated with limited adverse events (AEs) and serious adverse events (SAEs) observed to date. The urinary excretion of the compound has been shown to be less than 50% in healthy human volunteers, which makes the compound appropriate for use in subjects with CKD.

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. 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 HGB levels and changes in HGB. A significantly higher proportion of subjects with a successful HGB response at the end of treatment was observed with vadadustat treatment when compared with placebo. The dosing algorithm was effective in minimizing excessive HGB levels (>13.0 g/dL) and a consistent and sustained improvement in iron mobilization was observed with treatment with vadadustat. The safety profile of vadadustat in this study was generally consistent with that observed in prior studies.

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

4.3 Potential Benefits and Risks

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

Vadadustat offers the potential of flexible oral dosing that is easier to titrate than injectable hormone ESAs. This alternate therapeutic approach may avoid the overshoots and fluctuations in HGB levels seen with currently available injectable ESAs and provide for a controlled, steady rise in HGB concentration. This less aggressive approach to modifying the HGB concentration may be of benefit based on the FDA's suggestion that fluctuations in HGB concentrations, rapidly increasing HGB levels, and overshoots of the target level are associated with an increased risk of CV events (Unger 2007; Unger et al. 2010).

In addition, since HIFs downregulate the iron absorption regulator hepcidin, and upregulate the iron-mobilizing regulators ferroportin and transferrin (and its receptor) (Peyssonnaux et al. 2007), vadadustat will likely enhance iron metabolism and transport, thereby enhancing 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 (Chuvash polycythemia, etc). In the completed clinical studies, vadadustat has been generally well-tolerated.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

The primary objective of this study is to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with NDD-CKD after conversion from current ESA therapy.

5.2 Primary Efficacy Endpoint

The primary endpoint used to assess the efficacy objective will be the mean change in HGB between Baseline (mean pretreatment HGB) and the primary evaluation period (mean HGB from Weeks 24-36).

5.3 Secondary Efficacy Endpoints

Key secondary efficacy endpoints include the following:

- Mean change in HGB value between Baseline (mean pretreatment HGB) and the secondary evaluation period (Weeks 40-52)
- Proportion of subjects with mean HGB within the target range during the primary evaluation period (Weeks 24-36)
- Mean weekly dose of IV elemental iron administered from Baseline to Week 52
- Proportion of subjects receiving RBC transfusion(s) from Baseline to Week 52.

Other secondary efficacy endpoints include:

- Progression of CKD
- Proportion of HGB values within the target range during the maintenance period (Weeks 24-52)
- Confirmed HGB values <10.0 or >12.0 g/dL
- ESA rescue
- Dose adjustments
- Maintenance of iron sufficiency (defined as ferritin ≥100 ng/mL and transferrin saturation [TSAT] ≥20%)
- Receiving IV iron therapy.

5.4 Safety Endpoints

Safety endpoints in this study include the following:

- Major adverse cardiovascular events (MACE), defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke
- Individual components of MACE:
  - All-cause mortality
  - Non-fatal myocardial infarction
  - Non-fatal stroke
- Thromboembolic events: arterial thrombosis, deep vein thrombosis (DVT), pulmonary embolism (PE), or vascular access thrombosis
- HGB >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
- HGB increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
- AEs and SAEs
- Vital signs and clinical laboratory values
- Adrenal function assessment in a subset of subjects (see Appendix C: ACTH (Cosyntropin) Stimulation Test for Adrenal Function Monitoring).

6 STUDY DESIGN

6.1 Study Design

This is a Phase 3, randomized, open-label, active-controlled study of the efficacy and safety of vadadustat versus darbepoetin alfa for maintenance treatment of anemia after conversion from current ESA therapy in subjects with NDD-CKD. Target enrollment in this study is approximately 2100 subjects at approximately 450 investigative sites in North America, Latin America, Europe, and Asia Pacific.

Subjects will be randomized at the Baseline visit using an Interactive Web Response (IWR) system to receive either vadadustat or darbepoetin alfa. For all subjects, it is recommended that no additional ESA doses be administered after Screening visit 2 (SV2) and prior to the Randomization visit.

To monitor adrenal function, a subset of 100 subjects per treatment arm (200 subjects total) in the EU will also undergo sequential adrenocorticotropic hormone (ACTH [cosyntropin]) adrenal stimulation tests at Baseline (predose), as well as at the Week 12 and Week 52 study visits, or at the end of treatment (EOT) visit if the subject permanently discontinues study medication early prior to the Week 52 study visit (Appendix C: ACTH (Cosyntropin) Stimulation Test for Adrenal Function Monitoring).

Randomization will be stratified by geographic region (US versus EU versus rest of world [ROW]), New York Heart Association congestive heart failure (CHF) Class 0 or I versus II or III, and study entry HGB level (<10.0 g/dL versus ≥10.0 g/dL based on the most recent central laboratory HGB measurement prior to the Baseline/Randomization visit). Following randomization, there will be 3 periods during the study:

- Conversion and Maintenance Period (Weeks 0-52): conversion to study medication for maintaining HGB (Weeks 0-23), primary efficacy evaluation (Weeks 24-36), and secondary efficacy evaluation (Weeks 40-52)
- Long-term Treatment Period (Week 53-EOT): continued study medication to assess long-term safety
- Follow-up Period (EOT + 4 weeks): post-treatment visit for safety (either in person or via telephone).

A HemoCue® point of care device will be used throughout the study to monitor HGB to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be adjusted. From Weeks 0 to 12, HemoCue® will be used to monitor HGB every 2 weeks for dose adjustment. From Week 12 to Week 52, HGB will be monitored via HemoCue® every 4 weeks. From Week 53 through the end of study, HGB will continue to be monitored via HemoCue® to determine if the dose of study medication will be adjusted or suspended. Hemoglobin will also be assessed with a complete blood count (CBC) through the central laboratory for efficacy and safety evaluations; however, dose adjustments should be based on the HemoCue® HGB value.

The aim of the dosing strategy is to maintain HGB levels of 10.0 g/dL to 11.0 g/dL in the US and 10.0 g/dL to 12.0 g/dL outside of the US throughout the study.

Subjects assigned to vadadustat will initiate dosing at 2 tablets once daily at the Baseline visit. Adjustments to doses for vadadustat will be guided by an IWR system based on HGB concentration and a programmed Dose Adjustment Algorithm (Section 8.4.4.1, Vadadustat Dosing and Dose Adjustment Guidelines). Dosing will be suspended if HGB rises to >11.0 g/dL (US investigative sites) or >13.0 g/dL (non-US investigative sites), and will not be restarted until HGB levels are reduced to ≤10.5 g/dL (US investigative sites) or ≤12.5 g/dL (non-US investigative sites) (see Section 8.4.4.1, Vadadustat Dosing and Dose Adjustment Guidelines for details regarding dose suspension).

Subjects assigned to darbepoetin alfa will be dosed SC at the Baseline visit and the initial dose will be determined based on the approved local product label. Dose adjustments will be guided by an IWR system implementing a programmed Dose Adjustment Algorithm based on the local product label (Section 8.4.4.2, Darbepoetin Alfa Dosing and Dose Adjustment Guidelines). Darbepoetin alfa dosing is independent of the visit schedule, and the dosing schedule may shift per local standard of care and country specific dosing guidelines.

Investigators should prescribe iron supplementation as needed during the study to maintain ferritin ≥100 ng/mL and TSAT ≥20% (see Section 8.4.6, Iron Supplementation for details regarding iron supplementation during the study).

Clinical and safety assessments (including laboratory assays, PK evaluations [both vadadustat parent compound and metabolites], MACE endpoint data, vital sign measurements, and AEs) will be performed as indicated at Screening, during the Conversion and Maintenance Period (Weeks 0-52), during the Long-term Treatment Period (visits approximately every 3 months), and during the Follow-up Period (4 weeks after the EOT). Refer to Section 9, Study Procedures and Schedule of Activities and Appendix A: Schedule of Activities for additional details.

All subjects will remain in the study until approximately 631 MACE occur across 2 separately planned NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015), at which

time subjects will be scheduled for a final visit and the study will close (see Section 11.1.2, Sample Size for the Primary Safety Endpoint).

6.2 Rationale for Study Design

During prior clinical trials, vadadustat has been well-tolerated, and has demonstrated consistent, dose proportionate PK and PD. Vadadustat has demonstrated the desired and anticipated effects of raising EPO concentrations in a dose-dependent manner in Phase 1 and Phase 2 studies. The changes in EPO have been accompanied by dose responsive increases in iron mobilization (increased TIBC and transferrin and decreased hepcidin and ferritin). Together, these effects have stimulated an increase in reticulocytes and HGB. Vadadustat has generally been well-tolerated with limited AEs. Finally, the urinary excretion of vadadustat has been shown to be less than 50% in humans which makes the compound appropriate for evaluation in subjects with CKD. Based on the Phase 1 and Phase 2 study results, continued development of vadadustat as a treatment for anemia in patients with CKD is warranted.

In this study, darbepoetin alfa was chosen as an active comparator as it has a longer half-life than epoetin alfa and, therefore, requires less frequent dosing visits. Selection of a comparator is challenging in the current medical and regulatory climate given the accumulating trial findings that resulted in the FDA revising the prescribing information for the currently marketed ESAs. These trial results indicate an increased risk of death and adverse CV events, such as stroke and heart failure, particularly when using ESAs to achieve a higher HGB concentration. In the US, the mortality and CV risks associated with ESAs are outlined in a black-box warning in the prescribing information of ESAs, with a recommendation to use the lowest dose possible to avoid transfusions. While no similar major warnings exist in the EU SmPC or on the approved labeling for ESAs in Japan, the EU SmPCs for ESAs do suggest caution with the use of these drugs, with a recommendation to keep HGB levels below 12 g/dL. Recent clinical practice guidelines (Locatelli et al. 2013) recommend that risk factors for stroke and malignancy should also be taken into account when making treatment decisions to use ESAs for the treatment of anemia.

Given the concerns associated with marketed ESAs, a goal of this study will be to evaluate the CV events during the treatment of anemia with vadadustat. The inclusion of a MACE endpoint in this study will allow for a statistical comparison of the rates of CV events between vadadustat and darbepoetin alfa treatment groups when used to treat anemia associated with NDD-CKD. While the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (Pfeffer et al 2009b) compared different HGB targets, the present study will have similar HGB targets between treatment arms. Importantly, the HGB goals for this study are lower than those used in TREAT and are consistent with practice guidelines and prescribing information for approved ESAs.

This study will be performed as an open-label study. Because HGB values are objective and will be measured via a central laboratory for all efficacy endpoints, efficacy assessments are not considered to be subject to bias with an open-label design. Blinding of this study presented inherent practical problems, including potential dosing errors, inappropriate dose adjustments, and delays in dosing, which may also increase the safety risk to study participants. Given the differing dosing regimens and routes for vadadustat (oral) and darbepoetin alfa (SC injection), a double-dummy design would have been required which also created ethical concerns and required extensive coordination to maintain the blind. The Sponsor and contract research

organization (CRO) study teams will remain blinded to the randomization codes. In addition, the study will involve blinded adjudication of MACE, the use of an independent data monitoring committee (IDMC), and an identical schedule of visits, procedures, and assessments for both treatment groups in order to reduce the potential for bias. However, certain personnel directly involved in medical oversight of the study, regulatory reporting of safety information, and on-site monitoring activities may become unblinded to the treatment assignments of individual subjects during the course of the study.

6.3 Dose Justification

The starting dose and the proposed dosing algorithm in this study are designed to increase and maintain HGB in a predictable and controlled manner while minimizing abrupt increases or excessive rises in HGB levels. Based on plasma concentrations and PD measures from previously conducted clinical studies with vadadustat, a population PK/PD model was developed. Using this model and the proposed dosing algorithm, simulations were carried out to evaluate the effects of different starting doses and the resulting HGB responses to support the dosing rationale. Results of the simulations indicated that a starting dose regimen of 300 mg once daily along with the proposed dosing algorithm are optimal to increase and maintain HGB levels of 10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL outside of the US while minimizing excessive rises.

6.4 Independent Data Monitoring Committee

An IDMC will be established to review and discuss study safety data as subjects are enrolled and followed. The team will meet approximately twice per year throughout the course of the study. The IDMC will be unblinded and will include, at a minimum, a nephrologist, a cardiologist, and a biostatistician. The discussions of the IDMC will include a review of key safety data (ie, AEs, vital signs, and laboratory assessments). Written records of the IDMC meetings, the materials reviewed, and the decisions made will be maintained. Details on the roles and responsibilities of the IDMC and guidelines for monitoring study safety data will be described further in the IDMC charter.

6.5 Endpoint Adjudication Committee

An independent safety endpoint adjudication committee (EAC) will be formed prior to study commencement to adjudicate the primary safety endpoints (death, myocardial infarction, and stroke). Thromboembolic events will also be adjudicated by the EAC. The committee will be blinded throughout the course of the study. The EAC will be composed of independent experts with experience and training appropriate for adjudication of MACE and thromboembolic events. Details on the responsibilities of the EAC will be described further in the EAC charter.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 General Criteria

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

An optional Pre-Screen visit can be used to perform initial testing of the HGB level using a local point of care device to evaluate whether a subject should progress to full Screening procedures. A separate Pre-Screen informed consent (distinct from the full protocol informed consent) will be implemented for the Pre-Screen visit. To be eligible for the Pre-Screen HGB measurement, a study subject or their legally acceptable representative must provide valid informed consent prior to the Pre-Screen procedure. For a better understanding of the Pre-Screening visit, please see Section 9.3.1, Pre-Screening Visit.

7.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible:

1. At least 18 years of age
2. Diagnosis of CKD with an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation at Screening (see Appendix B: CKD-EPI Creatinine Equation) and not expected to start dialysis within 6 months of Screening
3. Currently maintained on ESA therapy with the last dose received within 8 weeks prior to Screening
4. Mean Screening HGB between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) outside of the US, as determined by the average of 2 HGB values measured by the central laboratory during Screening
5. Serum ferritin ≥100 ng/mL and TSAT ≥20% at Screening
6. Folate and vitamin B_{12} measurements ≥lower limit of normal (LLN) at Screening
7. 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 presenting with <u>any</u> of the following will not qualify for entry into the study:

1. Anemia due to a cause other than CKD or subjects with active bleeding or recent blood loss
2. Subjects with 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. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2.0 x upper limit of normal (ULN) at Screening. Subjects with a history of Gilbert's syndrome are not excluded.
5. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mmHg or systolic blood pressure >180 mmHg) at Screening
6. Severe heart failure at Screening (New York Heart Association Class IV)
7. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), urgent coronary revascularization, hospitalization for CHF, or stroke within 12 weeks prior to Screening
8. History of active malignancy within 2 years prior to Screening, except for curatively resected basal cell carcinoma of skin, squamous cell carcinoma of skin, cervical carcinoma in situ, or resected benign colonic polyps
9. History of DVT or PE requiring active treatment within 8 weeks prior to Screening

10. History of hemosiderosis or hemochromatosis
11. History of prior organ transplantation or scheduled organ transplant (subjects on kidney transplant wait-list are not excluded), or prior stem cell or bone marrow transplant (corneal transplants are not excluded)
12. 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 the Screening visit
13. Previous participation in this study, receipt of vadadustat in another study, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI)
14. Females who are pregnant or breast-feeding. Women of childbearing potential who are unable or unwilling to use an acceptable method of contraception (refer to Section 9.1.3, Contraception and Pregnancy Avoidance Measures)
15. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception (refer to Section 9.1.3, Contraception and Pregnancy Avoidance Measures)
16. 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

Subjects who fail to qualify for the study based on certain laboratory parameters may be retested and/or rescreened at the discretion of the Investigator.

7.4.1 Retesting

Subjects who initially fail to qualify for the study based on laboratory test results may have their laboratory value retested 1 time within the 28-day Screening period at the discretion of the Investigator. Retesting within the 28-day Screening period does not constitute rescreening; however, if retesting falls outside of the 28-day Screening period, it should be considered a rescreen. All Screening laboratories, including any repeat measurements, must be performed within the 28-day Screening window with a minimum of 4 days between the last qualifying repeat measurement and the Baseline visit.

For eligibility purposes, if HGB at SV1 is 11.1-11.5 g/dL in the US or 12.1-12.5 g/dL outside of the US, 1 retest CBC should be performed prior to SV2. If retest HGB is >11.0 g/dL in the US or >12.0 g/dL outside the US, the subject should not proceed with SV2. If the HGB at SV1 is >11.5 g/dL in the US or >12.5 g/dL outside of the US, the subject should not proceed with any further Screening at this time.

7.4.2 Rescreening

Subjects who fail to meet the qualifying criteria for HGB or eGFR during a Screening period may be considered for rescreening at the discretion of the Investigator if it is felt that the subject's status has progressed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} values may be considered for rescreening after receiving replacement therapy.

Screening is limited to 3 attempts (Screening and 2 additional rescreening attempts). If IV iron is used to replete iron stores, the last dose of IV iron must be administered at least 4 weeks prior to rescreening.

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 Subject Completion, Study Discontinuation, and Withdrawal of Subjects

7.5.1 Subject Completion

A subject will be considered as having completed the study, regardless of whether they are on or off study medication (vadadustat or darbepoetin alfa), if the subject is followed until the global study end date as determined by the accrual of MACE (see Section 11.1.2, Sample Size for the Primary Safety Endpoint). A post-treatment follow-up either in person or via telephone should occur approximately 4 weeks after the EOT visit. The need for rescue therapy does not constitute study completion and is not a criterion for subject withdrawal from the study. The occurrence of a safety endpoint also does not constitute study completion and is not a criterion for subject withdrawal from the study or study medication (vadadustat or darbepoetin alfa).

7.5.2 Entire 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, Criteria for Premature Termination or Suspension of the Study.

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, Criteria for Premature Termination or Suspension of Investigational Study Sites and Section 14.3, Procedures for Premature Termination or Suspension of the Study or Investigational Sites.

7.5.4 Individual Subject Discontinuation

During the course of this long-term study, it is anticipated that subjects may temporarily interrupt or permanently discontinue study medication (vadadustat or darbepoetin alfa) or study participation for any of the following reasons:

- Unacceptable toxicity or drug intolerability
- Investigator discretion
- Subject withdrawal of consent
- Subject becomes pregnant
- Development of end-stage kidney disease and initiation of ongoing chronic hemodialysis, peritoneal dialysis, or receipt of a kidney transplant. (Note that a subject who receives *transient acute* dialysis may still continue study medication per Investigator discretion.)
- Other reasons.

Subjects who temporarily interrupt or permanently discontinue study medication (vadadustat or darbepoetin alfa) early or are withdrawn from the study prior to Week 52 should continue with the Schedule of Activities and safety assessments through Week 52 and should be followed for safety assessments only after Week 52. Subjects who stop study medication after Week 52

should be followed for safety assessments only for the remainder of the study (See Sections 7.5.4.1, Temporary Interruption of Study Medication and 7.5.4.2, Permanent Discontinuation of Study Medication, and Appendix A: Schedule of Activities).

Receipt of rescue therapy is not a reason for permanent study medication discontinuation. While receiving ESA rescue, subjects must temporarily discontinue study medication (vadadustat or darbepoetin alfa), but should resume study medication once rescue therapy has ended, as detailed in Section 8.4.7, Rescue Therapy.

As part of the informed consent process, only subjects who fully understand and agree to full participation and long-term follow-up should be consented to participate.

7.5.4.1 Temporary Interruption of Study Medication

Subjects who temporarily interrupt study medication (vadadustat or darbepoetin alfa) treatment after the first dose and prior to completion of the study will continue with study visits and assessments. Unless contraindicated, treatment should be resumed wherever possible and routinely considered at every visit following study medication discontinuation. If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

7.5.4.2 Permanent Discontinuation of Study Medication

If a subject wishes to discontinue study medication (vadadustat or darbepoetin alfa) or withdraw from the study, the Investigator should encourage continued study participation, as described in Section 7.5.4.4, Procedures to Encourage Continued Study Participation. A subject who permanently discontinues treatment will be recorded as a discontinuation on the case report form (CRF), and the Investigator must document the primary reason for the discontinuation.

Subjects who permanently discontinue study medication early or are withdrawn from the study prior to Week 52 should continue with the Schedule of Activities and safety assessments through Week 52 and should be followed for safety assessments only after Week 52. Subjects who stop study medication after Week 52 should be followed for safety assessments only for the remainder of the study (See Appendix A: Schedule of Activities).

For subjects who permanently discontinue study medication, the Investigator should resume standard of care treatment, including ESAs and iron therapy, as deemed appropriate.

7.5.4.3 Complete Withdrawal from Further Study Visits/Assessments

Subjects may request to be withdrawn from the study or may be withdrawn prior to completion only for the following reasons of:

- Death
- Withdrawal of informed consent (complete withdrawal of consent requires a subject's refusal of ALL methods of follow-up noted in the informed consent form: procedures, participation in reduced procedures/study visits, telephone contact only or alternative contact only, source document or designated alternative contact, or access to medical records from alternative sources)
- Lost to follow-up (detailed procedures to prevent subjects from becoming lost to follow-up are provided in Section 7.5.4.5, Procedures to Prevent "Lost to Follow-up",

and these procedures must be followed by the Investigators, their staff, and all designated study personnel).

7.5.4.4 Procedures to Encourage Continued Study Participation

In all cases of impending study drug discontinuation or subject request for withdrawal, the Investigator should discuss with the subject their options of continuing in the study. If a subject wishes to discontinue study medication (vadadustat or darbepoetin alfa) or to withdraw from the study, the following procedures should take place:

1. The Investigator should understand the subject's motivation to discontinue or withdraw (eg, study visit fatigue, study medication intolerability, etc) and wherever possible make accommodations to prevent treatment discontinuation or complete withdrawal of consent and to maintain the fullest compliance with the protocol assessments (eg, provide necessary travel reimbursement, in-home visits, alternate visit scheduling, including during weekends). If the subject's wish is to discontinue study medication only, proceed to Step 2.
2. Ask the subject, "Would you be willing to continue if your dose of medication was lowered?" If the answer is "Yes", titrate the subject's dose down 1 level for vadadustat or reduce the dose or dosing frequency for darbepoetin alfa. Repeat this step if the subject continues to request withdrawal of consent. If the answer is "No" or if, once the lowest dose is reached, the subject continues to request discontinuation from study medication, proceed to Step 3.
3. Ask the subject, "If we temporarily interrupt your study medication would you be willing to later resume medication and continue with all visits and sample collections?" If the answer is "Yes", interrupt study medication but continue to follow all other study procedures for the subject until they restart treatment. If the answer is "No", proceed to Step 4.
4. Ask the subject, "If we discontinue your study medication permanently, would you continue with all visits and sample collections?" If the answer is "Yes", discontinue study medication, continue with all other assessments until Week 52, and then continue with safety assessments only for the remainder of the study after Week 52. If the answer is "No", proceed to Step 5.
5. If further study support, interruption, or permanent discontinuation of study medication does not resolve the subject's issues, further accommodations such as less frequent visits or blood draws may be used, so long as adequate safety monitoring can be ensured for those continuing study medication treatments. Less frequent visits or procedures should be offered only if they are required to maintain access to the subject's medical information and/or to encourage the subject to continue in the study. For subjects who are no longer on study medication after Week 52, study visits can be reduced to every 24 weeks for safety assessments only either in person or via telephone.

7.5.4.5 Procedures to Prevent "Lost to Follow-up"

The Investigator must make every effort to contact subjects who fail to return for scheduled visits so that they will not be declared "lost to follow-up." These actions must include, but are not limited to, the following:

1. Contact all numbers for the subject and their listed contacts (to be collected in source at the subject's entry into the study), as applicable. This includes making calls after normal business hours or on holidays and weekends.
2. Contact the subject's primary care physician, referring specialist, pharmacist, and/or other healthcare professional (using the contacts provided by the subject at entry into the study), as applicable
3. Send a text, email, and postal mail with certified (return-receipt requested) letters to the subject's addresses and all contacts, as applicable
4. Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures which may indicate the status of the subject (as allowed through release of medical record forms to be completed by the subject at study entry), as applicable
5. Utilize the internet to search for additional contact information (eg, reverse directory for phone numbers or new address information, Facebook, LinkedIn, or other social media for status updates), as applicable
6. Check local, regional, and national public records to locate the subject or search for mortality status as allowed by law, as applicable.

Once these actions have been exhausted and documented, the Sponsor's clinical research associate or Medical Monitor should be contacted for additional guidance.

8 STUDY PRODUCT AND TREATMENT OF SUBJECTS

8.1 Study Product, Supplies, and Storage

Oral vadadustat and darbepoetin alfa for injection will be provided and shipped by the Sponsor or its designated supplier/distributor. Both vadadustat and darbepoetin alfa will be supplied as open-label supplies. All study medication supplies must be kept in a temperature-controlled, locked facility, accessible only to authorized study personnel.

Cosyntropin for the adrenal function substudy will be sourced by the investigative site.

The Investigator or designated study personnel will be responsible for preparing study medication for dispensing to the subject (Section 8.2, Dispensing Procedures) and for study medication supply accountability (Section 8.3, Product Accountability and Destruction).

8.1.1 Vadadustat

Vadadustat will be provided as 150 mg white to off-white, round, bi-convex film-coated tablets for oral administration. The tablets will be packaged in high-density polyethylene bottles with child-resistant closures, polypropylene liner, and induction seal. Labeling will be in accordance with current Good Manufacturing Practices (GMP) and local regulatory requirements.

Dose levels utilized in this study will include: 150 mg (1 tablet), 300 mg (2 tablets), 450 mg (3 tablets), and 600 mg (4 tablets) per day.

Vadadustat should be stored at a controlled room temperature of 15°-30°C (59°-86°F).

8.1.2 Darbepoetin Alfa

Darbepoetin alfa will be provided in its commercially-approved primary packaging and stored per the local product label.

See the approved darbepoetin alfa local product label for further description and detail.

8.2 Dispensing Procedures

The Investigator will maintain record of all vadadustat tablets and darbepoetin alfa injections dispensed to and returned from each subject during the study. Subjects will receive either vadadustat tablets or darbepoetin alfa according to the randomization assignments provided via the IWR system (see Section 8.4.2, Randomization).

8.2.1 Dispensing of Vadadustat

Subjects will be provided with a supply of vadadustat at the Baseline visit according to the IWR system assignment. Resupply of additional vadadustat at subsequent visits will be managed via the IWR system and will be dependent on the current dose level of vadadustat and the number of tablets remaining in the subject's current vadadustat supply at a given study visit (Section 8.4.4.1, Vadadustat Dosing and Dose Adjustment Guidelines). Subjects will be instructed to finish 1 bottle before opening a new bottle.

At the Baseline visit, study subjects will be provided with 1 bottle of vadadustat. Each bottle of vadadustat will contain 100 tablets of vadadustat (150 mg tablets).

Subjects should be instructed to bring unused vadadustat 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 redispensed to the subject during the dosing phase of the study.

8.2.2 Dispensing of Darbepoetin Alfa

The initial darbepoetin alfa dose will be determined as follows:

- For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen.
- For subjects taking other ESAs, the initial dose of darbepoetin should be based on the approved local product label.

Dispensing of additional darbepoetin alfa at subsequent dosing visits will be managed by the IWR system (Section 8.4.4.2, Darbepoetin Alfa Dosing and Dose Adjustment Guidelines).

8.3 Product Accountability and Destruction

Product accountability should be an ongoing process throughout the study. All study medication (vadadustat and darbepoetin alfa) must be accounted for and any discrepancies explained. The Investigator or designated study personnel are responsible for keeping accurate records of the clinical supplies received from the Sponsor, all supplies retained in inventory at the investigative site, and study medication dispensed to or returned from each subject. Records will be maintained that accurately reflect the drug accountability of vadadustat and darbepoetin alfa 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 Investigator
- 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 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.

All unused and/or partially used vadadustat or darbepoetin alfa 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 vadadustat or darbepoetin alfa 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.

8.4 Treatment of Subjects

8.4.1 Treatment Group Assignments

Subjects will be randomized in a 1:1 ratio via the IWR system to either:

- Vadadustat (starting dose of 2 tablets once daily [300 mg/day])
- Darbepoetin alfa (starting dose based on the approved local product label)

For all subjects, it is recommended that no additional ESA doses be administered after SV2 and prior to the Randomization visit.

Target enrollment for each treatment group is approximately 1050 subjects.

8.4.2 Randomization

This study will be open to approximately 2100 subjects with NDD-CKD with an eGFR ≤60 mL/min/1.73 m^2 (pre-dialysis).

Using an IWR system, eligible subjects will be assigned using permuted block randomization and a 1:1 ratio to either vadadustat or darbepoetin alfa during their Baseline visit.

To maintain balance between vadadustat-treated and darbepoetin alfa-treated subjects, randomization will be stratified with respect to: 1) geographic region (US versus EU versus

ROW); 2) New York Heart Association CHF Class (0 or I versus II or III); and 3) study entry HGB level (<10.0 versus ≥10.0 g/dL, based on the most recent central laboratory HGB measurement prior to the Baseline/Randomization visit).

8.4.3 Blinding

This will be an open-label study. Treatment assignment will be done through the IWR system and the Investigator will not be aware of which treatment will be assigned next. Treatments will be administered in an open-label fashion; however, the Sponsor and CRO study teams will be blinded to the randomization codes. In addition, the study will involve blinded adjudication of MACE, the use of an IDMC, and an identical schedule of visits, procedures, and assessments for both treatment groups in order to reduce the potential for bias. However, certain personnel directly involved in medical oversight of the study, regulatory reporting of safety information, and on-site monitoring activities may become unblinded to the treatment assignments of individual subjects during the course of the study.

In geographies where regulatory approval does not require a formal analysis of MACE, efficacy and safety analyses may be performed upon the completion of 52 weeks of post-randomization follow-up in a sufficient number of subjects to support registration in that geography. The unblinding of the treatment assignments for this analysis will be detailed in the Statistical Analysis Plan (SAP). The EAC will remain blinded throughout the full course of the study.

8.4.4 Dosing and Dose Adjustment Guidelines

Dosing will be initiated at the Baseline visit, and the first dose of study medication (vadadustat or darbepoetin alfa) will be administered at the investigative site after other Baseline visit procedures have been completed. For all subjects, it is recommended that no additional ESA doses be administered after SV2 and prior to the Randomization visit.

Hemoglobin will be monitored via HemoCue® throughout the study to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be adjusted. From Weeks 0 to 12, HGB will be obtained via HemoCue® every 2 weeks for monitoring for dose adjustment. From Week 12 to Week 52, HGB will be monitored every 4 weeks via HemoCue®. From Week 53 through the study end, HGB will continue to be monitored via HemoCue® to determine if the dose of study medication will be adjusted or suspended. Hemoglobin will also be assessed with a CBC through the central laboratory for efficacy and safety evaluations; however, dose adjustments should be based on the HemoCue® HGB value.

<u>The aim is to maintain a HGB level of 10-11 g/dL in the US and 10-12 g/dL outside of the US throughout the study.</u>

Adjustments to doses for vadadustat and darbepoetin alfa will be guided by an IWR system based on HGB concentration and programmed Dose Adjustment Algorithms. The programmed Dose Adjustment Algorithm for vadadustat will follow the Dose Adjustment Guidelines (see below). The programmed Dose Adjustment Algorithm for darbepoetin alfa will be based on the local product label.

When adjusting therapy, consider HGB rate of rise, rate of decline, and variability, as well as the subject's clinical condition (ie, recent illness, volume depletion, volume overload, etc). In cases of extenuating clinical circumstances, the Investigator may elect to dose outside the IWR system

dosing recommendation to maintain the HGB within the target range. In such cases, the clinical circumstances must be documented in the subject's record and collected in the CRF.

8.4.4.1 Vadadustat Dosing and Dose Adjustment Guidelines

Subjects assigned to vadadustat will initiate dosing at 2 tablets once daily (300 mg/day). Dose levels of vadadustat utilized in this study include 150, 300, 450, and 600 mg (available tablet strength is 150 mg).

Dosing will be initiated at the Baseline visit and the first dose of vadadustat will be administered at the investigative site (study physician's clinic) after other Baseline visit procedures have been completed. Thereafter, vadadustat will be taken once daily on an outpatient basis. Subjects may take vadadustat with or without food and should be instructed to swallow the tablet(s) whole. Subjects should be instructed to take vadadustat at roughly the same time each day, preferably between 7 AM and 2 PM.

During the study, vadadustat should be dosed according to the following Dose Adjustment Guidelines.

For subjects enrolled in a **US investigative site**, the following guidelines should be followed:

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If a dose adjustment is required to maintain HGB at the desired level, the vadadustat dose is adjusted by 1 tablet (minimum dose of vadadustat is 150 mg/day [1 tablet]; maximum dose of vadadustat is 600 mg/day [4 tablets]).
- If the HGB rises rapidly (eg, >**1.0 g/dL** in any 2-week period), reduce the dose of vadadustat by 1 tablet.
- If the HGB falls below **10.0 g/dL**, increase the dose of vadadustat by 1 tablet.
- If the HGB level exceeds **11.0 g/dL**, interrupt vadadustat until the HGB decreases to 10.5 g/dL or less then resume dosing of vadadustat with 1 fewer tablet.

For subjects enrolled in **investigative sites outside of the US** (non-US), the following guidelines should be followed:

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If a dose adjustment is required to maintain HGB at the desired level, the vadadustat dose is adjusted by 1 tablet (minimum dose of vadadustat is 150 mg/day [1 tablet]; maximum dose of vadadustat is 600 mg/day [4 tablets]).
- If the HGB rises rapidly (eg, >**1.0 g/dL** in any 2-week period), reduce the dose of vadadustat by 1 tablet.
- If the HGB falls below **10.0 g/dL**, increase the dose of vadadustat by 1 tablet.
- If the HGB level exceeds **12.0 g/dL**, reduce the dose of vadadustat by 1 tablet. If the HGB level exceeds **13.0 g/dL**, interrupt vadadustat until the HGB decreases to 12.5 g/dL or less then resume dosing of vadadustat with 1 fewer tablet.

8.4.4.2 Darbepoetin Alfa Dosing and Dose Adjustment Guidelines

For subjects randomized to receive darbepoetin alfa, the initial dose will be determined as follows:

- For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen.
- For subjects taking other ESAs, the initial dose of darbepoetin should be based on the approved local product label.

Each subject will receive their first dose of darbepoetin alfa at the Baseline visit. Subsequent administration of darbepoetin alfa may occur at the clinic or may be self-administered at home per regional standard of care. Darbepoetin alfa dosing is independent of the visit schedule, and the dosing schedule may shift per local standard of care and country-specific darbepoetin alfa dosing guidelines.

8.4.5 Late or Missed Doses

Subjects on vadadustat 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 during the same day. If a forgotten dose is not remembered on the same day, the subject should skip the dose and resume the normal dosing schedule the following day. Subjects should not double-up on missed doses.

Subjects on darbepoetin alfa should be instructed to take the study medication, including handling of late or missed dosed, as described in the approved local product label.

Subjects should be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).

8.4.6 Iron Supplementation

Investigators should prescribe iron supplementation as needed during the study to maintain ferritin ≥100 ng/mL and TSAT ≥20%. In general, only oral iron should be used for therapy. Intravenous iron use is restricted and should only be administered to subjects who have documented intolerance to oral iron and are iron deficient (eg, ferritin <100 ng/mL and/or TSAT <20%). Discontinuation of IV iron is required once the subject is no longer iron deficient (ie, ferritin ≥100 ng/mL and TSAT ≥20%).

Important: Because of the potential for iron to reduce the bioavailability of vadadustat, the study medication should not be administered concurrently with an oral iron supplement (including multivitamins containing iron). The subject should be instructed to take any oral iron supplement at least 2 hours before or 2 hours after the dose of vadadustat.

8.4.7 Rescue Therapy

To ensure the safety of study subjects and to standardize the use of rescue in the study, rescue therapy guidelines are provided.

8.4.7.1 ESA Rescue (Optional)

Starting at Week 6, subjects in both treatment arms will be allowed (although will not be required) to have their HGB rescued with ESA therapy per the local standard of care. Drug product and supplies for ESA rescue will not be provided by the Sponsor.

If possible, a subject on vadadustat should be on a maximum dose of vadadustat for 2 weeks prior to ESA rescue. A subject on darbepoetin alfa may rescue with another ESA per the standard of care. To qualify for ESA rescue, a subject must fulfill ALL of the following:

- The subject has experienced a clinically significant worsening of their anemia or symptoms of anemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared with Baseline
- The subject's HGB is <9.0 g/dL
- Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal.

The ESA rescue therapy should be administered as per the local institution's guidelines and per the approved local product label. While receiving ESA rescue therapy, subjects must temporarily discontinue taking study medication (vadadustat or darbepoetin alfa). Hemoglobin will be monitored throughout the study at scheduled visits as defined in the Schedule of Activities using HemoCue®, and ESA rescue treatment should be stopped when HGB is ≥9.0 g/dL. A minimum interval must be observed prior to restarting vadadustat after the last dose of rescue medication, and treatment may be resumed after the following intervals:

- 2 days after last dose of epoetin rescue
- 7 days after last dose of darbepoetin alfa rescue
- 14 days after last dose of methoxy polyethylene glycol-epoetin beta rescue.

Following ESA rescue, the study medication should be resumed at the same dose as previously used and adjusted according to the Dose Adjustment Guidelines (Section 8.4.4, Dosing and Dose Adjustment Guidelines).

8.4.7.2 Red Blood Cell Transfusion

Investigators should use their local institution's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, a RBC transfusion should be administered as clinically indicated. In less severe instances but where there may be worsening of anemia or moderate to severe symptoms of anemia, RBC transfusions are permitted at the discretion of the Investigator given the medical necessity. Study medication (vadadustat or darbepoetin alfa) may be continued during the RBC transfusion period.

8.4.8 Phlebotomy

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

8.4.9 Treatment Compliance

Subjects will be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa). The Investigator will also maintain drug accountability logs itemizing all study medications dispensed to and returned from each subject during the study. Treatment compliance will be determined from these forms along with the subject questioning and the study medication dispensing CRFs.

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

Subjects will also be questioned regarding the timing of their last dose of vadadustat prior to the PK samples at the Week 4, 12, 28, and 52 study visits. The date and time of these doses will be recorded on the CRF.

8.4.10 Continuation of Treatment

Subjects may receive study medication (vadadustat or darbepoetin alfa) up until the EOT visit.

8.5 Prior and Concomitant Therapy

8.5.1 General

All medications taken within 30 days prior to the start of study medication and during the study should be recorded on the appropriate CRF. In addition, the ESA and iron treatment regimen prior to randomization and the date of last dose will be recorded.

8.5.2 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 the Screening visit. In addition, subjects should not have participated in a study with another HIF-PHI.

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

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

Please see Appendix A: Schedule of Activities for a detailed table of the Schedule of Activities.

This study includes the following visits:

- Optional Pre-Screening
- Two Screening visits (SV1 and SV2)
- Baseline/Randomization visit (Week 0/Day 1)
- Year 1 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 2, 4, 6, 8, 10, 12, and every 4 weeks thereafter until Week 52
- Year 2 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 64, 76, 88, and 104

- Year 3 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 116, 128, 140, and 156
- Year 4 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 168, 180, 192, and 208
- EOT visit
- Follow-up visit: 4 weeks after the EOT.

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

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent must be obtained prior to the subject entering into the study and before any protocol-directed procedures are performed (including Screening activities). Subjects participating in the optional Pre-Screening visit must sign an abbreviated consent form or full consent form prior to Pre-Screening and, if eligible, may proceed with the Screening visit after full consent has been obtained (see Section 9.3.1, Pre-Screening Visit and Section 15.3, Subject Information and Consent for additional details). Additionally, subjects may be asked to provide a separate, optional consent to obtain and store a blood sample(s) for future genetic analyses.

A subset of 200 subjects (100 subjects per treatment arm) in the EU will be selected to undergo sequential ACTH (cosyntropin) stimulation testing to monitor adrenal function (see Appendix C: ACTH (Cosyntropin) Stimulation Test for Adrenal Function Monitoring). A separate optional informed consent form must be signed at SV1 prior to participation in this substudy.

9.1.2 Documentation of Screen Failures

Investigators will maintain documentation of Pre-Screening activities, to include information on potential study candidates evaluated and reasons that subjects considered for the study did not qualify.

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

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

9.1.3 Contraception and Pregnancy Avoidance Measures

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 have not yet been conducted with vadadustat, and there are no data on the transmission of vadadustat in breast milk or the effect of vadadustat on infants.

Although the potential risk of vadadustat on the developing fetus is limited based on studies to date, the study requires that all subjects must agree to use adequate contraception throughout the study and for 30 days after the last dose of study medication.

Adequate contraception is defined as follows:

Female subjects must be surgically sterile, postmenopausal (no menses for at least one year), or have negative pregnancy test results at Screening (serum).

Female subjects not surgically sterile or postmenopausal (no menses for at least one year) and non-vasectomized male subjects must practice at least 1 of the following methods of birth control:

- Total abstinence from sexual intercourse (minimum 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 or intrauterine contraception/device
- Double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap *together with* spermicidal foam/gel/film/suppository).

9.1.4 Laboratory Accreditation and Reference Ranges

The Investigator and the Sponsor will maintain a copy of the laboratory accreditation and the reference ranges for the central laboratory used for clinical laboratory evaluations. Additionally, other accreditation(s) will be collected as required.

9.2 Study Procedures and Evaluations

9.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study:

- Medical history, demographics, and physical examination: Medical history, demographic information, and physical examination (including height) will be collected at SV2. 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. After SV2, an abbreviated, symptom-directed physical examination should be performed at the discretion of the Investigator as clinically indicated.
- Vital signs: Vital signs will include heart rate and blood pressure. Heart rate and blood pressure will be assessed in the seated position after 5 minutes of rest. Vital signs will be collected at SV1, SV2, Baseline, during study visits, and EOT and should be taken prior to blood draws when possible.
- Weight: Weight will be collected for all subjects at SV2, at Weeks 12, 24, 36, and 52, yearly thereafter, and at the EOT visit. For subjects on darbepoetin alfa, subjects will be weighed for dosing as per the local standard of care.

- 12-Lead electrocardiogram (ECG): A standard 12-lead ECG will be performed at Baseline. The ECG should be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and should be taken prior to vital sign assessments and blood draws when possible. With the subject in a supine position, obtain the 12-lead tracing. All ECGs will be reviewed by the Investigator for the presence of rhythms of potential clinical concern. A record of the tracing(s) will be made and retained with other source documents.
- Completion of MACE Endpoint Questionnaire: At each post-randomization study visit, the subject must specifically be questioned regarding the occurrence of any potential MACE endpoint event since the last study visit. **IMPORTANT: The endpoint questionnaire electronic CRF must be completed in full at each visit even if no potential MACE endpoints have occurred.** If a potential endpoint event is reported, the date of the event should be recorded and the appropriate source documents should be collected according to the endpoint packet checklist.
- AE Assessments: Beginning with the first dose of study medication (vadadustat or darbepoetin alfa) and through the global study end (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 (see Section 10, Adverse Events). Subjects must be followed for AEs until the final required protocol visit (global study end date) or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
- Concomitant Medication Recording: All medications (both prescription and non-prescription, and including vitamins, herbals, topicals, inhaled, and intranasal) taken within 30 days prior to the start of study medication (vadadustat or darbepoetin alfa) and through the EOT 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. In addition, the ESA and iron treatment regimen prior to randomization and date of last dose will be recorded.

9.2.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis. Detailed instructions for the collection, processing, and shipment of laboratory samples will be provided by the Sponsor and the central laboratory. The Investigator is responsible for reviewing laboratory results for clinical significance.

The following laboratory evaluations will be conducted during the course of the study:

- Pregnancy test: A serum pregnancy test will be performed at SV2 for females of childbearing potential. Additional serum or local urine pregnancy tests may be conducted throughout the study in sufficient number, as determined by the Investigator or required by local regulations, to establish the absence of pregnancy during the study. The SV2 results must be available and must be negative before the subject takes the first dose of study medication.

- CBC: A CBC with differential will be performed at Baseline and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208. At all other noted visits in Appendix A: Schedule of Activities, including SV1 and SV2, a CBC without differential will be performed. The CBC with differential will include: HGB, hematocrit, RBCs, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

  Hemoglobin assessed by central laboratory CBC will be used for evaluations of efficacy and safety, but should not be used for dose adjustments. Rather, HGB levels assessed by HemoCue® should be used for dose adjustments, as described in Section 8.4.4, Dosing and Dose Adjustment Guidelines.

  For eligibility purposes, if HGB at SV1 is 11.1-11.5 g/dL in the US or 12.1-12.5 g/dL outside of the US, 1 retest CBC should be performed prior to SV2. If retest HGB is >11.0 g/dL in the US or >12.0 g/dL outside the US, the subject should not proceed with SV2. If the HGB at SV1 is >11.5 g/dL in the US or >12.5 g/dL outside of the US, the subject should not proceed with any further Screening at this time. Refer to Sections 7.4.1, Retesting and 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening period.
- Point of care HGB: Using HemoCue®, HGB will be monitored throughout the study to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be adjusted or suspended as described in Section 8.4.4, Dosing and Dose Adjustment Guidelines.
- Reticulocyte count: An automated reticulocyte count (both absolute and percent) will be performed at Baseline and at Weeks 4, 12, 28, and 52.
- Coagulation tests: Blood samples will be drawn at Baseline to assess the prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Folate and Vitamin B_{12}: A blood sample will be drawn at SV2 to assess the folate and Vitamin B_{12} levels.
- Urine albumin-to-creatinine ratio (uACR): A random urine spot sample should be collected at the investigative site during the Baseline visit to provide the uACR. Subjects should refrain from heavy exercise 24 hours before the test.
- C-reactive protein: A blood sample for C-reactive protein will be collected at the Baseline visit.
- Serum Chemistry: Blood samples to assess serum chemistry will be collected at SV2, Baseline, and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208. At all other noted visits in Appendix A: Schedule of Activities, serum creatinine and eGFR will be performed. The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen (BUN), creatine phosphokinase (CPK), uric acid, albumin, and total protein.

Note: When a ≥50% decline in eGFR from the Baseline value is observed, a repeat central laboratory measure should be performed within 30 to 60 days.

- Liver Function Tests: Blood samples to assess liver function will be collected at SV2, Baseline, every 4 weeks through Week 28, every 8 weeks from Week 28 to Week 52, and twice annually from Week 53 through the end of the study. Blood samples will also be collected at the EOT visit. Liver function tests will include: total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, and lactate dehydrogenase (LDH).
- Iron indices: Blood samples to assess the iron indices will be collected at SV1, Baseline, every 4 weeks through Week 12, every 8 weeks from Week 12 to Week 52, and every 12 weeks from Week 53 through the end of the study. Blood samples will also be collected at the EOT visit. Assessments will include the following indices: ferritin, iron, TIBC, and TSAT.
- Lipid Profile: Blood samples will be collected at the Baseline, Week 28, and Week 52 visits to assess the cholesterol levels and will be tested for the following types of lipids: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.
- Biomarkers (hepcidin, vascular endothelial growth factor [VEGF]): Samples for biomarker analysis will be drawn at the Baseline, Week 12, Week 28, and EOT visits.
- EPO: Blood samples for EPO analysis will be obtained at Baseline and at Weeks 4, 12, 28, and 52.
- PK Evaluations (samples to be drawn only for subjects randomized to vadadustat): Plasma samples for PK evaluation will be collected to analyze for both the parent compound (vadadustat) and its metabolites. Collection time points for PK will include Weeks 4, 12, 28, and 52.

  Samples should be collected along with the other laboratory samples being collected at the study visit. Subjects will be questioned regarding the timing of their last dose of vadadustat prior to the collection of PK samples. The date and time of these doses will be recorded by the sites.
- Exploratory Samples: Additional blood and urine samples will be collected at Baseline and Week 28 which may be used for exploratory measurement of biomarkers (eg, factors relating to the activation of the HIF pathway). Subjects will also be asked to provide optional consent to obtain and store a blood sample for future genetic analyses (eg, DNA, mRNA).
- ACTH (Cosyntropin) Stimulation Test: An ACTH (cosyntropin) stimulation test will be performed at Baseline and at Weeks 12 and 52 (or at the EOT visit if the subject permanently discontinues study medication early prior to the Week 52 study visit) in a subset of 200 subjects in the EU. During the stimulation test, serum cortisol will be measured prior to cosyntropin administration, and again 30 and 60 minutes after cosyntropin administration. Cosyntropin will be administered 0.25 mg (full vial) IV push. Depending on the results of the test, early morning cortisol and ACTH measurements may be required to confirm the clinical significance of the results in

individual subjects (see Appendix C: ACTH (Cosyntropin) Stimulation Test for Adrenal Function Monitoring).

9.3 Schedule of Activities

The Schedule of Activities (see Appendix A: Schedule of Activities) 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 Pre-Screening Visit

To minimize Screen failures, there will be an optional Pre-Screening visit which will enable the subject to have a HemoCue® HGB prior to proceeding with full Screening. Subjects will need to sign an abbreviated Pre-Screening informed consent form or full consent form prior to Pre-Screening. If the Pre-Screen HemoCue® HGB is between 8.0 and 11.0 g/dL (inclusive) in the US or between 9.0 and 12.0 g/dL (inclusive) outside the US, the investigative site may proceed with SV1, which preferably will occur on the same day as Pre-Screening.

9.3.2 Screening Visits

Subjects will need to sign a full consent form prior to Screening. The Screening period is a maximum of 28 days in duration. Two Screening visits (SV1 and SV2) must be performed within 28 days prior to dosing (Baseline visit or Day 1). There must be a minimum of 4 days between the 2 Screening visits and a minimum of 4 days between SV2 and the Baseline visit.

The Investigator will maintain a log of subjects (both Pre-Screened and Screened) and indicate who of the Pre-Screened subjects were brought in for informed consent and Screening and who of the Screened subjects were enrolled or excluded and the reason for exclusion.

After obtaining informed consent and receiving a unique subject identification number, subjects will undergo a number of Screening activities.

9.3.2.1 Screening Visit 1 (SV1)

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

- Informed consent (including an additional optional consent for blood samples for future genetic analyses. Also includes an additional optional consent for a substudy of adrenal function in a subset of 200 subjects in the EU.)
- Review of eligibility criteria
- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Laboratory procedures:
    - CBC (without differential)
    - Iron indices.

If the HGB at SV1 is 11.1-11.5 g/dL in the US or 12.1-12.5 g/dL outside of the US, 1 retest CBC should be performed prior to SV2. If the retest HGB is >11.0 g/dL in the US or >12.0 g/dL outside the US, the subject should not proceed with SV2. If the HGB at SV1 is >11.5 g/dL in the US or >12.5 g/dL outside of the US, the subject should not proceed with any further Screening at this time. Refer to Sections 7.4.1, Retesting and 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening period.

9.3.2.2 Screening Visit 2 (SV2)

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

- Review of eligibility criteria
- Physical examination
- Demographics and medical history
- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws), as well as height and weight
- Laboratory procedures:
  - Folate and vitamin B_{12} levels
  - CBC (without differential)
  - Serum chemistry including serum creatinine and eGFR
  - Liver function tests
  - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method)
- Prior and current medication use.

The mean of 2 HGB values from the central laboratory must be between 8.0 and 11.0 g/dL (inclusive) in the US or between 9.0 and 12.0 g/dL (inclusive) outside the US to qualify for inclusion into the trial. If the subject's HGB does not qualify after SV1 and/or SV2 +/- 1 retest HGB, the subject should be considered a Screen failure.

9.3.2.3 Subject Retesting

Subjects who initially fail to qualify for the study based on laboratory test results may be retested once within the 28-day Screening period, per Investigator discretion (Section 7.4.1, Retesting).

9.3.3 Subject Rescreening

Subjects who fail to meet the qualifying criteria for HGB or eGFR during the Screening period may be considered for rescreening at the discretion of the Investigator if it is felt that the subject's status has progressed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} values may be considered for rescreening after receiving replacement therapy. Screening is limited to 3 attempts (Screening and 2 additional rescreening attempts) (Section 7.4.2, Rescreening).

9.3.4 Baseline Visit (Day 1)

The Baseline visit must be performed within 28 days of the 2 Screening visits (SV1 and SV2) and a minimum of 4 days must elapse between the last Screening visit (SV2) and the Baseline visit.

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

- Randomization
- 12-lead ECG (prior to vital sign assessments and blood draws)
- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Laboratory Procedures:
  - Random spot urine sample for uACR

  - Coagulation Tests
  - C-reactive protein
  - CBC (including differential)
  - Reticulocyte count
  - Serum chemistry including serum creatinine and eGFR
  - Liver function tests
  - Iron indices
  - Lipid profile
  - EPO
  - Biomarkers (hepcidin, VEGF)
  - Exploratory samples
  - ACTH (cosyntropin) stimulation test (for a subset of subjects in the EU)
- Review of medical history for new conditions since Screening visit
- Medication use since Screening visit
- Study medication assessments and procedures:
  - Subject will take their first dose of study medication at the investigative site during the Baseline visit
  - HGB by HemoCue® for dose initiation
  - Vadadustat dispensing
  - Darbepoetin alfa dispensing (per local product label)
  - Oral iron supplementation as needed to maintain ferritin ≥100 ng/mL and TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
- AE assessment as needed (after receiving the first dose of study medication).

9.3.5 Year 1 Treatment Period Visits (Day 2 through Week 52)

During the Year 1 Treatment Period visits at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, the following activities/procedures will be performed:

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Weight (Weeks 12, 24, 36, and 52)
- Laboratory procedures:
  - CBC (Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52; differential at Weeks 28 and 52)
  - Reticulocyte count (Weeks 4, 12, 28, and 52)
  - Serum chemistry (Weeks 28 and 52)
  - Serum creatinine and eGFR (Weeks 4, 8, 12, 20, 36, and 44; also at Weeks 28 and 52 as part of the serum chemistry)
  - Liver function tests (Weeks 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52)
  - Iron indices (Weeks 4, 8, 12, 20, 28, 36, 44, and 52)
  - Lipid profile (Weeks 28 and 52)
  - EPO (Weeks 4, 12, 28, and 52)
  - Biomarkers (Weeks 12 and 28)
  - PK (Weeks 4, 12, 28, and 52; see Section 9.2.2, Laboratory Evaluations; samples to be drawn only for subjects randomized to vadadustat)
  - Exploratory samples (Week 28)

  - ACTH (cosyntropin) stimulation test (Weeks 12 and 52 for a subset of subjects in the EU)
- Record date and time of subject's last dose of vadadustat prior to the PK sample (Weeks 4, 12, 28, and 52)
- Safety assessments:
  - AE assessment
  - RBC transfusions and ESA rescue collection
  - Therapeutic phlebotomy collection
  - MACE endpoint questionnaire
- Medication assessments and procedures:
  - Review of concomitant medications
  - HGB by HemoCue® for dose adjustment
  - Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
  - Vadadustat dispensing as needed per Section 8.2.1, Dispensing of Vadadustat
  - Darbepoetin alfa dispensing (per local product label)
  - Iron supplementation as needed to maintain ferritin ≥100 ng/mL and TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
  - Question subject regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).

9.3.6 Year 2 Treatment Period Visits (Weeks 53 through 104)

During the Year 2 Treatment Period visits at Weeks 64, 76, 88, and 104, the following activities/procedures will be performed:

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Weight (Week 104)
- Laboratory Procedures:
  - CBC (Weeks 64, 76, 88, and 104; differential at Weeks 76 and 104)
  - Serum chemistry including serum creatinine and eGFR (Weeks 76 and 104)
  - Liver function tests (Weeks 76 and 104)
  - Iron indices (Weeks 64, 76, 88, and 104)
- Safety assessments:
  - AE assessment
  - RBC transfusions and ESA rescue collection
  - Therapeutic phlebotomy collection
  - MACE endpoint questionnaire
- Medication assessments and procedures:
  - Review of concomitant medications
  - HGB by HemoCue® for dose adjustment
  - Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
  - Vadadustat dispensing as needed per Section 8.2.1, Dispensing of Vadadustat
  - Darbepoetin alfa dispensing (per local product label)

- Iron supplementation to maintain ferritin ≥100 ng/mL and TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
- Question subject regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).

9.3.7 Year 3/4 Treatment Period Visits (Weeks 116 through 208)

During the Year 3/4 Treatment Period visits at Weeks 116, 128, 140, 156, 168, 180, 192, and 208, the following activities/procedures will be performed:

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Weight (Weeks 156 and 208)
- Laboratory Procedures:
  - CBC (Weeks 116, 128, 140, 156, 168, 180, 192, and 208; differential at Weeks 128, 156, 180, and 208)
  - Serum chemistry including serum creatinine and eGFR (Weeks 128, 156, 180, and 208)
  - Liver function tests (Weeks 128, 156, 180, and 208)
  - Iron indices (Weeks 116, 128, 140, 156, 168, 180, 192, and 208)
- Safety assessments:
  - AE assessment
  - RBC transfusions and ESA rescue collection
  - Therapeutic phlebotomy collection
  - MACE endpoint questionnaire
- Medication assessments and procedures:
  - Review of concomitant medications
  - HGB by HemoCue® for dose adjustment
  - Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
  - Vadadustat dispensing as needed per Section 8.2.1, Dispensing of Vadadustat
  - Darbepoetin alfa dispensing (per local product label)
  - Iron supplementation to maintain ferritin ≥100 ng/mL and TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
  - Question subject regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).

9.3.8 End of Treatment Visit

End of treatment evaluations will be performed when the study is ended. Subjects who prematurely discontinue study medication for any reason should attend all subsequent protocol-defined study visits and be continually monitored according to the Schedule of Activities for the duration of the study.

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

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws), as well as weight
- Laboratory Procedures:
  - CBC (without differential)
  - Serum creatinine and eGFR
  - Liver function tests
  - Iron indices
  - Biomarkers (hepcidin, VEGF)
  - ACTH (cosyntropin) stimulation test (the test will only be performed at the EOT visit for subjects who are part of the adrenal function substudy and who have permanently discontinued study medication early prior to the Week 52 study visit.)
- Safety assessments:
  - AE assessment
  - RBC transfusions and ESA rescue collection
  - Therapeutic phlebotomy collection
  - MACE endpoint questionnaire
- Recording of concomitant medications
- Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
- Question subject regarding dosing compliance and whether they have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).

9.3.9 Follow-Up Visit

The Follow-up visit will be conducted in person or via the telephone 4 weeks after the EOT visit. The following activities/procedures will be performed:

- AE assessment
- RBC transfusions and ESA rescue collection
- Therapeutic phlebotomy collection
- MACE endpoint questionnaire.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

For the purposes of this study, an AE is any untoward medical occurrence 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, 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 (with the exception of kidney transplant, see below).

Pre-existing Conditions – In this study, a pre-existing condition (ie, a disorder present before the AE reporting period started and noted on the pretreatment 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 will 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 an AE. 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.

Worsening of Anemia – In this study, it is possible that some subjects may experience a worsening of anemia. As the primary endpoint of this study assesses HGB response, worsening of anemia is captured as part of this efficacy parameter. 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 over the course of this 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 valid and consistent reporting of renal events, the following guidelines are to be used when reporting a renal-related AE:

- Acute kidney injury – If a decline and recovery of renal function has occurred, the reported AE term should reflect whether the renal event was of a prerenal, intrarenal, or postrenal etiology (see below). Non-specific terms such as decreased eGFR or increased creatinine should be avoided whenever the underlying etiology is known.
    - Examples of AE terms for a prerenal etiology include: hypovolemia, hepatorenal syndrome, and heart failure
    - Examples of AE terms for an intrarenal etiology include: acute tubular necrosis, acute interstitial nephritis, and glomerulonephritis
    - Examples of AE terms for a postrenal etiology include: hydronephrosis, pelvicaliectasis, and urinary tract obstruction.
- Progression of CKD – If permanent loss of renal function due to underlying CKD has occurred, the reported AE term should reflect the underlying etiology of the pre-existing CKD. Non-specific terms such as decreased eGFR or increased creatinine should be avoided whenever the underlying etiology is known.
    - Examples of AE terms include: lupus nephritis, diabetic kidney disease, and glomerulonephritis
- Progression of CKD Associated with Chronic Dialysis – Subjects who undergo transition to chronic maintenance dialysis should have the event recorded as an AE and classified as serious (refer to Section 10.1.2, Serious Adverse Events); *the verbatim AE term should be "progression of CKD"* with the outcome denoted as "Chronic Dialysis".
- Transient Acute Dialysis - Subjects who undergo transient acute dialysis should have the event recorded as an AE and classified as serious (refer to Section 10.1.2, Serious Adverse Events); *the verbatim AE term should reflect the indication requiring dialysis* (eg, hyperkalemia, volume overload, acute kidney injury, etc.).

- Transplantation – During this long-term study, it is possible that some subjects may receive a kidney transplant. Subjects should have these events recorded as AEs and classified as serious (refer to Section 10.1.2, Serious Adverse Events). *The verbatim AE term should be "progression of CKD" with the outcome denoted as "Kidney Transplantation".*
- Medical conditions related to kidney disease but without loss of renal function – In these cases the complication should be reported instead of progression of CKD or acute kidney injury.
    - Examples of AE terms include: edema and hyperkalemia.

10.1.2 Serious Adverse Events

Each AE is to 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.

In addition to the above criteria for classifying AEs as serious, the following situations will also be classified as serious for purposes of this study:

- Dialysis or Transplantation-Events requiring transition to chronic, ongoing dialysis, or requiring an acute transient course of dialysis, or requiring an immediate kidney transplantation (ie, not pre-planned) will be classified as serious. Guidance for the reporting of these events is provided in Section 10.1.1, Adverse Events.

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 AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization – Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE unless an untoward event occurs

related to the procedure (eg, elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the course of the study).

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

10.2 Eliciting Adverse Event Information

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

10.3 Reporting

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

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

10.3.1 Reporting Period

The AE reporting period for this study begins upon receiving the first dose of study medication (vadadustat or darbepoetin alfa) and ends at the final protocol-required visit.

In addition, any AE that occurs subsequent to the AE reporting period that the Investigator assesses as possibly or probably related to the study medication should also be reported as an AE.

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 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
- A description of the event, including event term(s), seriousness criteria, and a clinical summary of the event
- Causality assessment.

Information about all SAEs (either initial or follow-up information) should be collected and recorded in English on the electronic SAE Report Form within the electronic data capture (EDC) system. The Investigator must assess the relationship to each specific component of the study treatment. When the form is completed, CRO personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the internet, a paper 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). When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up information relating to an SAE must be reported to the Sponsor's Medical Monitor or CRO designee within 24 hours of receipt by the Investigator by updating the electronic CRF with the new information or by submitting a paper SAE Report Form in the event that the EDC is not available. When the EDC system becomes available, the SAE information must be entered within 24 hours. The subject should be observed and monitored carefully until the condition resolves or stabilizes.

All deaths are to be thoroughly investigated and reported. Autopsy reports and death certificates are to be obtained, if possible.

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). 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 Reporting Study Endpoints

Investigators will be counseled to report any event that they assess as potentially being a study endpoint requiring adjudication (death, myocardial infarction, stroke, and thromboembolic events). All study endpoint events will be submitted blinded to the EAC for adjudication. To protect the integrity of the trial, these events that are adjudicated will not be unblinded or reported to either Health Authorities (HAs) or Investigators as safety reports unless otherwise requested by HAs or Ethics Committees. After study completion, these events will be included in the final analysis which will be unblinded and submitted to HAs with the study report.

10.3.5 Relationship to Study Medication

The causal relationship of the AE to study medication (vadadustat or darbepoetin alfa) 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 medication until proven otherwise. Examples of evidence that would suggest a causal relationship between the study medication 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 following definitions will be used for the assessment of relationship to study medication:

Probably Related: There is strong evidence to support a causal association between the AE and study medication (eg, the event occurred after the first dose, the characteristics of the AE are typical of a drug toxicity, and there is recurrence after rechallenge) and the AE cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs.

Possibly Related: There is some evidence to support a causal association between the AE and the study medication (eg, the AE resolved after study medication interruption and the characteristics of the AE are unusual for the study population) and alternative explanations, such as the subject's clinical state, other therapeutic interventions, or concomitant drugs, are less likely than study medication.

Unrelated: There is currently no evidence to support a causal association with study medication and the AE is clearly 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 "possibly related" category without supportive evidence for a causal relationship to study medication are generally uninformative and do not contribute meaningfully to the development of the safety profile of the drug or to subject protection.

10.3.6 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.

10.3.7 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 (ie, until a final report is completed for that subject).

In addition, all SAEs and those nonserious events assessed by the Investigator as possibly or probably 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.

10.4 Exposure In Utero

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

If any study participant becomes or is found to be pregnant while receiving a study medication (vadadustat or darbepoetin alfa) or within 30 days of discontinuing the study medication, the pregnancy must be recorded on the Pregnancy Reporting Form/Exposure in Utero Form in the EDC within 24 hours of awareness of the pregnancy or the Investigator should call the CRO SAE hotline within 24 hours of being made aware of the pregnancy.

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

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 classification as a SAE (ie, spontaneous abortion, stillbirth, neonatal death within 1 month of birth, or congenital anomaly [including that in an aborted fetus]), the Investigator should also follow the procedures for reporting a SAE within 24 hours of awareness. A pregnancy in 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 possibly or probably related to the in utero exposure to the study medication should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

10.5 Special Situations

Certain safety events, called 'Special Situations', that occur in association with study 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 medicinal product, eg, name confusion)
- Drug-drug interaction.

The Investigator should follow SAE criteria reporting guidelines for reporting Special Situations.

11 DATA ANALYSIS

Data collected throughout the study will be summarized using descriptive statistics and listed in by-subject listings. Continuous variables will be summarized using number of subjects with data, mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated. Summaries will be provided by treatment group within appropriate analysis populations (as defined in Section 11.2, Study Analysis Populations) and by time point/time period as appropriate.

For HGB, Baseline will be defined as the mean of all qualifying HGB values collected prior to the first dose of study medication (vadadustat or darbepoetin alfa). For subjects rescreened, only values for the last Screening period will be used for establishing the Baseline. For other parameters, unless otherwise specified, Baseline will be defined as the last available value prior to the first dose of study medication.

Hemoglobin values as assessed through the central laboratory will be used for efficacy and safety evaluations; local HemoCue® HGB values will be used only for dose adjustments.

In geographies where regulatory approval does not require a formal analysis of MACE, efficacy and safety analyses may be performed upon the completion of 52 weeks of post-randomization follow-up in a sufficient number of subjects to support registration in that geography. Such analysis will be documented in a geography-specific SAP.

11.1 Sample Size Determination

The goal of this study is to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with anemia secondary to NDD-CKD after conversion from current ESA therapy. The sample size is calculated to ensure sufficient power for testing both efficacy in this trial and the primary safety endpoints as part of a pooled analysis.

11.1.1 Sample Size for the Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the mean change in HGB from Baseline (mean pretreatment HGB) to the average HGB over the primary evaluation period (mean HGB from Weeks 24-36).

The primary efficacy objective of this study is to show that vadadustat is noninferior to darbepoetin alfa within the noninferiority margin. Noninferiority will be established based on a margin of -0.5 g/dL (for vadadustat minus darbepoetin alfa).

For the primary efficacy analysis in this study, it is assumed that the mean change from Baseline in HGB for vadadustat will be the same as for darbepoetin alfa, and the common standard deviation for the mean change from Baseline is assumed to be 1.5 g/dL. Noninferiority will be established based on a 2-sided 95% confidence interval for the difference between the vadadustat group and darbepoetin alfa and using a noninferiority margin of -0.5 g/dL. With these assumptions and approximately 1050 subjects per treatment group for the primary efficacy analysis, the noninferiority assessment will have >99% power.

11.1.2 Sample Size for the Primary Safety Endpoint

The primary safety endpoint is the time from first dose of study medication to the first (adjudicated) MACE (defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke).

The primary safety analysis will be based upon all events that accrue over 2 planned NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015). The sample size with respect to the MACE endpoint has been determined based on the number of events needed to demonstrate noninferiority of the 2-sided 95% confidence interval for the hazard ratio (vadadustat/darbepoetin alfa). It has been calculated that 631 events will be required overall to have 80% power to establish noninferiority with a margin of 1.25, and >90% power to establish noninferiority with a margin of 1.3, assuming no difference between treatment groups. The power is >90% to establish a noninferiority margin of 1.25 if the hazard ratio is 0.95 favoring vadadustat. A MACE rate of 10% annually is anticipated in both treatment arms based on a comprehensive review of available epidemiology and prospective clinical studies in the field. With 1050 subjects per treatment group enrolled in this study, approximately 20 months for accrual, and up to 36 months of follow-up, approximately 68% of the needed MACE would be captured, assuming the dropout rate is negligible. The remaining 32% of the needed MACE would be captured in Study AKB-6548-CI-0014.

11.2 Study Analysis Populations

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects
- Full analysis population: defined as randomized subjects receiving 1 or more doses of therapy
- Per protocol (PP) population: defined as all randomized subjects who received study medication (vadadustat or darbepoetin alfa) during the primary evaluation period, had at least 2 HGB assessments during the primary evaluation period, and received no rescue therapy in the 8 weeks prior to the evaluation period
- Safety population: defined as all subjects who received at least 1 dose of study medication

Efficacy analyses will utilize the randomized, full analysis, and PP populations while safety analyses will utilize the safety population.

11.3 Analysis of Demographic and Pretreatment Variables

Descriptive statistics will be generated for demographic and pretreatment variables for each analysis population defined in Section 11.2, Study Analysis Populations.

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

11.4 Disposition of Subjects

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

The number of randomized subjects who completed each period of study medication treatment (maintenance and long-term treatment), discontinued from study medication early, and completed or discontinued from the study and reasons for discontinuation will be summarized by treatment group and overall.

11.5 Missing Data

Subjects who stop study medication treatment after randomization and prior to completion of the study should continue with planned study visits and assessments unless they withdraw consent for participation in the study. Similarly, subjects will continue with study medication and study procedures following the initiation of rescue therapy, with the exception that the subjects must discontinue taking study medication while receiving an ESA rescue therapy. Treatment with study medication should be resumed after an appropriate interval following the ESA rescue therapy as described in Section 8.4.7, Rescue Therapy. Data will continue to be collected following initiation of the rescue therapy as per the study Schedule of Activities.

All data collected during the study, including at any point after the initiation of rescue therapy as well as after early discontinuation of study medication treatment, will be used for the primary analysis as well as main analyses of all efficacy endpoints. Sensitivity analyses, as described below, will be performed to assess an impact of rescue therapy on study conclusions.

In the primary analysis of the primary efficacy endpoint, all available qualifying HGB measurements during the pretreatment period and during the primary evaluation period (Weeks 24-36) will be used to calculate an average HGB during each period respectively. For any subject with no available HGB measurements during the primary evaluation period, the value (central laboratory data only) closest in time to the evaluation period will be used for the change from Baseline. Given the design of this study where the subjects will continue to be assessed after early study medication discontinuation, it is expected that only a minimal amount of missing data will be present and the primary analysis should not be substantially affected by the imputation.

All data pertaining to the MACE endpoint collected at any point during the study, both during study medication treatment and post study medication treatment discontinuation, and regardless of the rescue therapy, will be used for the primary analysis of the MACE endpoint and its individual components.

Unless stated otherwise, missing data for all other secondary efficacy and safety endpoints will not be imputed and the analysis will be based on observed data. For certain responder-type binary endpoints, subjects with no available data will be classified into one of the categories as described in the relevant sections below.

11.6 Efficacy Analyses

The primary efficacy endpoint as well as all key and other secondary endpoints will be summarized using descriptive statistics by treatment group, as well as by study visit and/or

analysis period as appropriate. Mean values of HGB as well as selected other efficacy parameters will be plotted across study visits/periods by treatment group.

11.6.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the mean HGB change from Baseline (mean pretreatment HGB) to the mean HGB from Weeks 24-36 (inclusive).

11.6.1.1 Primary Analysis of Primary Efficacy Endpoint

The primary analysis will use an analysis of variance (ANOVA) stratified by the randomization strata. Within this model the strata-specific differences between the treatments will be combined using weights proportionate to the stratum size. A 2-sided 95% confidence interval for the difference between the vadadustat group and the darbepoetin alfa group will be obtained from this model.

Noninferiority of vadadustat to darbepoetin alfa will be established by comparing the lower limit of the 95% confidence interval for the difference between treatment groups (vadadustat minus darbepoetin alfa) obtained from this model to the noninferiority margin of -0.5 g/dL.

The primary analysis will be performed using the full analysis population and the assigned treatment as described in Section 11.2, Study Analysis Populations. All data collected during the study for subjects included in the full analysis population at the time of analysis, including data collected at any point after the initiation of rescue therapy as well as after early discontinuation of study medication treatment, will be used for the primary analysis. Missing data will be handled by using the HGB data closest to the evaluation period, as described in Section 11.5, Missing Data.

In geographies where regulatory approval does not require a formal analysis of MACE, efficacy and safety analyses may be performed upon the completion of 52 weeks of post-randomization follow-up in a sufficient number of subjects to support registration in that geography. Details will be provided in a geography-specific SAP.

11.6.1.2 Sensitivity Analyses of Primary Efficacy Endpoint

The following sensitivity analyses will be conducted to investigate the impact of missing data and rescue treatment.

- Primary analysis will be repeated with change from Baseline to the primary evaluation period in HGB based upon the last HGB value before rescue for subjects receiving any form of rescue (transfusion or ESA) prior to the primary evaluation period (ie, during the conversion period Weeks 0-23).
- Primary analysis will be repeated using all randomized subjects.
- Primary analysis will be repeated using only subjects with available HGB data during the primary evaluation period, ie, excluding subjects with no available data during the primary evaluation period.
- Primary analysis will be repeated using the PP population with the actual treatment received.

11.6.2 Analysis of Key Secondary Efficacy Endpoints

Secondary efficacy endpoints analyses will be performed using the randomized and full analysis populations and the assigned treatment as described in Section 11.2, Study Analysis Populations. Analysis for the key secondary efficacy endpoints will be repeated using the PP population with the actual treatment received.

In order to control the overall Type I error rate, hierarchical testing procedures will be applied to the primary and secondary efficacy endpoints, and details will be provided in the SAP.

11.6.2.1 Analysis of Mean Change in HGB Value between Baseline (Mean Pretreatment HGB) and the Secondary Evaluation Period (Weeks 40-52)

This endpoint will be analyzed using the same methodology as specified for the primary efficacy endpoint, including the same method of imputation in absence of any measurements during the secondary evaluation period (Weeks 40-52).

Sensitivity analyses similar to those of the primary efficacy endpoint will be performed and details will be provided in the SAP.

11.6.2.2 Analysis of Proportion of Subjects with Mean HGB within the Target Range during the Primary Evaluation Period (Weeks 24-36)

Each subject will be classified using a binary variable ("yes"/"no") for the analysis of this endpoint. A classification of "yes" will be assigned to any subject with a mean HGB within the target range during the primary evaluation period (Weeks 24-36). All other subjects, including those with no available values during the primary evaluation period, will be classified to the "no" category. The between-treatment difference will be summarized with a confidence interval which uses Cochran-Mantel-Haenszel (CMH) weighting.

11.6.2.3 Analysis of Mean Weekly Dose of IV Elemental Iron Administered from Baseline to Week 52

For each subject a mean weekly dose (mg) of IV elemental iron administered at any time starting on Day 1 through Week 52 will be calculated based upon observed data. It will be calculated as a total cumulative dose (mg) of IV elemental iron administered from Day 1 through Week 52 divided by the number of weeks the subject remained in the study up to the Week 52 visit. The between-treatment difference will be summarized with a confidence interval similar to those used for the primary endpoint.

11.6.2.4 Analysis of Proportion of Subjects Receiving RBC Transfusion(s) from Baseline to Week 52

Each subject will be classified using a binary variable ("yes"/"no") for the analysis of this endpoint. A classification of "yes" will be assigned to any subject receiving RBC transfusion(s) at any time starting on Day 1 through Week 52. All other subjects will be classified to the "no" category. The between-treatment difference will be summarized with a confidence interval which uses CMH weighting. Time to first RBC transfusion will also be summarized.

11.6.3 Analysis of Additional Secondary Efficacy Endpoints

Descriptive summaries of all secondary efficacy endpoints will be presented using observed data without imputation. Analyses will consist of the presentation of descriptive statistics by

treatment group along with the presentation of 2-sided 95% confidence intervals for the treatment differences. The descriptive summaries of the secondary endpoints will be made without stratification.

11.7 Safety Analyses

11.7.1 Analysis of MACE

The primary safety endpoint, time to the first adjudicated MACE, will be analyzed as [date of the first MACE – the date of first dose of study medication]. A MACE is defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke. Subjects who have not experienced a MACE by study closure will be censored on the date of their last study assessment. The hazard ratio (vadadustat/darbepoetin alfa) and its 95% confidence interval will be obtained from a stratified Cox proportional hazards model. As this study has not been designed to provide a stand-alone assessment of MACE, this analysis will be considered a descriptive analysis. A similar analysis as described for the primary analysis of the MACE endpoint will be performed with censoring of subjects 4 weeks following discontinuation of study treatment if they did not have a MACE prior to that time.

The primary MACE analysis will be based upon all events that accrue over 2 separately planned NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015) (see Section 11.1.2, Sample Size for the Primary Safety Endpoint).

11.7.2 Analysis of Adverse Events

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

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

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

- SAEs
- Related AEs (including all categories for relationship to study medication other than “Unrelated”, as determined by the Investigator)
- AEs leading to early discontinuation of study medication.

11.7.3 Remaining Safety Endpoints

The following safety endpoints will be analyzed using time to event methods:

1) Individual components (death, myocardial infarction, stroke) of MACE
2) Thromboembolic events (defined as arterial thrombosis, DVT, PE, or vascular access thrombosis).

For these endpoints the incidence ("yes"/"no") of the endpoint will be presented for each treatment arm. Kaplan-Meier curves will be presented for each endpoint as the time of endpoint free survival (ie, time until endpoint or death).

The analysis of proportion of subjects with HGB >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL post-Baseline will classify a subject as a "yes" if:

- Any value HGB >12.0 g/dL at any time after Day 1
- Any confirmed value HGB >12.0 g/dL at any time after Day 1
- Any value HGB >13.0 g/dL at any time after Day 1
- Any confirmed value HGB >13.0 g/dL at any time after Day 1
- Any value HGB >14.0 g/dL at any time after Day 1
- Any confirmed value HGB >14.0 g/dL at any time after Day 1.

A HGB value above a set threshold will be considered as confirmed if there are 2 consecutive values above that threshold. The second of the 2 consecutive assessments should be done at most 12 weeks after the first assessment. Subjects with no available data post-Baseline will be excluded from this analysis. All other subjects will be classified to the "no" category.

The analysis of proportion of subjects with any HGB increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval post-Baseline will classify a subject as a "yes" if at least 1 of the following criteria at any point after Day 1 is met:

- HGB increase >1.0 g/dL within any 2-week interval
- HGB increase >2.0 g/dL within any 4-week interval.

Subjects with no available data post-Baseline will be excluded from this analysis. All other subjects will be classified to the "no" category.

Observed values of continuous and categorical parameters and changes from Baseline for continuous parameters to each study visit will be summarized descriptively for vital signs and clinical laboratory results. Graphical displays of selected laboratory parameters will also be provided.

11.8 Additional Assessments

11.8.1 Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug dictionary.

Prior medications will be defined as any medications that were taken before the date of the first dose of study medication. Concomitant medications will be defined as any medications taken at any time from the date of the first dose of study medication through the date of the last dose of the study medication.

The total number of transfusions, ESA rescue therapies, and therapeutic phlebotomy collections will be summarized by period as well as post-Baseline overall.

11.8.2 Biomarkers

Biomarkers (hepcidin and VEGF) will be summarized descriptively at Baseline and by visit post-Baseline.

11.8.3 Pharmacokinetics

Descriptive and graphical summaries will be generated for PK measurements.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms/Electronic Data Capture

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. Case report forms 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 Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

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

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

13.1 Investigative Site Monitoring Visits

During study conduct, the Sponsor or its agent 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 the 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 investigative site may also be subject to QA audits performed by the Sponsor or companies working with or on behalf of the Sponsor, 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 investigative site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the investigative site should notify the Sponsor or its designee (and IRB or IEC, as required). Significant 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 study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the study.

14.1 Criteria for Premature Termination or Suspension of the Study

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

- New information regarding the safety or efficacy of the study 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
- Significant 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 study for other valid administrative reasons.

14.2 Criteria for Premature Termination or Suspension of Investigational Study Sites

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

14.3 Procedures for Premature Termination or Suspension of the Study or Investigational Sites

In the event that the Sponsor elects to terminate or suspend the study or the participation of an investigational study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational study 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 (1996).

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/Independent Ethics Committee

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 or its designee.

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

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

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

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

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

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

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP, defined as a breach that will likely affect the safety or physical or mental integrity of subjects or the scientific value of the trial, 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, 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 (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

16 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator 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

Study Period	Optional Pre-Screen	Screening		Treatment Period																									Post Treatment	
				BL/ rand. [a]	Year 1																	Year 2				Year 3/Year 4					
Visit	**PS**	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22/ 26**	**23/ 27**	**24/ 28**	**25/ 29**	**End of Trtmt**	**Follow-up [b]**
Week		**-4 to 0**		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**104**	**116/ 168**	**128/ 180**	**140/ 192**	**156/ 208**	**EOT [c]**	**EOT +4 wks**
Procedures/Assessments																														
Informed Consent	X [d]	X [d]																												
Pre-Screening Local HGB [e]	X																													
I/E Criteria [f]	X	X	X																											
Vital Signs [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demographics, Med History			X																											
Physical Exam [h]			X																											
12-Lead ECG [i]				X																										
Randomization				X																										
Laboratory Procedures																														
Pregnancy Test [j]			X																											
Folate and Vitamin B_{12}			X [k]																											
Coagulation Tests [l]				X																										
C-Reactive Protein				X																										
Urine Albumin: Creatinine (uACR)				X																										
CBC [m] with periodic diff		X [k,n]	X [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Iron Indices [o]		X [k]		X		X		X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Serum Chem and eGFR [p]			X [k]	X		X		X		X		X		X		X		X		X		X		X		X		X	X	
Liver Function Tests [q]			X [k]	X		X		X		X	X	X	X	X		X		X		X		X		X		X		X	X	
Lipid Panel [r]				X										X						X										

Study Period	Optional Pre-Screen	Screening		Treatment Period																										Post Treatment	
				BL/ rand. [a]	Year 1																			Year 2				Year 3/Year 4					
Visit	**PS**	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22/ 26**	**23/ 27**	**24/ 28**	**25/ 29**	**End of Trtmt**	**Follow-up [b]**
Week		**-4 to 0**		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**104**	**116/ 168**	**128/ 180**	**140/ 192**	**156/ 208**	**EOT [c]**	**EOT +4 wks**
Biomarkers [s]				X						X				X															X	
Reticulocyte Count				X		X				X				X						X										
Erythropoietin				X		X				X				X						X										
PK [t]						X				X				X						X										
Exploratory Samples [u]				X										X																
ACTH (Cosyntropin) Stimulation Test [v]				X						X										X									X [w]	
Safety Assessments																															
MACE Endpoint Questionnaire [x]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment [y]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusions and ESA Rescue Collection					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Therapeutic Phlebotomy Collection					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Assessments and Procedures																															
Concomitant Med Review [z]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vadadustat Medication Dispensing [aa]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug Reconciliation					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visit Registration in IWR				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HGB via HemoCue® for Dose Adjustment [bb]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Darbepoetin Alfa				Dosing per approved local product label [cc]																											
Vadadustat Dose Adjustments [dd]				Start at 300 mg once daily, then adjust dose as per Dose Adjustment Guidelines																											

Study Period	Optional Pre-Screen	Screening		Treatment Period																								Post Treatment	
				BL/ rand. [a]	Year 1																	Year 2				Year 3/Year 4					
Visit	PS	SV1	SV2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22/ 26	23/ 27	24/ 28	25/ 29	End of Trtmt	Follow-up [b]
Week		-4 to 0		0	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52	64	76	88	104	116/ 168	128/ 180	140/ 192	156/ 208	EOT [c]	EOT +4 wks
Oral Iron Supplementation [ee]				As needed to maintain ferritin ≥100 ng/mL and TSAT ≥20%																										

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; ALT/SGPT = alanine aminotransferase/serum glutamic-pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BUN = blood urea nitrogen; CBC = complete blood count; CPK = creatine phosphokinase; CRF = case report form; diff = differential; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = end of treatment; ESA = erythropoiesis-stimulating agent; HDL = high density lipoprotein; HGB = hemoglobin; HIF = hypoxia inducible factor; ICF = informed consent form; I/E = inclusion/exclusion; INR = international normalized ratio; IWR = interactive web response; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MACE = major adverse cardiovascular event; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; med = medication; PK = pharmacokinetic; PS = Pre-Screening; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RDW = red cell distribution width; SV1 = Screening visit 1; SV2 = Screening visit 2; TIBC = total iron binding capacity; Trtmt = treatment; TSAT = transferrin saturation; uACR = urine albumin to creatinine ratio; VEGF = vascular endothelial growth factor; WBC = white blood cell; wks = weeks.

[a] The Screening period is a maximum of 28 days in duration. The Baseline visit must be performed within 28 days of the 2 Screening visits and a minimum of 4 days must elapse between the 2 Screening visits (SV1 and SV2) and between SV2 and the Baseline visit.

[b] The Follow-up visit can be performed either in person OR via the telephone.

[c] EOT will be performed when the study is ended. Subjects who prematurely discontinue study medication (vadadustat or darbepoetin alfa) for any reason should attend all subsequent study visits and be continually monitored according to the Schedule of Activities for the duration of the study.

[d] An abbreviated ICF will be used for Pre-Screening. If the subject is eligible for Screening, a separate full ICF will be used. An optional consent form for collection of blood samples for future genetic analysis will be provided at SV1. An additional optional consent form for participation in an adrenal function substudy in 200 subjects in the EU will also be provided at SV1.

[e] If the Pre-Screen HemoCue® HGB is between 8.0 and 11.0 g/dL (inclusive) within the US or between 9.0 and 12.0 g/dL (inclusive) outside of the US, the investigative site may proceed with Screening Visit 1 (SV1), preferably on the same day as Pre-Screening.

[f] Inclusion/Exclusion criteria will be reviewed at the Pre-Screening and Screening visits (SV1 and SV2). Final eligibility determination will occur following the Screening visits when all data are available.

[g] Vitals: Heart rate and blood pressure to be assessed in the seated position after 5 minutes of rest. Height (SV2 only) and weight (SV2, Weeks 12, 24, 36, and 52, yearly thereafter, and at the EOT visit) will also be measured.

[h] Physical exam: a physical exam is required at SV2 as outlined in the protocol. Thereafter, an abbreviated symptom-directed physical exam should be performed at the discretion of the Investigator as clinically indicated.

[i] ECG should be performed prior to blood draws when possible and obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes.

[j] Serum pregnancy will be tested in women of childbearing potential at SV2. (Eligible subjects will be advised to use an adequate contraceptive method.) Additional serum or local urine pregnancy tests should be conducted throughout the study in sufficient number, as determined by the Investigator or required by local regulations, to establish the absence of pregnancy during the study. If positive at SV2, the subject is not eligible to enter the study. If a subject becomes pregnant during the study, the subject must permanently discontinue study medication and should attend all subsequent study visits and be continually monitored according to the Schedule of Activities for the duration of the study.

[k] Subjects may be retested and/or rescreened as detailed in Sections 7.4.1, Retesting and 7.4.2, Rescreening.

[l] Coagulation tests: prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).

[m] A CBC with differential will be performed at Baseline and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208. At all other noted visits, a CBC without differential will be performed. CBC: hemoglobin, hematocrit, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

[n] If HGB at SV1 is 11.1-11.5 g/dL in the US or 12.1-12.5 g/dL outside the US, a single retest CBC should be performed prior to SV2. If retest HGB is >11.0 g/dL in the US or >12.0 g/dL outside the US, the subject should not proceed with SV2. If the HGB at SV1 is >11.5 g/dL in the US or >12.5 g/dL outside of the US, the subject should not proceed with any further Screening at this time.

[o] Iron indices: ferritin, iron, total iron binding capacity (TIBC), and transferrin saturation (TSAT).

[p] A full serum chemistry panel will be performed at SV2, Baseline, and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208. At all other noted visits, serum creatinine and eGFR will be performed. Serum chemistry: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen (BUN)/urea, creatine phosphokinase (CPK), uric acid, albumin, and total protein.
[q] Liver function tests: total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), and lactate dehydrogenase (LDH).
[r] Lipids: total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides.
[s] Hepcidin and vascular endothelial growth factor (VEGF) will be analyzed at Baseline and at Weeks 12, 28, and EOT.
[t] PK samples are to be drawn only for subjects randomized to vadadustat. Subjects will be questioned regarding the timing of their last dose of vadadustat.
[u] Additional blood and urine samples will be collected at Baseline and Week 28 which may be used for exploratory measurement of biomarkers (eg, factors relating to the activation of the HIF pathway). Subjects will also be asked to provide optional consent to obtain and store a blood sample for future genetic analyses (eg, DNA, mRNA, etc).
[v] The ACTH (cosyntropin) stimulation test will be performed on a subset of 100 subjects per treatment arm (200 subjects total) in the EU as part of a substudy on adrenal function.
[w] The ACTH (cosyntropin) stimulation test will only be performed at the EOT visit for subjects who are part of the adrenal function substudy and who have permanently discontinued study medication early prior to the Week 52 study visit.
[x] At each post-randomization study visit, the subject must specifically be questioned regarding the occurrence of any potential MACE endpoint events since the last study visit. If a potential endpoint event is reported, the date of the event should be recorded and the appropriate source documents should be collected according to the endpoint packet checklist.
[y] Adverse events should be documented and recorded at each visit. All adverse events (serious and non-serious, and related and non-related) will be documented and recorded through the follow-up visit. Subjects must be followed for adverse events until the final required protocol visit or until all drug-related toxicities and serious adverse events have resolved (or are considered chronic/stable).
[z] Concomitant medications should be collected and recorded at each visit as noted. All concomitant medications received up to and including 30 days prior to the start of study medication through the EOT visit will be recorded.
[aa] Subjects will be provided with a supply of vadadustat at the Baseline visit and will be resupplied at subsequent visits as needed. Subjects will be instructed to complete 1 bottle prior to opening the next bottle. The dose should be taken at approximately the same time each day, preferably between 7 AM and 2 PM.
[bb] Hemoglobin will be monitored via local HemoCue® throughout the study to determine if the dose of study medication will be adjusted or suspended.
[cc] Refer to the approved local product label. Vital signs and weight should be obtained prior to dosing per the local product label.
[dd] The dose will be adjusted in accordance with the Dose Adjustment Guidelines. Changes to dose will be accomplished by changing the number of tablets to be taken per day.
[ee] Iron supplementation should be prescribed as needed during the study to maintain ferritin ≥100 ng/mL and TSAT ≥20%. In general, only oral iron should be used for therapy. Vadadustat should not be administered concurrently with the oral iron supplement (including multivitamins containing iron). Oral iron supplement should be taken at least 2 hours before or 2 hours after the dose of study medication. (See study protocol for further details regarding iron administration and potential intravenous therapy).

APPENDIX B: CKD-EPI CREATININE EQUATION

The estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine (isotope dilution mass spectrometry [IDMS] calibrated in mg/dL) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Levey et al. 2009).

The CKD-EPI creatinine equation is:

$eGFR = 141 \times \min(SCr/k,1)^{\alpha} \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if female}] \times [1.159 \text{ if black}]$

where:

SCr is serum creatinine (in mg/dL)

k = 0.7 for females

k = 0.9 for males

α = -0.329 for females

α = -0.411 for males

min = the minimum of SCr/k or 1

max = the maximum of SCr/k or 1

APPENDIX C: ACTH (COSYNTROPIN) STIMULATION TEST FOR ADRENAL FUNCTION MONITORING

The adrenocorticotropic hormone (ACTH) stimulation test assesses the function of the adrenal glands and their ability to respond to ACTH. Adrenocorticotropic hormone is a hormone produced in the pituitary gland that stimulates the adrenal glands to release cortisol. Cosyntropin is a synthetic form of ACTH. The ACTH stimulation test is recognized as the gold standard assay of adrenal insufficiency.

Sequential ACTH (cosyntropin) stimulation tests will be conducted at European Union (EU) sites in the first 200 subjects randomized and who agree to participate in the testing (approximately 100 subjects per treatment arm). Testing will be performed at the Baseline (predose), Week 12, and Week 52 study visits, or at the end of treatment (EOT) visit if the subject permanently discontinues study medication early prior to the Week 52 study visit.

Female subjects who have taken estrogens within 30 days of the first dose of study medication should be excluded from the adrenal function monitoring substudy.

Test details:

- Obtain blood sample for pretest serum cortisol measurement (collected prior to administering cosyntropin)
- Administer 0.25 mg cosyntropin via intravenous (IV) push
- Obtain blood samples for serum cortisol measurements at 30 minutes and 60 minutes after dosing of cosyntropin

Samples for cortisol measurements will be sent to the central laboratory for analysis.

CLINICAL PROTOCOL

PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ORAL VADADUSTAT FOR THE MAINTENANCE TREATMENT OF ANEMIA IN SUBJECTS WITH NON-DIALYSIS-DEPENDENT CHRONIC KIDNEY DISEASE (NDD-CKD) (PRO$_2$TECT - CONVERSION)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0015
US IND Number:	102,465
EudraCT Number	2015-004774-14
Phase:	Phase 3
Status/Date:	Amendment 7-COL ([redacted] Colombia-specific protocol amendment) Amendment 6-COL ([redacted]; Colombia-specific protocol amendment) Amendment 5-COL ([redacted]; Colombia-specific protocol amendment) Amendment 4-COL ([redacted]; Colombia-specific protocol amendment) Amendment 3-COL ([redacted]; Colombia-specific protocol amendment) Amendment 2-COL ([redacted]; Colombia-specific protocol amendment) Amendment 2 ([redacted]) Amendment 1 ([redacted]) Original protocol ([redacted])
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Cambridge, MA 02142 United States of America

1 SIGNATURE PAGES

1.1 Protocol Approval

[redacted]
Signature [redacted] Date
[redacted] Clinical Development

[redacted]
Signature Date

[redacted] Biostatis

Signature Date

[redacted] Drug Safety and Pharmacovigilance

[redacted]
Date

[redacted], Clinical

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 Harmonisation Guidance for Industry, Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Phone Number

Full Address

TABLE OF CONTENTS

2 PROTOCOL SYNOPSIS

Study Title	Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy and Safety of Oral Vadadustat for the Maintenance Treatment of Anemia in Subjects with Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD) (PRO_2TECT - CONVERSION)
Protocol Number	AKB-6548-CI-0015
Study Phase	Phase 3
Investigational Product	Vadadustat; 150 mg tablets
Reference Medicinal Product	Darbepoetin alfa; Amgen, Inc.
Study Population	The study population will consist of subjects ≥18 years of age with NDD-CKD, estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2, and hemoglobin (Hb) between 8.0 and 11.0 g/dL (inclusive) in the United States (US) and between 9.0 and 12.0 g/dL (inclusive) outside of the US, who are currently treated with an erythropoiesis-stimulating agent (ESA) for anemia.
Investigative Sites	Approximately 480 investigative sites in North America, Latin America, Europe, and Asia Pacific.
Planned Number of Subjects	Approximately 1850 subjects.
Primary Objective	Demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with NDD-CKD after conversion from current ESA therapy.
Study Design Overview	Phase 3, randomized, open-label, active-controlled study of the efficacy and safety of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia after conversion from current ESA therapy. Following a Screening period of up to 8 weeks (56 days), subjects who meet all inclusion and no exclusion criteria will be randomized 1:1 to vadadustat or darbepoetin alfa. Randomization will be stratified by: • Geographic region (US versus European Union [EU] versus Rest of World [ROW]) • New York Heart Association congestive heart failure (CHF) Class 0 (no CHF) or I versus II or III • Study entry Hb (<10.0 versus ≥10.0 g/dL). Following randomization, there will be 3 periods during the study: • **Conversion and Maintenance Period (Weeks 0-52):** conversion to study treatment for maintaining Hb (Weeks 0-23), primary efficacy evaluation (Weeks 24-36), and secondary efficacy evaluation (Weeks 40-52) • **Long-Term Treatment Period (Weeks 53-End of Treatment [EOT])**: continued study medication to assess long-term safety • **Follow-Up Period (EOT + 4 weeks):** post-treatment visit (either in person or via telephone) for safety.

Study Duration	The study will be considered completed (end of trial) when approximately 631 major adverse cardiovascular events (MACE) have accrued over the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015) and all enrolled subjects have had the the opportunity to have their Visit 13 (+/- 5 days). All subjects will remain in the study until the global study completion (end of trial) at which time subjects will be scheduled for a final visit and the study will close. Sites will be notified of global study completion date approximately 3 months prior to study closure (based on accrual of MACE across the 2 studies) and will have any subject that is active complete the EOT visit and Follow-Up visit, as applicable, and confirm the End of Study (EOS) status.
Inclusion Criteria	1. ≥18 years of age 2. Diagnosis of CKD with an eGFR ≤60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation during Screening and not expected to start dialysis within 6 months of Screening 3. Currently maintained on ESA therapy, with a dose received within 6 weeks prior to or during Screening 4. Mean Screening Hb between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) outside of the US, as determined by the average of 2 Hb values measured by the central laboratory during Screening 5. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening 6. Folate and vitamin B_{12} measurements ≥lower limit of normal during Screening 7. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.
Exclusion Criteria	1. Anemia due to a cause other than CKD or subjects with active bleeding or recent blood loss 2. Subjects with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia 3. Red blood cell (RBC) transfusion within 8 weeks prior to randomization. 4. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2.0 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded. 5. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mmHg or systolic blood pressure >180 mmHg) during Screening 6. Severe heart failure during Screening (New York Heart Association Class IV) 7. 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 HF, or stroke within 12 weeks prior to or during Screening 8. History of active malignancy within 2 years prior to or during Screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ 9. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) within

	12 weeks prior to randomization 10. History of hemosiderosis or hemochromatosis 11. 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) 12. 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 the Screening visit 13. Previous participation in this study, or previous participation in a study with a hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) other than vadadustat 14. Females who are pregnant or breast-feeding. Women of childbearing potential who are unable or unwilling to use an acceptable method of contraception 15. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception 16. Any other reason that in the opinion of the Investigator would make the subject not suitable for participation in the study 17. Hypersensitivity to darbepoetin or vadadustat, or to any of their excipients
Retesting/Rescreening	Retesting is defined as repeating laboratory tests within the same Screening period. Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 8-week Screening period, per Investigator discretion. Subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} values may receive replacement therapy based on the investigative sites' standard of care during the screening period and retest the laboratory parameter(s). Subjects who receive iron replacement may retest screening Hb a minimum of 3 weeks after completion of iron replacement therapy. Subjects who fail to meet the qualifying criteria for Hb or eGFR during a Screening period may be considered for rescreening at the discretion of the Investigator if it is felt that the subject's status has progressed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} 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	**Primary** • Mean change in Hb between Baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36) **Key Secondary** • Mean change in Hb value between Baseline (mean pretreatment Hb) and the secondary evaluation period (Weeks 40-52) • Proportion of subjects with Hb values within the target range during the primary evaluation period (Weeks 24-36) • Proportion of subjects with Hb values within the target range during the secondary evaluation period (Weeks 40-52) **Other Secondary** • Proportion of time with Hb values within the target range during the primary evaluation period (Weeks 24-36) • Proportion of time with Hb values within the target range during the secondary evaluation period (Weeks 40-52)

	• Proportion of subjects with Hb increase of >1.0g/dL from Baseline • Time to achieve Hb increase of >1.0g/dL from Baseline • Mean change in Hb value between Baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36) stratified by pre-baseline ESA exposure • Progression of CKD • Proportion of subjects receiving IV iron therapy from Baseline to Week 52 • • Mean monthly dose of IV elemental iron administered from Baseline to Week 52 in subjects who have received IV iron • Proportion of subjects receiving RBC transfusion(s) from Baseline to Week 52 • ESA rescue • Dose adjustments from Baseline to Week 52

Safety Endpoints	• MACE, defined as all-cause mortality, non-fatal myocardial infarction (MI), or non-fatal stroke
	• Individual components of MACE:
	  o All-cause mortality
	  o Non-fatal myocardial infarction
	  o Non-fatal stroke
	• Thromboembolic events: arterial thrombosis, DVT, PE, or vascular access thrombosis
	• Hospitalization for heart failure (HF)
	• Expanded MACE, defined as all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, hospitalization for HF, or thromboembolic event
	• Fatal/non-fatal MI
	• Fatal/non-fatal stroke
	• Sudden death
	• Cardiovascular death
	• Non-cardiovascular death
	• Hospitalization
	• Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL
	• Hb < 8.0 g/dL
	• Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
	• Adverse events (AEs) and serious adverse events (SAEs)
	• Vital signs and clinical laboratory values.
	• Adrenal function assessment in a subset of subjects

Exploratory Endpoints	• Biomarkers (including, but not limited to, hepcidin and vascular endothelial growth factor [VEGF] • Time to achieve stable Hb values within the target range • Proportion of subjects with Hb values within target range without evidence of iron overload
Dosage and Regimens	Subjects will be randomized 1:1 to either:

Vadadustat starting dose: 2 tablets once daily (300 mg/day)

Darbepoetin alfa subcutaneous (SC): initial dose as follows

- For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen.
- For subjects taking other ESAs, the initial dose of darbepoetin should be based on the current. Package Insert (PI) for investigational sites in the US, and the European Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult patients with CKD not on dialysis.

For all subjects, it is recommended that no additional ESA doses be administered after Screening visit 2 (SV2) and prior to the Randomization visit.

Dose Adjustment Guidelines – All Treatment Groups

Dosing will be initiated at the Baseline visit, and the first dose of study medication (vadadustat or darbepoetin alfa) will be administered at the investigative site after other Baseline procedures have been completed. The investigator may elect to postpone the initial dose of study medication until a subsequent visit based on the subject's Hb level or Hb trajectory assessed at the Baseline visit, or based on timing of the last ESA dose given during screening.

For all subjects, it is recommended that no additional ESA doses be administered after SV2 and prior to the Randomization visit.

Hemoglobin will be monitored via HemoCue® point of care device throughout the study to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be adjusted, interrupted, or maintained.

Year 1-4 Treatment Period Visits

From Weeks 0 to 12, Hb will be measured via HemoCue every 2 weeks for monitoring for dose adjustment. From Week 12 to Week 52, Hb via HemoCue will be monitored every 4 weeks.

From Week 53 through the end of the study, Hb will continue to be monitored via HemoCue to determine if the dose of study medication will be adjusted,interrupted, or maintained. Hemoglobin will also be assessed with a complete blood count (CBC) through the central laboratory for efficacy and safety evaluations; however, dose adjustments should be based on the local HemoCue Hb value. If the Investigator has an immediate clinical concern about a subject's HemoCue value, the Investigator may use clinical judgment and repeat the HemoCue Hb, use local lab values or wait for central lab results. The test method utilized to inform the treatment decision must be recorded in the appropriate CRF and the subject's source.

Year 2-4 Monthly Hb Monitoring

Additionally, after Week 52 visit, the Hb drawn as part of the local standard of care labs must be monitored monthly for dosing oversight. Per the vadadustat or darbepoetin alfa dosing algorithms, if the Hb value suggests a dose adjustment is needed, an unscheduled visit must be performed.

If monthly standard of care labs are not available, a study unscheduled visit must be performed. This visit will include, at minimum, the Hb measurement via HemoCue dose adjustment assessment, and adverse events assessment.

The monthly Hb monitoring method is flexible between study visits after Week 52 to minimize unnecessary travel or redundant blood sampling for the subject.

The aim is to maintain a Hb level of 10.0-11.0 g/dL in the US and 10.0-12.0 g/dL outside the US throughout the study.

	Dose adjustments will be guided by Hb concentration and the Dose Adjustment Algorithms. The Dose Adjustment Algorithm for darbepoetin alfa will follow the Package Insert (PI) for investigational sites in the US, and the European Summary of Product Characteristics (SmPC) for all other investigational sites (non-US). . This protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, Hb variability, and ESA responsiveness. In cases where the Investigator does not follow the dosing algorithm, the clinical circumstances must be documented in the subject's source. For subjects who progress to dialysis dependent – chronic kidney disease (DD-CKD), and remain on study treatment, the dose adjustment should be based on the Dose Adjustment Algorithms (Appendix C & D) **Vadadustat** Vadadustat should be dosed according to the Dose Adjustment Algorithms in Appendix C **Darbepoetin alfa** Subjects who are randomized to receive darbepoetin alfa, the initial dose will be according to the Dose Adjustment Algorithm (Appendix D). • For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen. For subjects taking other ESAs, the initial dose of darbepoetin should be based on the Package Insert (PI) for investigational sites in the US, and the European Summary of Product Characteristics (SmPC) for all other investigational sites (non-US). Following the dose conversion, darbepoetin alfa will be dosed SC, with dose adjustments according to the Dose Adjustment Algorithm. Darbepoetin alfa dosing is independent of the visit schedule, and the dosing schedule may shift per local standard of care and per Investigator discretion.
Dosing Instructions	**Vadadustat** All subjects will start with 2 tablets daily (300 mg/day). Dose levels of vadadustat include 150, 300, 450, and 600 mg (available tablet strength is 150 mg). Each subject will take his/her first dose of vadadustat at the investigative site at the Baseline visit. Thereafter, vadadustat will be taken once daily on an outpatient basis. Subjects may take vadadustat with or without food. The full dose should be taken at approximately the same time each day. The subject should be instructed to take any oral iron supplements (including multivitamins containing iron), iron containing phosphate binders, or any medications containing iron at least 2 hours before or 2 hours after the dose of vadadustat. **Darbepoetin alfa** Darbepoetin alfa will be administered, stored, and dispensed based on the Dosing Algorithms, and Package Insert (PI) for investigational sites in the US, and the European Summary of Product Characteristics (SmPC) for all other investigational sites (non-US).
Iron Supplementation	Investigators will prescribe iron supplementation during the study to maintain ferritin ≥100 ng/mL or TSAT ≥20%. In general, oral iron should be considered before initiating IV iron. Subjects already receiving oral iron supplementation as part of their treatment plan may continue their current treatment regimen. **Important:** Because of the potential for oral iron to reduce the bioavailability of vadadustat, the study medication is not to be administered concurrently with an oral

	iron supplement (including multivitamins containing iron), iron containing phosphate binders, or any medications containing iron. The subject should be instructed to take these medications at least 2 hours before or 2 hours after the dose of vadadustat.
Rescue Therapy Guidelines	To ensure the safety of study subjects and to standardize the use of rescue in the study, rescue therapy guidelines are provided. 1. **ESA Rescue:** Starting at Week 6, subjects in both treatment arms will be allowed (although will not be required) to have their Hb rescued with ESA therapy, per the local standard of care. If possible, a subject on vadadustat should be on the maximum dose of vadadustat for 2 weeks prior to ESA rescue. A subject on darbepoetin alfa may rescue with another ESA per the standard of care. To qualify for ESA rescue, a subject must fulfill BOTH of the following: • The subject has experienced worsening of symptoms of anemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared with Baseline • The subject's Hb is <9.0 g/dL However, in the event the subject does not meet the above criteria for ESA rescue, ESA rescue is permitted when medically necessary at the discretion of the investigator. Reasons for ESA use will be captured in the appropriate CRF. The ESA rescue therapy should be administered as per the local institution's guidelines and per the approved local product label. While receiving ESA rescue therapy, subjects must temporarily discontinue taking study medication (vadadustat or darbepoetin alfa). Hemoglobin will be monitored throughout the study at scheduled visits as defined in the Schedule of Activities using a HemoCue point of care device, and ESA rescue treatment should be stopped when Hb is ≥9.5 g/dL. A minimum interval must be observed prior to restarting vadadustat after the last dose of rescue medication, and treatment may be resumed after the following intervals: • 2 days after last dose of epoetin rescue • 7 days after last dose of darbepoetin alfa rescue • 14 days after last dose of methoxy polyethylene glycol-epoetin beta rescue. Following ESA rescue, the study medication should be resumed at the same dose as previously used or one dose higher and adjusted according to the Dose Adjustment Algorithms. 2. **RBC Transfusion:** Investigators will use their local institution's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, a RBC transfusion should be administered as clinically indicated. In less severe instances but where there may be worsening of anemia or moderate to severe symptoms of anemia, RBC transfusions are permitted at the discretion of the Investigator given the medical necessity. Reasons for RBC use will be captured in the appropriate CRF. Study medication (vadadustat or darbepoetin alfa) may be continued during the transfusion period.

Phlebotomy	If a subject's Hb exceeds 14.0 g/dL or the rate of rise of Hb raises concern to the Investigator, the subject may be phlebotomized based on the Investigator's judgment. The method of phlebotomy will be in accordance with the investigative site's standard clinical practice.
Study Medication Stopping Rules	Study medication must be permanently discontinued if a subject meets one of the criteria. • ALT **or** AST >3x Upper Limit of Normal (ULN) **and** total bilirubin >2x ULN • ALT **or** AST >3x ULN **and** INR >1.5 • ALT **or** AST >8x ULN • ALT **or** AST remains >5x ULN over 2 weeks* • ALT **or** AST >3x ULN with symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash) **or** eosinophilia **Re-challenge generally should be avoided with ALT or AST >5x ULN unless there are no other good therapeutic options.*
Study Completion, Subject Completion, Premature Termination of Study Medication, or Withdrawal from the Study	**Study Completion** The study will be considered completed (end of trial) when approximately 631 MACE events have accrued across the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015), and all enrolled subjects in this study have had the opportunity to have their Visit 13 (+/- 5 days). **Subject Completion** A subject will be considered as having completed the study, regardless of whether the subject is on or off study medication, and the subject is followed until global study end date as determined by the accrual of MACE. Subjects who continue on the study medication up to global study completion will complete the EOT visit, followed by the Follow-up visit, which will include recording the end of study (EOS) status. It is important to note that a subject's need for rescue therapy or initiation of dialysis, or the occurrence of MACE event(s): • Does not constitute study completion and • Is not criteria for subject withdrawal from the study or • Is not a requirement for permanent discontinuation of study medication (vadadustat or darbepoetin alfa). **Discontinuation of Study Medication Treatment** Subjects who discontinue study medication prior to global study completion are expected to continue to be followed post discontinuation of study medication. These subjects are to have their EOT visit at the time of discontinuing study medication, have the Follow-up visit and continue to be followed through global study completion. At the time of global study completion, each subject will have an EOS assessment to complete participation in the study. Receipt of rescue therapy is not a reason for permanent study medication discontinuation. While receiving ESA rescue, subjects must temporarily discontinue study medication, but are to resume study medication following the end of rescue therapy. During this study, it is anticipated that some subjects may permanently discontinue study medication (vadadustat or darbepoetin alfa) for any of the following reasons: • Unacceptable toxicity or drug intolerability • Investigator discretion

	• Subject withdrawal of consent • Subject becomes pregnant • Receipt of a kidney transplant • Lack of efficacy • Other reasons. Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or darbepoetin alfa) permanently discontinued. **It is important to continue to follow subjects that permanently discontinue study medication through global study completion. Please, see "Procedures to Avoid Withdrawal or Lost to Follow-Up" for options to maintain subjects in the study.** **Complete Withdrawal from Study Visits/Assessments** A subject has the right to withdraw consent for participation in the study at any time. Withdrawal of consent is a subject's refusal of ALL methods of follow-up noted in the informed consent form: procedures, participation in reduced procedures/study visits, telephone contact only or alternative contact only, source document or designated alternative contact, or access to medical records from alternative sources.It is important for the Investigator to review options with a subject that would allow follow-up through global study completion before the subject withdraws consent. For patients considering withdrawal of consent, the Investigator should consult with the Medical Monitor to ensure all options have been explored and that there is complete understanding by the subject for what withdrawal of consent constitutes.
Procedures to Avoid Withdrawal or Lost to Follow-Up	**Avoiding Withdrawal of Consent or Lost to Follow-Up** As part of the informed consent process, only subjects who fully understand and agree to full participation and long-term follow-up should be consented to participate. It is important that subjects understand the long-term duration and purpose of a cardiovascular outcome trial and that the subject (or designee) continue to allow follow-up through global study completion which could be several years, even post subject's permanent discontinuation of study medication. In all cases of impending study medication discontinuation or subject request for stopping study visits, Investigators will discuss with the subject their options of continuing in the study. It is important to continue to follow subjects that discontinue study medication through global study completion at a frequency and approach that is agreed to between the Investigator and subject. Visit schedule and assessments are flexible and at the discretion of the Investigator and subject and will be clearly documented in the medical chart. Optimal data collection would include the following assessments through global study completion. • EOS subject status (must collect at minimum) • MACE Endpoint Questionnaire • AE Assessment Alternative options to support continued follow-up include but are not limited to the following: 1. Reduced frequency of on-site visits 2. Telephone visits in lieu of on-site visits 3. Telephone or any contact method

	4. Telephone or any contact method with an alternative person (family member or medical designee) 5. Study team access to medical records for reporting MACE data or vital status 6. Reporting of vital status at the EOS visit which will occur at global study completion In the most extreme case, the protocol will accommodate minimal contact with a subject or alternative method to obtain vital status at the global study completion. The objective is to keep a subject's study status active to ascertain, at a minimum, vital status (alive or deceased) even if study medication is permanently discontinued (Section 7.5.5.2) or there is a significant change in a subject's personal or medical situation (i.e., home move, dialysis unit/provider change, kidney transplant, long-term care facility admission). The Investigator will ensure understanding and documentation of the reasons for a subject's desire to stop study procedures or stop study medication. **Minimizing Lost to Follow-Up** The Investigator must make every effort to contact subjects who fail to return for scheduled visits so that they will not be declared "lost to follow-up" (LFTU). These actions must include, but are not limited to, the following: 1. Contact all telephone numbers for the subject and his/her listed contacts (to be collected in the source at the subject's entry into the study), as applicable. This includes making phone calls after normal business hours or on holidays or weekends. 2. Contact the subject's primary care physician, referring specialist, pharmacist, or other healthcare professional, as applicable. 3. Send email, text, and postal mail with registered (traceable or trackable) letters to all the subject's addresses and contact persons, as applicable. Registered (traceable or trackable) letters need to be returned with a copy of the signature from whomever signed, which can be compared to the ICF for vital status data. If undeliverable, then send non-registered standard letters, which may be forwarded to a new address if the subject has moved. 4. Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the subject, as applicable. 5. Utilize the internet to search for additional contact information, as applicable. 6. Check local, regional, and national public records to locate the subject or search for mortality status as allowed by law, as applicable. It is important to obtain vital status at the global study completion for subjects that have been LTFU during the study. The Sponsor may utilize a third-party provider in accordance with all applicable guidelines and legislation to assist the site in locating contact information for all subjects during the study or in locating the vital status for all of their randomized subjects in anticipation of global study completion (end of trial).
Study Termination/ Individual Study Site Termination	The entire study may be suspended or terminated by the Sponsor for safety or other unanticipated reasons or upon request of regulatory agencies. If this occurs, prompt notification will be given to Investigators, Institutional Review Boards (IRBs)/Institutional Ethics Committees (IECs), and regulatory authorities in accordance with regulatory requirements. The Investigator must notify the Sponsor if the study is terminated by the Investigator or the IRB/IEC at the investigative site. If the Investigator, IRB/IEC, or Sponsor decides to terminate or suspend the study conducted at a particular investigative site for safety, non-enrollment, non-compliance with the protocol, or other unanticipated reasons, the above parties will be promptly notified.

Statistical Considerations	**Primary Efficacy Endpoint Analysis** The primary efficacy endpoint is defined as the mean Hb change from Baseline (mean pretreatment Hb) to the mean Hb from Weeks 24-36 (inclusive). The primary analysis will use an analysis ofcovariance (ANCOVA) with multiple imputation, stratified by the randomization strata and using Baseline Hb as the covariate. A 2-sided, 95% confidence interval will be calculated for the difference between the vadadustat group and control group. Noninferiority of vadadustat will be established if the lower limit of this confidence interval is ≥-0.75 g/dL. **Analysis of MACE and Expanded MACE Components** The MACE endpoint (adjudicated result) will be analyzed as the time (days) from randomization dateto first MACE +1. Subjects who have not experienced an adjudicated MACE by study closure will be censored as of their last assessment time. Major adverse cardiovascular events will be analyzed using a stratified Cox proportional hazards model with a model containing treatment group. The randomization strata will be used in this analysis. The primary MACE analysis will take place at study conclusion and will be based upon all subjects in the randomized population. The hazard ratio (vadadustat/control) will be estimated, together with its 95% confidence interval. As this individual study has not been powered to provide a stand alone assesment of MACE, this interval will be considered as descriptive. The time to first MACE will also be graphically presented using Kaplan-Meier curves. These analyses will be repeated with censoring occurring 4 weeks following early discontinuation of study medication. The following safety endpoints will also be summarized using time to event methods as for MACE: 1) Individual components (all-cause mortality, non-fatal myocardial infarction, non-fatal stroke) of MACE 2) Thromboembolic events (defined as arterial thrombosis, DVT, PE, or vascular access thrombosis) 3) Hospitalization for heart failure 4) Expanded MACE, defined as all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, hospitalization for HF, or thromboembolic event For these endpoints the incidence ("yes"/"no") of the endpoint will be presented for each treatment arm. Kaplan-Meier curves will be presented for each endpoint as the time of endpoint free survival (ie, time until endpoint or death). An independent statistical analysis center will perform analyses in support of the Independent Data Monitoring Committee (IDMC).
Sample Size Estimation	For the primary efficacy analysis in this study, it will be assumed that the difference in mean change in Hb for vadadustat will be the same as the active control, darbepoetin alfa, and the common standard deviation for the mean change will be assumed to be 1.5 g/dL. The noninferiority margin of -0.75 g/dL will be used. With these assumptions and approximately 925 subjects per treatment group, the noninferiority evaluation will have > 90% power. The primary MACE analysis will be based upon all events that accrue across the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015). It has been calculated that 631 events will be required overall to have 80% power to establish noninferiority with a margin of 1.25, when evaluated with a 2-sided 95% confidence interval assuming no difference between the treatments. The power is >90% to establish a noninferiority margin of 1.25 if the hazard ratio is 0.95 favoring vadadustat.

	A MACE rate of 10% annually is anticipated in both treatment arms based on a comprehensive review of available epidemiology and prospective clinical studies in the field.
Independent Data Monitoring Committee	An IDMC will be established to review and discuss the available study safety data as subjects are enrolled and followed. The team will meet approximately twice per year throughout the course of the study. The IDMC will be unblinded and will include, at a minimum, a nephrologist, a cardiologist, and a biostatistician. The discussions of the IDMC will include a review of key safety data (ie, AEs, vital signs measurements, and laboratory assessments).
Endpoint Adjudication Committee (EAC)	An independent safety EAC, blinded to treatment group, will be formed prior to study commencement to adjudicate the components of the primary safety endpoints (eg, all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke). Thromboembolic events and hospitalization for HF will also be adjudicated by the EAC.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AST	aspartate aminotransferase (SGOT)
β-HCG	beta human chorionic gonadotropin
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CBC	complete blood count
CHF	congestive heart failure
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CS	clinically significant
CV	cardiovascular
CVD	cardiovascular disease
DD-CKD	dialysis-dependent chronic kidney disease
DILI	Drug-Induced Liver Injury
dL	deciliter
DNA	deoxyribonucleic acid
DVT	deep venous thrombosis
EAC	Endpoint Adjudication Committee
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ESC	Executive Steering Committee
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GMP	Good Manufacturing Practice
HA	health authority
Hb	hemoglobin
HDL	high-density lipoprotein

HF	heart failure
HIF	hypoxia-inducible factor
HIFPH	hypoxia-inducible factor prolyl-hydroxylase
HIF-PHI	hypoxia-inducible factor prolyl-hydroxylase inhibitor
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonization
ID	identification
IDMC	Independent Data Monitoring Committee
IDMS	isotope dilution mass spectrometry
IEC	independent ethics committee
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRB	institutional review board
IV	intravenous(ly)
IWR	interactive web response
JSDT	Japanese Society for Dialysis Therapy
JSN	Japanese Society of Nephrology
KDIGO	Kidney Disease: Improving Global Outcomes
kg	kilogram
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of normal
LTFU	Lost to Follow Up
MACE	major adverse cardiovascular events
MCH	mean corpuscular (cell) hemoglobin
MCHC	mean corpuscular (cell) hemoglobin concentration
MCV	mean corpuscular (cell) volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
µM	micromolar
mg	milligram
mL	milliliter
mmhg	millimeters of mercury
mRNA	messenger ribonucleic acid
NDD-CKD	non-dialysis dependent chronic kidney disease
ng	nanogram
NYHA	New York Heart Association
PD	pharmacodynamics(s)
PE	pulmonary embolism
PHD	prolyl 4-hydroxylase domain
PI	package insert
PK	pharmacokinetic(s)
PP	per protocol
PT	prothrombin time
PTT	partial thromboplastin time
QA	quality assurance

QC	quality control
RBC	red blood cell
RDW	red cell distribution width
ROW	rest of world
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SCr	serum creatinine
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SmPC	summary of product characteristics
SV	Screening visit
TIBC	total iron binding capacity
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
TSAT	transferrin saturation
uACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VHP	Voluntary Harmonisation Procedures
WBC	white blood cell
WHO	World Health Organization

4 BACKGROUND INFORMATION

Chronic kidney disease (CKD), defined as the presence of kidney damage or a decreased level of kidney function, is a major public health problem worldwide. Globally, CKD is estimated to affect between 8-16% of the population (Jha et al. 2013; KDIGO 2013). At the most advanced stages of CKD, end-stage renal disease (ESRD), patients require chronic dialysis or kidney transplantation to sustain life. Chronic kidney disease is not only a cause of ESRD, but is also a significant risk factor for cardiovascular disease (CVD), infection, cancer, and mortality (Iseki and Kohagura 2007).

Renal anemia often develops during the progression of CKD and is present in almost all patients with ESRD. Anemia is defined as a decrease in circulating red blood cell (RBC) mass that is usually detected by low hemoglobin (Hb) concentration. The causes of anemia in CKD include blood loss, shortened RBC lifespan, iron deficiency, erythropoietin (EPO) deficiency, and inflammation (Nurko 2006). Although many factors contribute to anemia in CKD, it occurs primarily due to an inadequate synthesis of EPO by the kidneys, leading to a deficiency in the production of RBC progenitor cells by the bone marrow. Also contributing to anemia in CKD are impaired iron homeostasis and iron loss, which often necessitate iron supplementation (Nurko 2006). Anemia in CKD patients usually occurs when the glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m^2, and is present in >90% of the patients undergoing dialysis (CKD Stage 5) (Goodkin et al. 2011).

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 and Fan 2014). In patients with anemia related to CKD, compensatory changes occur in cardiac structure and function, including an increase in cardiac output, the development of left ventricular hypertrophy, and, eventually, the development of heart failure (Metivier et al. 2000). Risk of stroke also increases with anemia, which may be an underlying mechanism leading to stroke in CKD (Abramson et al., 2003; Iseki and Kohagura 2007). 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 these patients (Iseki and Kohagura 2007; NICE 2011). Overall, anemia contributes to a poorer prognosis in patients with CKD (Nurko 2006; Iseki and Kohagura 2007).

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

Clinical practice guidelines and prescribing information for approved ESAs and guidelines provided by the United States (US) Food and Drug Administration (FDA), the European Union (EU), the Japanese Society of Nephrology, and the Japanese Society for Dialysis Therapy Guideline Committee differ slightly in their recommendations for treatment of renal anemia, as summarized in Table 1.

Table 1 Treatment Guidelines and Prescribing Information for Renal Anemia in NDD-CKD

KDIGO guidelines	Treatment should occur in symptomatic patients and when Hb generally falls below 10 g/dL (Kidney Disease: Improving Global Outcomes [KDIGO] 2012).
US darbepoetin alfa label	Same as other approved ESAs, but also recommend that if Hb exceeds 10 g/dL in adults not on dialysis, the dose of ESA should be reduced or interrupted (darbepoetin alfa [Aranesp®] US Package Insert 2017).
EU practice guidelines	Recommend that in high-risk patients with non-dialysis dependent CKD (NDD-CKD), treatment with ESAs should be initiated when the Hb levels are between 9 g/dL and 10 g/dL, although in low-risk patients and those in whom a clear benefit of quality of life can be foreseen, the initiation of ESA therapy could be considered at higher Hb levels (Locatelli 2013). Detailed information on darbepoetin alfa in the EU is available on the European Medicines Agency web site.
Japan practice guidelines	JSDT recommends that ESA treatment be initiated when Hb is below 11 g/dL following a diagnosis of renal anemia in NDD-CKD. JSN 2013 does not provide a clear recommendation or maintenance range for Hb. Both guidelines recommend that if the Hb exceeds 13 g/dL, the dose of ESA should be reduced or interrupted. In patients with CVD or complications, ESA treatment should be reduced or interrupted if the Hb exceeds 12 g/dL (Tsubakihara 2010; Japanese Society of Nephrology 2014).

Abbreviations: CVD = cardiovascular disease; ESA = erythropoietin stimulating agent; EU = European Union; Hb = hemoglobin; JSDT = Japanese Society for Dialysis Therapy; JSN = Japanese Society of Nephrology; KDIGO = Kidney Disease Improving Global Outcomes; NDD-CKD = non-dialysis dependent chronic kidney disease; US = United States.

The majority of patients with CKD currently receive interventional therapy in the form of iron therapy, and may initiate therapy with an ESA if other interventions fail and Hb levels fall below 9 to 11 g/dL, dependent upon local clinical practice guidelines.

A number of large, prospective, randomized controlled trials in CKD (Stages 3 to 5) have explored the potential benefit of ESAs in patients with CKD with respect to overall mortality, cardiovascular (CV) events, and progression of CKD with higher Hb targets (≥13 g/dL) (Besarab et al. 1998; Drüeke et al. 2006; Singh et al. 2006; Pfeffer et al. 2009a; Pfeffer et al. 2009b). These trials did not demonstrate the expected beneficial effects of correcting anemia on these outcomes, but suggested an increased risk of death and CV events when targeting higher Hb levels (Besarab et al. 1998; Drüeke et al. 2006; Singh et al. 2006; Pfeffer et al. 2009a; Pfeffer et al. 2009b). Additional analyses from these trials suggest that the risk of death or CV events appears to be highest in CKD patients who fail to respond to ESAs, as indicated by lower achieved Hb levels and higher average ESA dose requirements (Szczech et al. 2008; Solomon et al. 2010). This suggests that in some subjects the ESAs themselves, and not the Hb level, may be causative of the increase in events. This is supported by studies in CKD patients on dialysis with naturally high Hb levels and no increase in CV events (Goodkin et al. 2011).

The risks identified with ESAs from these trials have led to changes in prescribing information and practice guidelines in the US, the EU, and Japan that guide clinicians toward more cautious use of ESAs and targeting lower Hb levels. In the US, the mortality and CV risks associated with ESAs are outlined in a black-box warning in the prescribing information of ESAs with a recommendation to use the lowest dose possible to avoid transfusions. While no similar major warnings exist in the EU Summary of Product Characteristics (SmPC) or on the approved labeling for ESAs in Japan, the EU SmPCs for ESAs do suggest caution with the use of these drugs, with a recommendation to keep Hb levels below 12 g/dL, while the Japanese practice

guidelines recommend ESA treatment be reduced or interrupted if the Hb exceeds 12 g/dL in patients with CVD or complications. Further, recent EU clinical practice guidelines (Locatelli et al. 2013) recommend 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 decisions to use ESAs for the treatment of anemia.

The risks associated with ESAs, including an increased risk of death and CV events, highlight the need for additional therapies that might minimize or avoid these risks when compared to currently available recombinant protein-based ESAs. Therefore, the unmet medical need for the treatment of anemia in non-dialysis dependent CKD (NDD-CKD) patients remains high, especially from a CV safety perspective. To fulfill this unmet need, the vadadustat clinical program is focused on developing an orally active therapeutic for the treatment of anemia in patients with CKD.

4.1 Hypoxia-Inducible Factor Prolyl-Hydroxylase Inhibitors

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

Vadadustat is a synthetic, orally bioavailable, small molecule being developed as an inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIFPHs) for the treatment of anemia associated with CKD. Hypoxia-inducible factor prolyl-hydroxylase enzymes are also referred to as prolyl 4-hydroxylase domains (PHDs), of which the 2 most commonly expressed are PHD2 and PHD3. Vadadustat is a slightly more potent inhibitor of PHD3 (50% inhibitory concentration [IC_{50}] = 0.08 μM) than of PHD2 (IC_{50} = 0.19 μM). The inhibition of PHD3 and PHD2 stabilizes hypoxia-inducible factor (HIF)-2α and HIF-1α, which in turn stimulates the production of EPO. In vivo animal efficacy and messenger ribonucleic acid (mRNA) data indicate that vadadustat induces the production of EPO from both renal and extra-renal sites (liver and brain), and this increase in EPO results in an increase in RBC production in the bone marrow. In clinical trials, vadadustat has been shown to facilitate iron homeostasis by decreasing hepcidin and increasing transferrin levels in healthy adult male volunteers and male and female CKD patients. This enables iron transport mechanisms that should enhance the terminal steps of erythropoiesis. Vadadustat offers the potential of flexible oral dosing that provides a more gradual and reliable means of titration than injectable hormones. Therefore, vadadustat is being developed as an alternative to the existing protein hormone ESAs.

4.2 Summary of Clinical Experience

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

To date, the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of vadadustat have been characterized in 9 completed Phase 1 studies in healthy volunteers, including 1 ethno-bridging study in Caucasian and Japanese subjects, 1 completed Phase 1 study in subjects undergoing chronic hemodialysis, 3 completed Phase 2a studies in NDD-CKD subjects, 1 completed Phase 2b study in NDD-CKD subjects, and 1 completed Phase 2 study in DD-CKD subjects. The Phase 2a studies evaluated Stages 3, 4, and 5 CKD (not on dialysis) subjects in a single-dose PK study, a multi-dose, 28-day, open-label, dose escalation pilot study, and a randomized, placebo-controlled study with 5 different dose groups dosed for 42 days. The Phase 2b study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 20 weeks. The phase 2

study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. In the studies completed to date, a total of 548 subjects have received vadadustat, including 200 healthy volunteers and 348 subjects with CKD.

Vadadustat showed dose-dependent increases in EPO concentrations in Phase 1 and Phase 2a studies. The changes in EPO have been accompanied by an increase in reticulocytes as well as dose responsive increases in total iron binding capacity [TIBC] and decreases in hepcidin and ferritin. Overall, the safety profile for vadadustat has been acceptable and has supported further development. Vadadustat has demonstrated dose proportional PK and dose-dependent PD (changes in serum EPO and/or Hb) in Phase 1 and Phase 2 studies covering the dose range of 80 mg to 1200 mg after single administration and 500 to 900 mg after repeated daily administration. The plasma half-life of vadadustat was about 4 – 5 hours, 7 – 8 hours, and 9 to 10 hours in healthy subjects, NDD-CKD patients, and DD-CKD patients, respectively.

Vadadustat is extensively metabolized. Vadadustat and its metabolites are eliminated from the body by dual routes of elimination, renal and fecal. The urinary excretion of vadadustat and its metabolites has been shown to be less than 60% in healthy human volunteers. In a clinical study conducted to evaluate the effect of hemodialysis on the exposures to vadadustat, hemodialysis did not have an effect on the exposures of vadadustat or its metabolites. Given its short half-life and the dual routes of elimination, vadadustat is unlikely to accumulate in patients with CKD.

The 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. 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. Compared with the placebo group, the vadadustat-treated group demonstrated a significantly higher proportion of responders, defined as subjects achieving a Hb≥11.0 g/dL or an increase ≥1.2 g/dL from baseline (54.9% versus 10.3%). Few vadadustat subjects exhibited Hb excursions >13.0 g/dL (4.0%), and favorable changes in iron mobilization and utilization were observed with treatment with vadadustat. The safety profile of vadadustat in this study supported further development.

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

4.3 Potential Benefits and Risks

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

Trials of injectable erythropoiesis-stimulating agents (ESAs) in patients with anemia secondary to NDD-CKD or DD-CKD have demonstrated an increased risk of cardiovascular events associated with higher Hb targets (Besarab 1998; Singh 2006; Pfeffer 2009). Post-hoc analyses performed by the FDA and others have shown an association between these adverse outcomes and supraphysiologic serum EPO levels and/or Hb oscillations and overshoots (McCullough 2013, Unger 2010). In studies to date, oral vadadustat daily increased mean Hb with few excursions above the target range. In addition, serum EPO levels remained well below those

reported with ESAs in the literature. As a result, there is the potential for the investigational drug vadadustat to provide an effective and safe therapeutic option for the treatment of renal anemia.

In addition, vadadustat may enhance iron metabolism and transport. Phase 1 and Phase 2 trials have demonstrated a consistent dose-dependent increase in TIBC and decrease in ferritin and hepcidin. Mechanistic studies have demonstrated that HIF stabilization downregulates the iron absorption regulator hepcidin, and upregulates the iron-mobilizing regulators ferroportin and transferrin (and its receptor) (Peyssonnaux et al. 2007). Potential clinical benefits include enhanced erythropoiesis and decreased exogenous iron requirements.

The toxicological profile of vadadustat supports continued development in the ongoing Phase 3 clinical trials. Dose-limiting toxicity noted in the exploratory toxicology studies was due to hemoglobinuric nephropathy (rat) and emesis associated with body weight loss (dog). Dose-limiting toxicity noted in the sub-chronic and chronic toxicology studies was due to exaggerated pharmacology and the sequelae of events related to polycythemia (increased RBC mass, blood hyperviscosity and fibrin thrombi); polycythemia-related toxicity was consistent across species, monitorable and reversible. In the completed clinical studies, vadadustat has had an acceptable safety profile to support further development.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

The primary objective of this study is to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with NDD-CKD after conversion from current ESA therapy.

5.2 Primary Efficacy Endpoint

The primary endpoint used to assess the efficacy objective will be the mean change in Hb between Baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36).

5.3 Secondary Efficacy Endpoints

The key secondary efficacy endpoints include the following:

- Mean change in Hb value between Baseline (mean pretreatment Hb) and the secondary evaluation period (Weeks 40-52)
- Proportion of subjects with Hb values within the target range during the primary evaluation period (Weeks 24-36)
- Proportion of subjects with Hb values within the target range during the secondary evaluation period (Weeks 40-52)

Other secondary efficacy endpoints include:

- Proportion of time with Hb values within the target range during the primary evaluation period (Weeks 24-36)
- Proportion of time with Hb values within the target range during the secondary evaluation period (Weeks 40-52)
- Proportion of subjects with Hb increase of >1.0 g/dL from Baseline

- Time to achieve Hb increase of >1.0 g/dL from Baseline
- Mean change in Hb between Baseline (mean pretreatment Hb) and the primary evaluation period (mean Hb from Weeks 24-36) stratified by pre-baseline ESA exposure
- Progression of CKD
- Proportion of subjects receiving IV iron therapy from Baseline visit to Week 52
- Mean monthly dose of IV elemental iron administered from Baseline to Week 52 in subjects who have received IV iron
- Proportion of subjects receiving RBC transfusion(s) from Baseline to Week 52
- ESA rescue
- Dose adjustments from Baseline to Week 52
-

5.4 Safety Endpoints

Safety endpoints in this study include the following:

- Major adverse cardiovascular events (MACE), defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke
- Individual components of MACE:
  - All-cause mortality
  - Non-fatal myocardial infarction
  - Non-fatal stroke
- Thromboembolic events: arterial thrombosis, deep vein thrombosis (DVT), pulmonary embolism (PE), or vascular access thrombosis
- Hospitalization for heart failure (HF)
- Expanded MACE, defined as all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, hospitalization for HF, or thromboembolic event
- Fatal/non-fatal MI
- Fatal/non-fatal stroke
- Sudden death
- Cardiovascular death
- Non-cardiovascular death
- Hospitalization
- Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dLHb < 8.0 g/dL
- Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval
- AEs and SAEs
- Vital signs and clinical laboratory values

5.5 Exploratory Endpoints

- Biomarkers (including by not limiter to hepcidin, and vascular endothelial growth factor [VEGF])
- Time to achieve stable Hb values within the target range
- Proportion of subjects with Hb values within the target range without evidence of iron overload

6 STUDY DESIGN

6.1 Study Design

This is a Phase 3, randomized, open-label, active-controlled study of the efficacy and safety of vadadustat versus darbepoetin alfa for maintenance treatment of anemia after conversion from current ESA therapy in subjects with NDD-CKD. Target enrollment in this study is approximately 1850 subjects at approximately 480 investigative sites in North America, Latin America, Europe, and Asia Pacific.

Subjects will be randomized at the Baseline visit using an Interactive Web Response (IWR) system to receive either vadadustat or darbepoetin alfa (based on the current PI for investigational sites in the US, and the SmPC for all other investigational sites (non-US) for adult patients with CKD not on dialysis). For all subjects, it is recommended that no additional ESA doses be administered after Screening visit 2 (SV2) and prior to the Randomization visit.

Randomization will be stratified by geographic region (US versus EU versus rest of world [ROW]), New York Heart Association congestive heart failure (CHF) Class 0 (no CHF) or I versus II or III, and study entry Hb level (<10.0 g/dL versus ≥10.0 g/dL based on the most recent central laboratory Hb measurement prior to the Baseline/Randomization visit). Following randomization, there will be 3 periods during the study:

- Conversion and Maintenance Period (Weeks 0-52): conversion to study medication for maintaining Hb (Weeks 0-23), primary efficacy evaluation (Weeks 24-36), and secondary efficacy evaluation (Weeks 40-52)
- Long-term Treatment Period (Week 53-EOT): continued study medication to assess long-term safety
- Follow-up Period (EOT + 4 weeks): post-treatment visit for safety (either in person or via telephone).

A HemoCue® point of care device will be used throughout the study to monitor Hb to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be adjusted. From Weeks 0 to 12, HemoCue will be used to monitor Hb every 2 weeks for dose adjustment. From Week 12 to Week 52, Hb will be monitored via HemoCue every 4 weeks. From Week 53 through the end of study, Hb will continue to be monitored via HemoCue to determine if the dose of study medication will be adjusted, interrupted, or maintained. Hemoglobin will also be assessed with a complete blood count (CBC) through the central laboratory for efficacy and safety evaluations; however, dose adjustments should be based on the HemoCue Hb value.

The aim of the dosing strategy is to maintain Hb levels of 10.0 g/dL to 11.0 g/dL in the US and 10.0 g/dL to 12.0 g/dL outside of the US throughout the study.

Subjects assigned to vadadustat will initiate dosing at 2 tablets once daily at the Baseline visit. Adjustments to doses for vadadustat will be guided by Hb concentration and Dose Adjustment Algorithms (Section 8.4.4.1, Vadadustat Dosing and Dose Adjustment Algorithms).

Subjects assigned to darbepoetin alfa will be dosed SC at the Baseline visit and the initial dose will be determined based on the current PI for investigational sites in the US, and the SmPC for all other investigational sites (non-US) for adult patients with CKD not on dialysis. Dose adjustments will be based on Hb concentration and Dose Adjustment Algorithms (Section

8.4.4.2, Darbepoetin Alfa Dosing and Dose Adjustment Algorithms). Darbepoetin alfa dosing is independent of the visit schedule, and the dosing schedule may shift per local standard of care and per Investigator discretion.

Investigators will prescribe iron supplementation during the study to maintain ferritin ≥100 ng/mL or TSAT ≥20% (see Section 8.4.6, Iron Supplementation for details regarding iron supplementation during the study). Subjects already receiving oral iron supplementation as part of their treatment plan may continue their current treatment regimen.

Clinical and safety assessments (including laboratory assays, PK evaluations [both vadadustat parent compound and metabolites], MACE endpoint data, vital sign measurements, and AEs) will be performed as indicated at Screening, during the Conversion and Maintenance Period (Weeks 0-52), during the Long-term Treatment Period (visits approximately every 3 months), and during the Follow-up Period (4 weeks after the EOT). Refer to Section 9, Study Procedures and Schedule of Activities and Appendix A: Schedule of Activities for additional details.

The study will be considered completed (end of trial) when approximately 631 major adverse cardiovascular events (MACE) have accrued over the 2- NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015), and all enrolled subjects have had the opportunity to have their Visit 13 (+/- 5 days). All subjects will remain in the study until the global study completion (end of trial), at which time subjects will be scheduled for a final visit, and the study will close (see Section 11.1.2, Sample Size for the Primary Safety Endpoint).

6.2 Rationale for Study Design

During prior clinical trials, vadadustat has demonstrated dose proportionate PK and dose-dependent PD. Vadadustat showed dose-dependent increases in EPO concentrations in Phase 1 and Phase 2 studies. The changes in EPO have been accompanied by an increase in reticulocytes as well as dose responsive increases in TIBC and decreases in hepcidin and ferritin. Overall, the safety profile for vadadustat has been acceptable and has supported further development. Finally, the urinary excretion of vadadustat and its metabolites has been shown to be less than 60% in humans.Given its short half life and the dual routes of elimination, vadadustat is unlikely to accumulate in patients with CKD. Based on the Phase 1 and Phase 2 study results, continued development of vadadustat as a treatment for anemia in patients with CKD is warranted.

In this study, darbepoetin alfa was chosen as an active comparator as it has a longer half-life than epoetin alfa and, therefore, requires less frequent dosing visits. Selection of a comparator is challenging in the current medical and regulatory climate given the accumulating trial findings that resulted in the FDA revising the prescribing information for the currently marketed ESAs. These trial results indicate an increased risk of death and adverse CV events, such as stroke and heart failure, particularly when using ESAs to achieve a higher Hb concentration. In the US, the mortality and CV risks associated with ESAs are outlined in a black-box warning in the prescribing information of ESAs, with a recommendation to use the lowest dose possible to avoid transfusions. While no similar major warnings exist in the EU SmPC or on the approved labeling for ESAs in Japan, the EU SmPCs for ESAs do suggest caution with the use of these drugs, with a recommendation to keep Hb levels below 12 g/dL. Recent clinical practice guidelines (Locatelli et al. 2013) recommend that risk factors for stroke and malignancy should also be taken into account when making treatment decisions to use ESAs for the treatment of anemia.

Given the concerns associated with marketed ESAs, a goal of this study will be to evaluate the CV events during the treatment of anemia with vadadustat. The inclusion of a MACE endpoint in this study will allow for a statistical comparison of the rates of CV events between vadadustat and darbepoetin alfa treatment groups when used to treat anemia associated with NDD-CKD. While the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) (Pfeffer et al 2009b) compared different Hb targets, the present study will have similar Hb targets between treatment arms. Importantly, the Hb goals for this study are lower than those used in TREAT and are consistent with practice guidelines and prescribing information for approved ESAs.

This study will be performed as an open-label study. Because Hb values are objective and will be measured via a central laboratory for all efficacy endpoints, efficacy assessments are not considered to be subject to bias with an open-label design. Blinding of this study presented inherent practical problems, including potential dosing errors, inappropriate dose adjustments, and delays in dosing, which may also increase the safety risk to study participants. Given the differing dosing regimens and routes for vadadustat (oral) and darbepoetin alfa (SC injection), a double-dummy design would have been required which also created ethical concerns and required extensive coordination to maintain the blind.

To minimize bias, Sponsor and contract research organization (CRO) study teams will remain blinded to 'by treatment' aggregated analyses, except for the unblinded statistician. In addition, the study will involve blinded adjudication of MACE, the use of an independent data monitoring committee (IDMC), and an identical schedule of visits, procedures, and assessments for both treatment groups in order to reduce the potential for bias. However certain personnel directly involved in medical oversight of the study, regulatory reporting of safety information, and on-site monitoring activities may become unblinded to the treatment assignments of individual subjects during the course of the study.

In addition, to reduce subjectivity of dose adjustment, adjustments to doses for vadadustat and darbepoetin alfa will be guided by Hb concentration and the Dose Adjustment Algorithms.

6.3 Dose Justification

The starting dose and the proposed dosing algorithm in this study are designed to increase and maintain Hb in a predictable and controlled manner while minimizing abrupt increases or excessive rises in Hb levels. Based on plasma concentrations and PD measures from previously conducted clinical studies with vadadustat, a population PK/PD model was developed. Using this model and the proposed dosing algorithm, simulations were carried out to evaluate the effects of different starting doses and the resulting Hb responses to support the dosing rationale. Results of the simulations indicated that a starting dose regimen of 300 mg once daily along with the proposed dosing algorithm are optimal to increase and maintain Hb levels of 10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL outside of the US while minimizing excessive rises.

6.4 Executive Steering Committee and Independent Data Monitoring Committee

6.4.1 Executive Steering Committee

An Executive Steering Committee (ESC) will be established, which will be blinded to the randomization, and will oversee the study and provide expert input to assure a high scientific standard. The ESC may function as the Publication Committee. The ESC membership will comprise recognized academic leaders, including those from the field of nephrology and

cardiology. Details on the roles and responsibilities of the ESC will be described further in the ESC charter.

6.4.2 Independent Data Monitoring Committee

An IDMC will be established to review and discuss study safety data as subjects are enrolled and followed. The team will meet approximately twice per year throughout the course of the study. The IDMC will be unblinded and will include, at a minimum, a nephrologist, a cardiologist, and a biostatistician. The discussions of the IDMC will include a review of key safety data (ie, AEs, vital signs, and laboratory assessments). Written records of the IDMC meetings, the materials reviewed, and the decisions made will be maintained. Details on the roles and responsibilities of the IDMC and guidelines for monitoring study safety data will be described further in the IDMC charter.

6.5 Endpoint Adjudication Committee

An independent safety endpoint adjudication committee (EAC) will be formed prior to study commencement to adjudicate the primary safety endpoints (all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke). Thromboembolic events and hospitalization for HF will also be adjudicated by the EAC. The committee will be blinded throughout the course of the study. The EAC will be composed of independent experts with experience and training appropriate for adjudication of MACE, thromboembolic events, and hospitalization for HF. Details on the responsibilities of the EAC will be described further in the EAC charter.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 General Criteria

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

An optional Pre-Screen visit can be used to perform initial testing of the Hb level using a HemoCue point of care device to evaluate whether a subject should progress to full Screening procedures. A separate Pre-Screen informed consent (distinct from the full protocol informed consent) will be implemented for the Pre-Screen visit. To be eligible for the Pre-Screen Hb measurement, a study subject or their legally acceptable representative must provide valid informed consent prior to the Pre-Screen procedure. For a better understanding of the Pre-Screening visit, please see Section 9.3.1, Pre-Screening Visit.

7.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible:

1. At least 18 years of age
2. Diagnosis of CKD with an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation during Screening (see Appendix B: CKD-EPI Creatinine Equation) and not expected to start dialysis within 6 months of Screening

3. Currently maintained on ESA therapy with a dose received within 6 weeks prior to or during Screening
4. Mean Screening Hb between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) outside of the US, as determined by the average of 2 Hb values measured by the central laboratory during Screening
5. Serum ferritin ≥100 ng /mL and TSAT ≥20% during Screening
6. Folate and vitamin B_{12} measurements ≥lower limit of normal (LLN) during Screening
7. 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 presenting with any of the following will not qualify for entry into the study:

1. Anemia due to a cause other than CKD or subjects with active bleeding or recent blood loss
2. Subjects with sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia
3. RBC transfusion within 8 weeks prior to randomization
4. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2.0 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded.
5. Uncontrolled hypertension (confirmed diastolic blood pressure >110 mmHg or systolic blood pressure >180 mmHg) during Screening
6. Severe heart failure during Screening (New York Heart Association Class IV)
7. 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 HF, or stroke within 12 weeks prior to or during Screening
8. History of active malignancy within 2 years prior to or during Screening, except for treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ
9. History of DVT or PE within 12 weeks prior to randomization
10. History of hemosiderosis or hemochromatosis
11. 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)
12. 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 the Screening visit
13. Previous participation in this study, or previous participation in a study with a hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) other than vadadustat
14. Females who are pregnant or breast-feeding. Women of childbearing potential who are unable or unwilling to use an acceptable method of contraception (refer to Section 9.1.3, Contraception and Pregnancy Avoidance Measures)
15. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception (refer to Section 9.1.3, Contraception and Pregnancy Avoidance Measures)

16. Any other reason that in the opinion of the Investigator would make the subject not suitable for participation in the study
17. Hypersensitivity to darbepoetin or vadadustat, or to any of their excipients

7.4 Retesting and Rescreening

Subjects who fail to qualify for the study based on certain laboratory parameters may be retested and/or rescreened at the discretion of the Investigator.

7.4.1 Retesting

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

Subjects who initially fail to qualify for the study based on laboratory test results may have any individual laboratory parameter retested 1 time within the 8-week Screening period at the discretion of the Investigator. Retesting within the 8-week Screening period does not constitute rescreening; however, if retesting falls outside of the 8-week Screening period, it should be considered a rescreen. All Screening laboratories, including any repeat measurements, must be performed within the 8-week Screening window with a minimum of 4 days between the last qualifying repeat measurement and the Baseline visit.

For eligibility, the average of 2 Hb values measured by the central laboratory during Screening (SV1, SV2, or retest) must be < 11.0 g/dl in the US or < 12.0 g/dl outside the US.

Subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} values may receive replacement therapy based on the investigative sites' standard of care during the screening period and retest the laboratory parameter(s). Subjects who receive iron replacement may retest screening Hb a minimum of 3 weeks after completion of iron replacement therapy.

7.4.2 Rescreening

Subjects who fail to meet the qualifying criteria for Hb or eGFR during a Screening period may be considered for rescreening at the discretion of the Investigator if it is felt that the subject's status has progressed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} values may be considered for rescreening after receiving replacement therapy.

Screening is limited to 3 attempts (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, Subject Completion, Study Discontinuation, and Withdrawal of Subjects

7.5.1 Study Completion

The study will be considered completed (end of trial) when approximately 631 MACE events have accrued across the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015), and all enrolled subjects have had the opportunity to have their Visit 13 (+/- 5 days). These 2 NDD-CKD studies were sized based on power considerations for the primary safety analysis of MACE events, and thus each study is highly powered (>90%) for the primary and

key secondary efficacy analysis. Thus, primary efficacy analyses will be based on the randomized population and every subject will have completed (or had the opportunity to complete) the primary evaluation period (Weeks 24-36).

7.5.2 Subject Completion

A subject will be considered as having completed the study, regardless of whether they are on or off study medication (vadadustat or darbepoetin alfa), if the subject is followed until global study completion (end of trial). The table outlines the different categories of subjects and handling the global study completion activities.

Subject Status at time of Global Study Completion	End of Treatment (EOT)	End of Study (EOS)
Subject on study medication (includes those on temporary interruption)	After announcement of global study completion: • Perform EOT visit • Perform the Follow-up visit 4 weeks after EOT visit and include End of Study (EOS) subject status	Not applicable The EOS subject status will be captured as part of the Follow-up visit
Subject permanently discontinued study medication and continues to be followed in the study	At time of permanent discontinuation of study medication: • Perform EOT visit • Perform the Follow-up visit 4 weeks after EOT visit	Optimal data collection would include the following assessments: • EOS subject status (must collect at minimum) • MACE Endpoint Questionnaire • AE Assessment
Subject Lost to Follow-up	Not applicable	Work with third party vendor to ascertain vital status and complete EOS subject status If subject-site contact is reestablished and possible, collect available information for EOS subject status
Subject Withdrawn Consent	Not applicable	Complete the EOS subject status form at time of withdrawal of consent, absolute refusal of ALL methods of MACE and health status follow-up

Subject Death	Not applicable	Complete the EOS subject status form at the time of death (see Section 10 Adverse Events for more details on other actions related to reporting a death)

The need for rescue therapy does not constitute study completion and is not a criterion for subject withdrawal from the study. Also, the occurrence of a safety endpoint, or if a subject progressed to chronic dialysis dependent CKD (DD-CKD), does not constitute study completion and is not a criterion for subject withdrawal from the study or study medication (vadadustat or darbepoetin alfa).

7.5.3 Entire 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, Criteria for Premature Termination or Suspension of the Study.

7.5.4 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, Criteria for Premature Termination or Suspension of Investigational Study Sites and Section 14.3, Procedures for Premature Termination or Suspension of the Study or Investigational Sites.

7.5.5 Individual Subject Discontinuation

During this study, it is anticipated that some subjects may permanently discontinue study medication (vadadustat or darbepoetin alfa) for any of the following reasons:

- Unacceptable toxicity or drug intolerability
- Investigator discretion
- Subject withdrawal of consent
- Subject becomes pregnant
- Receipt of a kidney transplant
- Lack of efficacy
- Other reasons.

Lack of efficacy is defined as inadequate response to darbepoetin alfa or vadadustat in the investigator's opinion.

Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or darbepoetin alfa) permanently discontinued.

See Section 9.4, Study Medication Stopping Rules for additional details on the management of subjects with ALT and AST abnormalities.

It is important to continue to follow subjects that permanently discontinue study medication. Please see Sections 7.5.5.1, Temporary Interruption of Study Medication and 7.5.5.2, Permanent Discontinuation of Study Medication, and Appendix A: Schedule of Activities).

Receipt of rescue therapy is not a reason for permanent study medication discontinuation. While receiving ESA rescue, subjects must temporarily discontinue study medication (vadadustat or darbepoetin alfa), but should resume study medication once rescue therapy has ended, as detailed in Section 8.4.7, Rescue Therapy.

As part of the informed consent process, only subjects who fully understand and agree to full participation and long-term follow-up should be consented to participate.

7.5.5.1 Temporary Interruption of Study Medication

Subjects who temporarily interrupt study medication (vadadustat or darbepoetin alfa) treatment after the first dose and prior to completion of the study will continue with study visits and assessments. Unless contraindicated, treatment should be resumed wherever possible and routinely considered at every visit following study medication discontinuation. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. If a subject's study medication has been temporarily interrupted for more than 60 days, the Investigator should contact the Medical Monitor before resuming study medication.

7.5.5.2 Permanent Discontinuation of Study Medication

Subjects who permanently discontinue study medication prior to global study completion are expected to continue to be followed post discontinuation of study medication. These subjects are to have their EOT visit at the time of permanent discontinuation of study medication have the Follow-up visit 4 weeks after the EOT visit and continue to be followed through global study completion. At global study completion, each subject will have an End of Study (EOS) assessment to complete participation in the study. Receipt of rescue therapy is not a reason for permanent study medication discontinuation. While receiving ESA rescue, subjects must temporarily discontinue study medication but should resume study medication following the end of rescue therapy.

For subjects who permanently discontinue study medication, the Investigator will resume standard of care treatment, including ESAs and iron therapy, as deemed appropriate.

It is important to continue to follow subjects that permanently discontinue study medication.

7.5.5.3 Complete Withdrawal from Further Study Visits/Assessments

A subject has the right to withdraw consent for participation in the studyWithdrawal of consent is a subject's refusal of ALL methods of follow-up noted in the informed consent form: procedures, participation in reduced procedures/study visits, telephone contact only or alternative contact only, source document or designated alternative contact, or access to medical records from alternative sources.

It is important to provide options for the subject to consider for long-term follow-up before the subject withdraws consent. It is important for the Investigator to review options with a subject that would allow follow-up through global study completion before the subject withdraws consent. For subjects considering withdrawal of consent, the Investigator should consult with the Medical Monitor

to ensure all options have been explored and that there is complete understanding by the subject for what constitutes withdrawal of consent.

7.5.5.4 Procedures to Support Continued Study Participation

As part of the informed consent process, only subjects who fully understand and agree to full participation and long-term follow-up should be consented to participate. **It is important that subjects understand the long-term duration and purpose of a cardiovascular outcome trial and that the subject (or designee) continue to allow follow-up through global study completion which could be several years, even post subject's permanent discontinuation of study medication.**

In all cases of impending study medication discontinuation or subject request for stopping study visits, the Investigator will discuss with the subject their options of continuing in the study.

It is important to continue to follow every randomized subject, even if discontinued study medication, through global study completion at a frequency and approach that is agreed to between the Investigator and subject. Visit schedule and assessments are flexible and at the discretion of the Investigator and subject and will be clearly documented in the medical chart. Optimal data collection would include the following assessments through global study completion:

- EOS subject status (must collect at minimum)
- MACE Endpoint Questionnaire
- AE Assessment

The protocol allows flexibility of follow-up to maintain the subjects in active status post permanent discontinuation of study medication. For those subjects who decline full participation in the study post discontinuation of study medication, other options for continued follow-up on a subject include (but are not limited to):

1. Reduced frequency of on-site visits
2. Telephone visits in lieu of on-site visits
3. Telephone or any contact method (e.g., email, site staff visit subject's home, etc.) to verify vital status
4. Telephone or any contact method with an alternative person (family member or medical designee)
5. Study team access to medical records for reporting MACE data or vital status

In the most extreme case, the protocol will accommodate minimal contact with a subject or alternative method to obtain the subject's vital status. The objective is to **keep a subject's study status active** to ascertain at a minimum vital status (alive or deceased) at the global study completion.

The Investigator will ensure understanding and documentation of the reason(s) for a subject's desire to stop study procedures or stop study medication.

7.5.5.5 Procedures to Prevent "Lost to Follow-up"

The Investigator must make every effort to contact subjects who fail to return for scheduled visits so that they will not be declared "lost to follow-up." These actions must include, but are not limited to, the following:

1. Contact all numbers for the subject and their listed contacts (to be collected in source at the subject's entry into the study), as applicable. This includes making calls after normal business hours or on holidays and weekends.
2. Contact the subject's primary care physician, referring specialist, pharmacist, and/or other healthcare professional (using the contacts provided by the subject at entry into the study), as applicable
3. Send email, text, and postal mail with registered (traceable or trackable) letters to all the subject's addresses and contact persons, as applicable. Registered (traceable or trackable) letters will be returned with a copy of the signature from whomever signed, which can be compared to the ICF for vital status data. If undeliverable, then send non-registered standard letters, which may be forwarded to a new address if the subject has moved.
4. Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the subject, as applicable
5. Utilize the internet to search for additional contact information as applicable.
6. Check local, regional, and national public records to locate the subject or search for mortality status as allowed by law, as applicable.

It is important to obtain at a minimum vital status (alive or deceased) at the global study completion for all randomized subjects, including those that have been LTFU during the course of the study.

The Sponsor may utilize a third-party provider in accordance with all applicable guidelines and legislation to assist the site in locating contact information for all subjects during the study or in locating the vital status for all of their randomized subjects in anticipation of global study completion (end of trial).

8 STUDY PRODUCT AND TREATMENT OF SUBJECTS

8.1 Study Product, Supplies, and Storage

Oral vadadustat and darbepoetin alfa for injection will be provided and shipped by the Sponsor or its designated supplier/distributor. Both vadadustat and darbepoetin alfa will be supplied as open-label supplies. All study medication supplies must be kept in a temperature-controlled, locked facility, accessible only to authorized study personnel.

The Investigator or designated study personnel will be responsible for preparing study medication for dispensing to the subject (Section 8.2, Dispensing Procedures) and for study medication supply accountability (Section 8.3, Product Accountability and Destruction).

8.1.1 Vadadustat

Vadadustat will be provided as 150 mg white to off-white, round, bi-convex film-coated tablets for oral administration. The tablets will be packaged in high-density polyethylene bottles with child-resistant closures, polypropylene liner, and induction seal. Labeling will be in accordance with current Good Manufacturing Practices (GMP) and local regulatory requirements.

Dose levels utilized in this study will include: 150 mg (1 tablet), 300 mg (2 tablets), 450 mg (3 tablets), and 600 mg (4 tablets) per day.

Vadadustat should be stored per the product label. Please consult the Pharmacy Manual for details on storage and managing temperature excursions.

8.1.2 Darbepoetin Alfa

Darbepoetin alfa will be provided in its commercially-approved primary packaging and stored per the Package Insert (PI) for investigational sites in the US, and the European Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult patients with CKD not on dialysis..

8.2 Dispensing Procedures

The Investigator will maintain record of all vadadustat tablets and darbepoetin alfa injections dispensed to and returned from each subject during the study. Subjects will receive either vadadustat tablets or darbepoetin alfa according to the randomization assignments provided via the IWR system (see Section 8.4.2, Randomization).

8.2.1 Dispensing of Vadadustat

Subjects will be provided with a supply of vadadustat at the Baseline visit according to the IWR system assignment. Resupply of additional vadadustat at subsequent visits will be managed via the IWR system and will be dependent on the current dose level of vadadustat and the number of tablets remaining in the subject's current vadadustat supply at a given study visit (Section 8.4.4.1, Vadadustat Dosing and Dose Adjustment Algorithms). Subjects will be instructed to finish 1 bottle before opening a new bottle.

At the Baseline visit, study subjects will be provided with 1 bottle of vadadustat. Each bottle of vadadustat will contain 100 tablets of vadadustat (150 mg tablets).

Subjects should be instructed to bring unused vadadustat 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 during the dosing phase of the study.

A Vadadustat Dosing Information Sheet will be provided to the subject at dispensing of study medication.

8.2.2 Dispensing of Darbepoetin Alfa

Darbepoetin alfa will be dispensed according to the IWR system assignment as follows:

- For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen.

- For subjects taking other ESAs, the initial dose of darbepoetin should be based on the Package Insert (PI) for investigational sites in the US, and the European Summary of Product Characteristics (SmPC) for all other investigational sites (non-US) for adult patients with CKD not on dialysis. .

Dispensing of additional darbepoetin alfa at subsequent dosing visits will be managed by the IWR system (Section 8.4.4.2, Darbepoetin Alfa Dosing and Dose Adjustment Algorithms).

Darbepoetin alfa doses may be self-administered or staff administered at the site facility or by the subject at home according to the investigator's determination and local practice.

Subjects should be instructed to bring the darbepoetin boxes to each study visit for drug accountability. There will be no physical accountability performed with used syringes. The investigative site will maintain site drug accountability records of the actual syringes dispensed and used by a subject.

A Darbepoetin Alfa Dosing Information Sheet will be provided to the subject at dispensing of study medication.

8.3 Product Accountability and Destruction

Product accountability should be an ongoing process throughout the study. All study medication (vadadustat and darbepoetin alfa) must be accounted for and any discrepancies explained. The Investigator or designated study personnel are responsible for keeping accurate records of the clinical supplies received from the Sponsor, all supplies retained in inventory at the investigative site, and study medication dispensed to or returned from each subject. Records will be maintained that accurately reflect the drug accountability of vadadustat and darbepoetin alfa 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 Investigator
- 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 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 study material accountability, return, and/or destruction, and copies will be sent to the Sponsor.

All unused and/or partially used vadadustat or darbepoetin alfa 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 vadadustat or darbepoetin alfa 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.

8.4 Treatment of Subjects

8.4.1 Treatment Group Assignments

Subjects will be randomized in a 1:1 ratio via the IWR system to either:

- Vadadustat (starting dose of 2 tablets once daily [300 mg/day])
- Darbepoetin alfa (starting dose based on the current PI for investigational sites in the US, and the SmPC for all other investigational sites (non-US) for adult patients with CKD not on dialysis)

For all subjects, it is recommended that no additional ESA doses be administered after SV2 and prior to the Randomization visit.

Target enrollment for each treatment group is approximately 925 subjects.

8.4.2 Randomization

This study will be open to up to approximately 1850 subjects with NDD-CKD with an eGFR ≤60 mL/min/1.73 m^2 (pre-dialysis).

Using an IWR system, eligible subjects will be assigned using permuted block randomization and a 1:1 ratio to either vadadustat or darbepoetin alfa during their Baseline visit.

To maintain balance between vadadustat-treated and darbepoetin alfa-treated subjects, randomization will be stratified with respect to: 1) geographic region (US versus EU versus ROW); 2) New York Heart Association CHF Class (0 (no CHF) or I versus II or III); and 3) study entry Hb level (<10.0 versus ≥10.0 g/dL, based on the most recent central laboratory Hb measurement prior to the Baseline/Randomization visit).

8.4.3 Blinding

This will be an open-label study. Treatment assignment will be done through the IWR system and the Investigator, Sponsor, and CRO teams will not be aware of which treatment will be assigned next. Treatments will be administered in an open-label fashion.The Sponsor and CRO study teams will be blinded to'by treatment' aggregated analyses except for the unblinded statistician. In addition, the study will involve blinded adjudication of MACE, the use of an IDMC, and an identical schedule of visits, procedures, and assessments for both treatment groups in order to reduce the potential for bias. However certain Sponsor personnel directly involved in medical oversight of the study, regulatory reporting of safety information, and on-site monitoring activities may become unblinded to the treatment assignments of individual subjects during the course of the study.

The EAC will remain blinded throughout the full course of the study.

8.4.4 Dosing and Dose Adjustment Guidelines

Dosing will be initiated at the Baseline visit, and the first dose of study medication (vadadustat or darbepoetin alfa) will be administered at the investigative site after other Baseline visit procedures have been completed. The investigator may elect to postpone the initial dose of study medication until a subsequent visit based on the subject's Hb level or Hb trajectory assessed at the Baseline visit, or based on timing of last ESA dose given during Screening.

For all subjects, it is recommended that no additional ESA doses be administered after SV2 and prior to the Randomization visit.

Year 1-4 Treatment Period Visits

Hemoglobin will be monitored via HemoCue throughout the study to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be adjusted, interrupted, or maintained. From Weeks 0 to 12, Hb will be obtained via HemoCue every 2 weeks for monitoring for dose adjustment. From Week 12 to Week 52, Hb will be monitored every 4 weeks via HemoCue.

From Week 53 through the study end, Hb will continue to be monitored via HemoCue to determine if the dose of study medication will be adjusted, interrupted, or maintained. Any unscheduled measurement taken between study visits will be recorded in the appropriate CRF and the subject's source when a Hemocue is taken. Hemoglobin will also be assessed with a CBC through the central laboratory for efficacy and safety evaluations; however, dose adjustments should be based on the HemoCue Hb value. If the Investigator has an immediate clinical concern about a subject's HemoCue value, the Investigator may use clinical judgment and repeat the HemoCue Hb, use local lab values, or wait for central lab results. The test method utilized to inform your treatment decision must be recorded in the appropriate CRF and subject's source.

Year 2-4 Monthly Hb Monitoring

Additionally, after Week 52, the Hb drawn as part of the local standard of care labs must be monitored monthly for dosing oversight. Per the Dosing Algorithms, if the Hb value suggests a dose adjustment is needed, an unscheduled visit must be performed.

If monthly standard of care labs are not available, a study unscheduled visit must be performed. This visit will include, at minimum, the Hb measurement via HemoCue, dose adjustment assessment, and adverse events assessment.

The monthly Hb monitoring method is flexible between study visits after Week 52 to minimize unnecessary travel or redundant blood sampling for the subject.

The aim is to maintain a Hb level of 10.0-11.0 g/dL in the US and 10.0-12.0 g/dL outside of the US throughout the study.

Dose adjustments for vadadustat and darbepoetin alfa will be guided by Hb concentration and the Dose Adjustment Algorithms. TheDose Adjustment Algorithm for darbepoetin alfa will follow the Package Insert (PI) for investigational sites in the US, and the European Summary of Product Characteristics (SmPC) for all other investigational sites (non-US).

This protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should

be based on the Investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, Hb variability, and ESA responsiveness.

In cases where the Investigator does not follow the dosing algorithm, the clinical circumstances must be documented in the subject's source.

8.4.4.1 Vadadustat Dosing and Dose Adjustment Algorithms

Subjects assigned to vadadustat will initiate dosing at 2 tablets once daily (300 mg/day). Dose levels of vadadustat utilized in this study include 150, 300, 450, and 600 mg (available tablet strength is 150 mg).

Dosing will be initiated at the Baseline visit and the first dose of vadadustat will be administered at the investigative site (study physician's clinic) after other Baseline visit procedures have been completed. The Investigator may elect to postpone the initial dose of study medication until a subsequent visit based on the subject's Hb level or Hb trajectory assessed at the Baseline visit, or based on timing of the last ESA dose given during screening.

Thereafter, vadadustat will be taken once daily on an outpatient basis. Subjects may take vadadustat with or without food and should be instructed to swallow the tablet(s) whole. Subjects should be instructed to take vadadustat at roughly the same time each day.

During the study, vadadustat should be dosed according to the Dose Adjustment Algorithm in Appendix C: Vadadustat Dosing and Dose Adjustment Algorithms.

For subjects progressed to DD-CKD, and continuing on vadadustat, the dose adjustment should be based on the Dose Adjustment Algorithms (Appendix C: Vadadustat Dosing and Dose Adjustment Algorithms).

8.4.4.2 Darbepoetin Alfa Dosing and Dose Adjustment Algorithms

For subjects randomized to receive darbepoetin alfa, the initial dose will be determined as follows:

- For subjects already on darbepoetin, the initial dosing regimen in the study should be based on the prior dosing regimen.
- For subjects taking other ESAs, the initial dose of darbepoetin should be based on the PI for investigational sites in the US, and the SmPC for all other investigational sites (non-US) for adult patients with CKD not on dialysis.

For subjects progressed to DD-CKD and continuing on darbepoetin alfa, the dose adjustment should be based on the Dose Adjustment Algorithms (Appendix D: Darbepoetin Alfa Dosing and Dose Adjustment Algorithms).

Each subject will receive their first dose of darbepoetin alfa at the Baseline visit. The Investigator may elect to postpone the initial dose of study medication until a subsequent visit based on the subject's Hb level or Hb trajectory assessed at the Baseline visit, or based on timing of the last ESA dose given during screening.

Subsequent administration of darbepoetin alfa may occur at the clinic or may be self-administered at home per regional standard of care. Darbepoetin alfa dosing is independent

of the visit schedule, and the dosing schedule may shift per local standard of care and Investigator discretion.

8.4.5 Late or Missed Doses

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

Subjects on darbepoetin alfa should be instructed to take the study medication, including handling of late or missed dosed, as described in the PI or SmPC..

Subjects should be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).

8.4.6 Iron Supplementation

Investigators will prescribe iron supplementation during the study to maintain ferritin ≥100 ng/mL or TSAT ≥20%. In general, oral iron should be considered before initiating IV iron.

The use of iron-based phosphate binders (eg, ferric citrate) is permitted. For subjects who initiate dialysis, iron maintenance therapy via dialysate (eg, ferric pyrophosphate citrate) is also permitted. However, the duration, dosage, and frequency of intradialytic iron should be documented in CRF.

Important: Because of the potential for oral iron to reduce the bioavailability of vadadustat, the study medication is not to be administered concurrently with an oral iron supplement (including multivitamins containing iron), iron containing phosphate binders, or medications containing iron. The subject should be instructed to take these medications at least 2 hours before or 2 hours after the dose of vadadustat.

8.4.7 Rescue Therapy

To ensure the safety of study subjects and to standardize the use of rescue in the study, rescue therapy guidelines are provided.

8.4.7.1 ESA Rescue (Optional)

Starting at Week 6, subjects in both treatment arms will be allowed (although will not be required) to have their Hb rescued with ESA therapy per the local standard of care. Drug product and supplies for ESA rescue will not be provided by the Sponsor.

If possible, a subject on vadadustat should be on a maximum dose of vadadustat for 2 weeks prior to ESA rescue. A subject on darbepoetin alfa may rescue with another ESA per the standard of care. To qualify for ESA rescue, a subject must fulfill BOTH of the following:

- The subject has experienced worsening of symptoms of anemia (eg, fatigue, weakness, shortness of breath, chest pain, confusion, or dizziness) compared with Baseline
- The subject's Hb is <9.0 g/dL

However, in the event the subject does not meet the above criteria for ESA rescue, ESA rescue is permitted when medically necessary at the discretion of the Investigator. Reasons for ESA use will be captured in the appropriate CRF.

The ESA rescue therapy should be administered as per the local institution's guidelines and per the approved local product label. While receiving ESA rescue therapy, subjects must temporarily discontinue taking study medication (vadadustat or darbepoetin alfa). Hemoglobin will be monitored throughout the study at scheduled visits as defined in the Schedule of Activities using HemoCue, and ESA rescue treatment should be stopped when Hb is ≥9.5 g/dL. A minimum interval must be observed prior to restarting vadadustat after the last dose of rescue medication, and treatment may be resumed after the following intervals:

- 2 days after last dose of epoetin rescue
- 7 days after last dose of darbepoetin alfa rescue
- 14 days after last dose of methoxy polyethylene glycol-epoetin beta rescue.

Following ESA rescue, the study medication should be resumed at the same dose as previously used or one dose higher and adjusted according to the Dose Adjustment Algorithms (Section 8.4.4, Dosing and Dose Adjustment Guidelines). If a subject's study medication has been temporarily interrupted for more than 60 days, the Investigator should contact the Medical Monitor before resuming study medication.

8.4.7.2 Red Blood Cell Transfusion (Optional)

Investigators will use their local institution's transfusion guidelines when determining whether to transfuse a study subject. In general, in the event of an acute or severe loss of blood, a RBC transfusion should be administered as clinically indicated. In less severe instances but where there may be worsening of anemia or moderate to severe symptoms of anemia, RBC transfusions are permitted at the discretion of the Investigator given the medical necessity. Reasons for RBC transfusion will be captured in the appropriate CRF (e.g., worsening anemia due to CKD, blood loss, surgery, etc.). Study medication (vadadustat or darbepoetin alfa) may be continued during the RBC transfusion period.

8.4.8 Phlebotomy (Optional)

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

8.4.9 Treatment Compliance

Subjects will be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa). The Investigator will also maintain drug accountability logs itemizing all study medications dispensed to and returned from each subject during the study. Treatment compliance will be determined from these forms along with the subject questioning and the study medication CRFs. Dosing compliance for vadadustat or darbepoetin alfa is defined as 80 to 120% over the course of the Treatment Period.

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

Subjects will also be questioned regarding the timing of their last dose of vadadustat prior to the PK samples at the Week 4, 12, 28, and 52 study visits. The date and time of these doses will be recorded on the CRF.

8.4.10 Continuation of Treatment

Subjects may receive study medication (vadadustat or darbepoetin alfa) up until the EOT visit.

8.5 Prior and Concomitant Therapy

8.5.1 General

All medications taken during the screening period and during the study should be recorded on the appropriate CRF. If the duration of the screening period is less than 30 days, all medications taken within 30 days prior to first dose of study medication will be recorded. In addition, the ESA, blood transfusion, and iron treatment regimen prior to randomization and the date of last dose will be recorded.

To ensure adequate collection of prior ESA dosing history, a minimum of 8 weeks of ESA therapy prior to start of study medication will be recorded.

8.5.2 Erythropoiesis-stimulation Agents

For all subjects, it is recommended that no additional ESA doses be administered after Screening visit 2 (SV2) and prior to the Randomization visit.

Non-protocol ESAs are prohibited from Randomization until the end of the study, unless the subject is receiving ESA rescue therapy, interrupts study medication for other reasons, or permanently discontinues study medication. Reasons for ESA use will be captured in the appropriate CRF (e.g., adverse event, inadvertent administration, etc.).

Concomitant use of an ESA with study medication is strictly prohibited.

In the setting of ESA rescue therapy, the initial dose of ESA rescue therapy may be administered on the same day as the last vadadustat dose prior to vadadustat dose interruption (see Section 7.5.5.1, Temporary Interruption of Study Medication) if deemed medically necessary at the discretion of the Investigator. Guidelines for ESA administration as rescue therapy are provided in Section 8.4.7.1, ESA Rescue.

All efforts will be made to avoid inadvertent administration of ESAs resulting from following routine ESA hemodialysis protocols (e.g., dialysis center ESA protocols for subjects on hemodialysis). If ESA is inadvertently administered to subjects actively receiving vadadustat treatment, vadadustat treatment will be stopped and the event will be reported as a protocol deviation

8.5.3 Transfusions

Documentation of transfusions will be collected. The receipt of any transfusions for 4 weeks prior to Screening will be recorded.

8.5.4 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 the Screening visit. In addition, subjects should not have participated in a study with another HIF-PHI.

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

8.5.5 HMG-CoA Reductase Inhibitors (Statins)

Exposures to atorvastatin and an active metabolite (para-hydroxy atorvastatin) were mildly increased in the setting of vadadustat co-administration in healthy adults. No dose adjustment of atorvastatin is recommended.

Exposures to simvastatin and an active metabolite (beta-hydroxy acid) were both mildly to moderately increased with co-administration of vadadustat in healthy adults. For subjects taking vadadustat who are concomitantly taking simvastatin, the recommended maximum daily dose of simvastatin is 20 mg. Investigators should review simvastatin dosing and consider clinical guidelines and local prescribing information including specific guidance in product labels with reference to renal impairment as well as hepatic impairment, concomitant medications and other medical factors relevant to the management of the subject.

Exposure to rosuvastatin was moderately increased with co-administration of vadadustat based on a study in healthy adults. For subjects taking vadadustat who are concomitantly taking rosuvastatin, the recommended maximum daily dose of rosuvastatin is 10 mg. Investigators should review rosuvastatin dosing and consider clinical guidelines and local prescribing information including specific guidance in product labels with reference to renal impairment as well as hepatic impairment, concomitant medications, and other medical factors relevant to the management of the subject.

Exposure to pravastatin was studied in the setting of vadadustat co-administration in healthy adults. There was no interaction. No dose adjustment of pravastatin is recommended.

Exposures to the other statins may be increased with co-administration of vadadustat. When used with vadadustat, upward titration of other statins to higher doses should be carried out with caution.

A summary of results and management of concomitant administration of vadadustat with the various statins is provided below:

Statin	Change in Statin Exposure When Dosed with Vadadustat*	Recommended Statin Dosing in Subjects Receiving Concomitant Vadadustat
Atorvastatin	Mild increase	No dose adjustment
Pravastatin	No increase	No dose adjustment
Rosuvastatin	Moderate increase	Maximum daily dose of 10 mg
Simvastatin	Mild-to-moderate increase	Maximum daily dose of 20 mg
Other statins	Not studied	Upward titration to higher doses should be done with caution

* Based on FDA guidance, an increase in exposure of ≥ 1.25- to < 2-fold, ≥ 2- to < 5-fold, or ≥ 5-fold is classified as a mild, moderate, or strong interaction, respectively (FDA 2017).

8.5.6 Sulfasalazine and Other BCRP Substrates

Exposure to sulfasalazine was moderately increased with co-administration of vadadustat based on a study in healthy adults; mesalamine exposure was mildly increased, and no increase was observed in exposure to the metabolite sulfapyridine. Sulfasalazine and other breast cancer resistant protein (BCRP) substrates should be used with caution when taken concomitantly with vadadustat.

9 STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

Please see Appendix A: Schedule of Activities for a detailed table of the Schedule of Activities.

This study includes the following visits:

- Optional Pre-Screening
- Two Screening visits (SV1 and SV2)
- Baseline/Randomization visit (Week 0/Day 1)
- Year 1 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 2, 4, 6, 8, 10, 12 (± 3 days), and every 4 weeks thereafter until Week 52 (± 5 days)
- Year 2 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 64, 76, 88, and 104 (± 10 days)
- Year 3 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 116, 128, 140, and 156 (± 10 days)
- Year 4 Treatment Period Study Visits/Evaluations while receiving study medication: Weeks 168, 180, 192, and 208 (± 10 days)
- EOT visit (± 7 days)
- Follow-up visit: 4 weeks after the EOT (± 7 days).
- Unscheduled Visit(s)

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

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent must be obtained prior to the subject entering into the study and before any protocol-directed procedures are performed (including Screening activities). Subjects participating in the optional Pre-Screening visit must sign an abbreviated consent form or full consent form prior to Pre-Screening and, if eligible, may proceed with the Screening visit after full consent has been obtained (see Section 9.3.1, Pre-Screening Visit and Section 15.3, Subject Information and Consent for additional details). Additionally, subjects may be asked to provide a separate, optional consent to obtain and store a blood sample(s) for future genetic analyses.

9.1.2 Documentation of Screen Failures

Investigators will maintain documentation of Pre-Screening activities, to include information on potential study candidates evaluated and reasons that subjects considered for the study did not qualify.

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

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

9.1.3 Contraception and Pregnancy Avoidance Measures

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 have not yet been conducted with vadadustat, and there are no data on the transmission of vadadustat in breast milk or the effect of vadadustat on infants.

Although the potential risk of vadadustat on the developing fetus is limited based on studies to date, the study requires that all subjects must agree to use adequate contraception throughout the study and for 30 days after the last dose of study medication.

Adequate contraception is defined as follows:

Female subjects must be surgically sterile, postmenopausal (no menses for at least one year), or have negative pregnancy test results at Screening (serum).

Female subjects not surgically sterile or postmenopausal (no menses for at least one year) and non-vasectomized male subjects must practice at least 1 of the following methods of birth control:

- Total abstinence from sexual intercourse (minimum 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 medication administration or intrauterine contraception/device 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 SV1, throughout the study, and for 30 days after the last dose of study medication).

9.1.4 Laboratory Accreditation and Reference Ranges

The Investigator and the Sponsor will maintain a copy of the laboratory accreditation and the reference ranges for the central laboratory used for clinical laboratory evaluations. Additionally, other accreditation(s) will be collected as required.

9.2 Study Procedures and Evaluations

9.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study:

- Medical history, demographics, and physical examination: Medical history, demographic information, and physical examination (including height) will be collected at SV2. 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. After SV2, an abbreviated, symptom-directed physical examination should be performed at the discretion of the Investigator as clinically indicated.
- Vital signs: Vital signs will include heart rate and blood pressure. Heart rate and blood pressure should be assessed in the seated position after 5 minutes of rest. Vital signs will be collected at SV1, SV2, Baseline, during study visits, and EOT and should be taken prior to blood draws when possible.
- Weight: Weight will be collected for all subjects at SV2, at Weeks 12, 24, 36, and 52, yearly thereafter, and at the EOT visit. For subjects on darbepoetin alfa, subjects will be weighed for dosing as per the local standard of care.
- 12-Lead electrocardiogram (ECG): A standard 12-lead ECG will be performed at Baseline. The ECG should be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and should be taken prior to vital sign assessments and blood draws when possible. With the subject in a supine position, obtain the 12-lead tracing. All ECGs will be reviewed by the Investigator for the presence of rhythms of potential clinical concern. A record of the tracing(s) will be made and retained with other source documents.
- Completion of MACE Endpoint Questionnaire: At each post-randomization study visit, the subject must specifically be questioned regarding the occurrence of any potential MACE endpoint event since the last study visit. **IMPORTANT: The endpoint questionnaire electronic CRF must be completed in full at each visit even if no potential MACE endpoints have occurred.** If a potential endpoint event is reported, the date of the event should be recorded and the appropriate source documents should be collected according to the endpoint packet checklist.
- AE Assessments: AE collection will begin from time of randomization through global study completion. The Investigator and study personnel will review each subject's laboratory and clinical evaluation findings and query the subject directly regarding AEs (see Section 10, Adverse Events). Subjects must be followed for AEs until the final required protocol visit or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
- Concomitant Medication Recording: All medications (both prescription and non-prescription, and including vitamins, herbals, topicals, inhaled, and intranasal) taken during the screening period and throughout the study, ending at the final protocol required visit, should be recorded on the appropriate CRF. If the duration of screening period is less than 30 days, all medications taken within 30 days prior to the start of study medication (vadadustat or darbepoetin alfa). 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. In addition, for any subject with ESA, blood transfusion or IV iron use, the date of last treatment of ESA, blood transfusion, or iron treatment regimen prior to randomization and date of last dose will be recorded.

9.2.2 Laboratory Evaluations

Samples for laboratory assays will be sent to a central laboratory for analysis. Detailed instructions for the collection, processing, and shipment of laboratory samples will be provided by the Sponsor and the central laboratory. The Investigator is responsible for reviewing laboratory results for clinical significance.

The following laboratory evaluations will be conducted during the course of the study:

- Pregnancy test: A serum pregnancy test will be performed at SV2 for females of childbearing potential. Additional serum or local urine pregnancy tests may be conducted throughout the study in sufficient number, as determined by the Investigator or required by local regulations, to establish the absence of pregnancy during the study. The SV2 results must be available and must be negative before the subject takes the first dose of study medication.

- Complete Blood Count (CBC): A CBC with differential will be performed at Baseline and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208. At all other noted visits in Appendix A: Schedule of Activities, including SV1 and SV2, a CBC without differential will be performed. The CBC with differential will include: Hb, hematocrit, RBCs, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

  Hemoglobin assessed by central laboratory CBC will be used for evaluations of efficacy and safety.Hemoglobin levels assessed by HemoCue should be used for dose adjustments as described in Section 8.4.4 Dosing and Dose Adjustment Guidelines). lf the Investigator has an immediate clinical concern about a subject's HemoCue value, the Investigator may use clinical judgment and repeat the HemoCue Hb, use local lab values, or wait for central lab results. The test method utilized to inform the treatment decision must be recorded in the appropriate CRF and subject’s source.

  For eligibility purposes, one retest for Hb may be performed during the screening window, The average of 2 Hb values measured by the central laboratory during Screening (SV1, SV2, or retest) must be < 11.0 g/dl in the US and <12.0 g/dl outside the US.

  Refer to Sections 7.4.1, Retesting and 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening period.

- Point of care Hb: Using HemoCue, Hb will be monitored throughout the study to determine if the dose of study medication (vadadustat or darbepoetin alfa) will be

adjusted, interrupted, or maintained as described in Section 8.4.4 Dosing and Dose Adjustment Guidelines.

- Reticulocyte count: An automated reticulocyte count (both absolute and percent) will be performed at Baseline and at Weeks 4, 12, 28, and 52.
- Coagulation tests: Blood samples will be drawn at Baseline to assess the prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Folate and Vitamin B_{12}: A blood sample will be drawn at SV1 to assess the folate and Vitamin B_{12} levels.
- Urine albumin-to-creatinine ratio (uACR): A random urine spot sample should be collected at the investigative site during the Baseline, Weeks 28, 52, 104, 156, 208, and EOT to assess the uACR. Subjects should refrain from heavy exercise 24 hours before the test.
- C-reactive protein (CRP): A blood sample for CRP will be collected at the Baseline, Weeks 28, 52, 104, 156, and EOT.
- Serum Chemistry: Blood samples to assess serum chemistry will be collected at SV1, Baseline, and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208, EOT. At all other noted visits in Appendix A: Schedule of Activities, serum creatinine and eGFR will be performed only at Weeks 4, 8, 12, 20, 36, 44. The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen (BUN), creatine phosphokinase (CPK), uric acid, albumin, total protein, and eGFR calculation.

  Note: When a ≥50% decline in eGFR from the Baseline value is observed, a repeat central laboratory measure should be performed within 30 to 60 days.
- Liver Function Tests: Blood samples to assess liver function will be collected at SV1, Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 36, 44, 52, 64, 76, 88, 104, 116, 128, 140, 156, 168, 180, 192, 208, and EOT. Liver function tests will include: total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, and lactate dehydrogenase (LDH).
- Iron indices: Blood samples to assess the iron indices will be collected at SV1, Baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, 64, 76, 88, 104, 116, 128, 140, 156, 168, 180, 192, 208, and EOT. Assessments will include the following indices: ferritin, iron, TIBC, and TSAT.
- Lipid Profile: Blood samples will be collected at the Baseline, Week 28, and Week 52 visits to assess the cholesterol levels and will be tested for the following types of lipids: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides.
- Biomarkers (including, but not limited to, hepcidin, vascular endothelial growth factor [VEGF]): Samples for biomarker analysis will be drawn at the Baseline, Weeks 12, 28, 52, 104, 156, and EOT.
- EPO: Blood samples for EPO analysis will be obtained at Baseline and at Weeks 4, 12, 28, and 52.

- PK Evaluations (samples to be drawn only for subjects randomized to vadadustat): Plasma samples for PK evaluation will be collected to analyze for both the parent compound (vadadustat) and its metabolites. Collection time points for PK will include Study Day 1 (Baseline), and Weeks 4, 12, 28, and 52.
    - Study Day 1 (Baseline Visit): Vadadustat will be administered on Study Day 1 (Baseline Visit) in the clinic after the Baseline procedures, and the PK sample will be collected between 15 minutes to 1 hour after vadadustat administration. The times of vadadustat dose and the PK sampling will be documented.
    - Weeks 4, 12, 28, and 52 study visits: PK sampling will also be performed along with other study laboratory samples being collected at the Weeks 4, 12, 28, and 52 study visits. The date and times of vadadustat administration and PK sampling will be documented.
      Samples should be collected along with the other laboratory samples being collected at the study visit. Subjects will be questioned regarding the timing of their last dose of vadadustat prior to the collection of PK samples. The date and time of these doses will be recorded by the sites.
- Exploratory Samples: Additional blood and urine samples will be collected at Baseline, Weeks 28, 52, 104, 156, and EOT which may be used for exploratory measurement of biomarkers (eg, factors relating to the activation of the HIF pathway). Subjects will also be asked to provide optional consent to obtain a blood sample at Baseline and EOT, to be stored for future genetic analyses (eg, DNA, mRNA).

9.3 Schedule of Activities

The Schedule of Activities (see Appendix A: Schedule of Activities) 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 Pre-Screening Visit

To minimize Screen failures, there will be an optional Pre-Screening visit which will enable the subject to have a HemoCue Hb prior to proceeding with full Screening. Subjects will need to sign an abbreviated Pre-Screening informed consent form or full consent form prior to Pre-Screening. If the Pre-Screen HemoCue Hb is between 8.0 and 11.0 g/dL (inclusive) in the US or between 9.0 and 12.0 g/dL (inclusive) outside the US, the investigative site may proceed with SV1, which preferably will occur on the same day as Pre-Screening.

9.3.2 Screening Visits

Subjects will need to sign a full consent form prior to SV1 procedures. The consent form may be signed in advance of SV1 procedures. The Screening period starts at the time the informed consent is signed and will be a maximum of 8 weeks in duration. Two Screening visits (SV1 and SV2) must be performed within 8 weeks prior to dosing (Baseline visit or Day 1). There must be a minimum of 4 days between the 2 Screening visits and a minimum of 4 days between SV2 or last retest and the Baseline visit.

The Investigator will maintain a log of subjects (both Pre-Screened and Screened) and indicate who of the Pre-Screened subjects were brought in for informed consent and Screening and who of the Screened subjects were enrolled or excluded and the reason for exclusion.

After obtaining informed consent, subjects will undergo a number of Screening activities.

9.3.2.1 Screening Visit 1 (SV1)

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

- Informed consent (including an additional optional consent for blood samples for future genetic analyses.
- Review of eligibility criteria
- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Laboratory procedures:
  - CBC (without differential)
  - Iron indices
  - Folate and vitamin B_{12} levels
  - Serum chemistry including serum creatinine and eGFR
  - Liver Function Tests
- Visit registration in IWR

Refer to Sections 7.4.1, Retesting and 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening period.

9.3.2.2 Screening Visit 2 (SV2)

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

- Review of eligibility criteria
- Physical examination
- Demographics and medical history
- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws), as well as height and weight
- Laboratory procedures:
  - CBC (without differential)
- Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method)
- Prior and current medication use.

The mean of 2 Hb values from the central laboratory must be between 8.0 and 11.0 g/dL (inclusive) in the US or between 9.0 and 12.0 g/dL (inclusive) outside the US to qualify for inclusion into the trial. If the subject's Hb does not qualify after SV1,SV2, or retest - Hb, the subject should be considered a Screen failure.

9.3.2.3 Subject Retesting

Subjects who initially fail to qualify for the study based on laboratory test results may be retested once within the 8-week Screening period, per Investigator discretion (Section 7.4.1, Retesting).

9.3.3 Subject Rescreening

Subjects who fail to meet the qualifying criteria for Hb or eGFR during the Screening period may be considered for rescreening at the discretion of the Investigator if it is felt that the

subject's status has progressed and that the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} values may be considered for rescreening after receiving replacement therapy. Screening is limited to 3 attempts (Screening and 2 additional rescreening attempts) (Section 7.4.2, Rescreening).

9.3.4 Baseline Visit (Day 1)

The Baseline visit must be performed at a minimum of 4 days from the last Screening visit (SV2) procedure including retest(s).

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

- Randomization
- 12-lead ECG (prior to vital sign assessments and blood draws).
- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Laboratory Procedures:
  - Random spot urine sample for uACR
  - Coagulation Tests
  - CRP
  - CBC (including differential)
  - Reticulocyte count
  - Serum chemistry including serum creatinine and eGFR
  - Liver function tests
  - Iron indices
  - Lipid profile
  - EPO
  - Biomarkers
  - PK (see Section 9.2.2, Laboratory Evaluations; samples to be drawn only for subjects randomly assigned to vadadustat)
  - Exploratory samples
- Review of medical history for new conditions since Screening visit
- Medication use since Screening visit
- Study medication assessments and procedures:
  - Subject will take their first dose of study medication at the investigative site during the Baseline visit
  - Hb by HemoCue for dose initiation
  - Vadadustat dispensing
  - Darbepoetin alfa dispensing)
  - Oral iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
- AE assessment as needed (after receiving the first dose of study medication).
- Visit Registration in IWR

9.3.5 Year 1 Treatment Period Visits (Day 2 through Week 52)

During the Year 1 Treatment Period visits at Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52, the following activities/procedures will be performed:

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Weight (Weeks 12, 24, 36, and 52)
- Laboratory procedures:
  - Random spot urine sample for uACR (Weeks 28 and 52)
  - CBC (Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52; differential at Weeks 28 and 52)
  - Reticulocyte count (Weeks 4, 12, 28, and 52)
  - Serum chemistry (Weeks 28 and 52)
  - Serum creatinine and eGFR (Weeks 4, 8, 12, 20, 36, and 44; also at Weeks 28 and 52 as part of the serum chemistry)
  - Liver function tests (Weeks 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52)
  - Iron indices (Weeks 4, 8, 12, 20, 28, 36, 44, and 52)
  - Lipid profile (Weeks 28 and 52)
  - EPO (Weeks 4, 12, 28, and 52)
  - CRP (Weeks 28 and 52)
  - Biomarkers (Weeks 12, 28, and 52)
  - PK (Weeks 4, 12, 28, and 52; see Section 9.2.2, Laboratory Evaluations; samples to be drawn only for subjects randomized to vadadustat)
  - Exploratory samples (Weeks 28 and 52)
- Record date and time of subject's last dose of vadadustat prior to the PK sample (Weeks 4, 12, 28, and 52)
- Safety assessments:
  - AE assessment
  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
  - MACE endpoint questionnaire
- Medication assessments and procedures:
  - Review of concomitant medications
  - Hb by HemoCue for dose adjustment
  - Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
  - Vadadustat dispensing as needed per Section 8.2.1, Dispensing of Vadadustat
  - Darbepoetin alfa dispensing
  - Iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
  - Question subject regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).
- Visit Registration in IWR

9.3.6 Year 2-4 Monthly Hb Monitoring

- Monthly monitoring of Hb as part of local standard of care labs or at unscheduled visits for dose adjustment.

9.3.7 Year 2 Treatment Period Visits (Weeks 53 through 104)

During the Year 2 Treatment Period visits at Weeks 64, 76, 88, and 104, the following activities/procedures will be performed:

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Weight (Week 104)
- Laboratory Procedures:
  - Random spot urine sample for uACR (Week 104)
  - CBC (Weeks 64, 76, 88, and 104; differential at Weeks 76 and 104)
  - Serum chemistry including serum creatinine and eGFR (Weeks 76 and 104)
  - Liver function tests (Weeks 64, 76, 88, and 104)
  - Iron indices (Weeks 64, 76, 88, and 104)
  - CRP (Week 104)
  - Biomarkers (Week 104)
  - Exploratory samples (Week 104)
- Safety assessments:
  - AE assessment
  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
  - MACE endpoint questionnaire
- Medication assessments and procedures:
  - Review of concomitant medications
  - Hb by HemoCue for dose adjustment
  - Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
  - Vadadustat dispensing as needed per Section 8.2.1, Dispensing of Vadadustat
  - Darbepoetin alfa dispensing
  - Iron supplementation to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
  - Question subject regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).
- Visit Registration in IWR

9.3.8 Year 3/4 Treatment Period Visits (Weeks 116 through 208)

During the Year 3/4 Treatment Period visits at Weeks 116, 128, 140, 156, 168, 180, 192, and 208, the following activities/procedures will be performed:

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Weight (Weeks 156 and 208)
- Laboratory Procedures:
  - Random spot urine sample for uACR (Weeks 156 and 208)
  - CBC (Weeks 116, 128, 140, 156, 168, 180, 192, and 208; differential at Weeks 128, 156, 180, and 208)

- Serum chemistry including serum creatinine and eGFR (Weeks 128, 156, 180, and 208)
- Liver function tests (Weeks 116, 128, 140, 156, 168, 180, 192, and 208)
- Iron indices (Weeks 116, 128, 140, 156, 168, 180, 192, and 208)
- CRP (Week 156)
- Biomarkers (Week 156)
- Exploratory samples (Week 156)

- Safety assessments:
  - AE assessment
  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
  - MACE endpoint questionnaire
- Medication assessments and procedures:
  - Review of concomitant medications
  - Hb by HemoCue for dose adjustment
  - Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
  - Vadadustat dispensing as needed per Section 8.2.1, Dispensing of Vadadustat
  - Darbepoetin alfa dispensing (per PI for investigational sites in the US, and the SmPC for all other investigational sites (non-US)
  - Iron supplementation to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.6, Iron Supplementation)
  - Question subject regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).
- Visit Registration in IWR

9.3.9 End of Treatment (EOT) Visit

The EOT visit will be performed at the time a subject permanently discontinues study medication or for subjects on study medication at the time of notification of global study completion (See Appendix A: Schedule of Activities).

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

- Vital signs including heart rate and blood pressure (assessed in seated position after 5 minutes of rest and prior to blood draws), as well as weight
- Laboratory Procedures:
  - Random spot urine sample for uACR
  - CBC (without differential)
  - Serum chemistry including serum creatinine and eGFR
  - Liver function tests
  - Iron indices
  - Biomarkers
  - CRP
  - Exploratory samples
- Safety assessments:
  - AE assessment

  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
  - MACE endpoint questionnaire
- Recording of concomitant medications
- Drug reconciliation: Study medication (vadadustat or darbepoetin alfa) reconciliation will be conducted per the pharmacy manual instructions.
- Question subject regarding dosing compliance and whether they have experienced any problems related to the dosing of study medication (vadadustat or darbepoetin alfa).
- Visit Registration in IWR

9.3.10 Follow-Up Visit

The Follow-up visit will be conducted in person or via the telephone 4 weeks after the EOT visit. The following activities/procedures will be performed:

- AE assessment
- RBC transfusions and ESA rescue
- Therapeutic phlebotomy
- MACE endpoint questionnaire.
- Recording of concomitant medications

9.3.11 Unscheduled Visits

Unscheduled assessments may be conducted at any time as medically warranted. The following activities/procedures will be performed. At a minimum,

- MACE Endpoint Questionnaire
- AE assessments
- Any other procedures that are medically warranted at the discretion of the Investigator

9.3.12 End of Study Subject Status

The End of Study (EOS) assessment documents the subject status at the global study completion or at the time of subject withdrawal of consent or when subject is deemed LTFU or upon death. The table below outlines how to handle each subject based on their status.

The following activities/procedures will be performed. At minimum,

- EOS subject status

Subject Status	Global Study Completion
Subject on Study Medication (includes those on temporary interruption) at time of global study completion	• Perform EOT visit • Perform the Follow-up visit 4 weeks after EOT and include EOS subject status

Subject permanently discontinued study medication and continues to be followed in the study	Optimal data collection would include the following assessments: • EOS subject status (must collect at minimum) • MACE Endpoint Questionnaire • AE Assessment NOTE: EOT and the Follow-up visit 4 weeks after EOT visit to be performed at time study medication is permanently discontinued.
Subject Lost to Follow-up	Work with third party vendor to ascertain vital status and complete EOS subject status. If subject-site contact is reestablished and possible, collect available information for EOS subject status.
Subject Withdrawn Consent	Complete the EOS subject status form at the time of withdrawal of consent, absolute refusal of ALL methods of MACE and health status follow-up.
Subject Death	Complete the EOS subject status form at the time of death (see Section 10 Adverse Events for more details on other actions related to reporting a death).

9.4 Study Medication Stopping Rules

Study medication must be permanently discontinued if a subject meets one of the criteria in Table 2 below

Table 2. Study Medication Stopping Rules

ALT **or** AST >3x ULN **and** total bilirubin >2x ULN	Permanently Discontinue Treatment
ALT **or** AST >3x ULN **and** INR >1.5	Permanently Discontinue Treatment
ALT **or** AST >8x ULN	Permanently Discontinue Treatment
ALT **or** AST remains >5x ULN over 2 weeks*	Permanently Discontinue Treatment
ALT **or** AST >3x ULN with symptoms including e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash **or** eosinophilia	Permanently Discontinue Treatment

* Re-challenge generally should be avoided with ALT or AST >5 times ULN unless there are no other good therapeutic options.

ALT: alanine transferase; AST: asparagine transferase; INR: international normalized ratio; ULN: upper limit of normal

See Section 10.1.1, Adverse Events for reporting requirements related to a subject being permanently discontinued based on meeting the laboratory abnormalities list above in Table 2.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

For the purposes of this study, an AE is any untoward medical occurrence (including an 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 medication or otherwise
- All AEs secondary to any medication overdose, medication error, abuse, withdrawal, sensitivity, or toxicity
- Illnesses apparently unrelated to study medication, 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 and dyspnea, 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 (with the exception of kidney transplant, see below).

Pre-existing Conditions – In this study, a pre-existing condition (ie, a disorder present before the AE reporting period started and noted on the pretreatment 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 will 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 an AE. An expected laboratory abnormality from a condition that is part of the medical history is not considered clinically significant for the purposes of the study unless it represents a worsening of the condition.

Abnormalities in ALT, AST and Total Bilirubin - Abnormalities in ALT, AST and Total Bilirubin should be reported to the Sponsor's Medical Monitor or CRO designee within 24 hours of awareness as SAE with "medical significance" criteria selected, if the following conditions are met:

- New elevation in ALT or AST > 3 times ULN, with or without an elevation of total serum bilirubin > 2 times ULN; AND

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

- Temporary discontinuation of Investigational Medicinal Product (IMP);
- Repeat testing of ALT, AST, ALP, and total bilirubin, should be completed within 48 to 72 hours to confirm the abnormalities and to determine trend;
- IMP should not be resumed until monitoring indicates abnormalities have resolved or have stabilized.

Details on the management of subjects with other ALT and AST abnormalities are further described in Section 9.4, Study Medication Stopping Rules.

Worsening of Anemia – In this study, it is possible that some subjects may experience a worsening of anemia. As the primary endpoint of this study assesses Hb response, worsening of anemia is captured as part of this efficacy parameter. 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.

Transplantation – During this long-term study, it is anticipated that some subjects may receive a kidney transplant. These events will not be recorded as AEs. Subjects will discontinue study medication for receipt of a kidney, other solid organ, hematopoietic stem cell or bone marrow transplant and should continue with the Schedule of Activities and safety assessments as described in Section 7.5.5.2, Permanent Discontinuation of Study Medication.

Malignancy – During this long-term study, some subjects may develop a newly diagnosed malignancy or a recurrence of a malignancy. At the discretion of the Investigator, these subjects may continue study medication (vadadustat or darbepoetin alfa). For reporting of adverse events of malignancy, see Section 10.1.2 Serious Adverse Events.

Renal-Related Events - Some subjects will experience a progression of their CKD over the course of this 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 seriousness criterion "medically important," if no other seriousness criteria are met (see Section 10.1.2, Serious Adverse Events):
  - Progression of CKD leading to chronic dialysis: When a subject undergoes transition to chronic maintenance dialysis an SAE should be reported using the verbatim term of "end-stage renal disease", with the outcome denoted as recovered with sequelae of chronic dialysis.
  - Any medical event requiring transient acute dialysis: When a subject undergoes transient acute dialysis, an SAE should be reported using the verbatim term reflecting the indication for the dialysis. Examples of verbatim AE terms include: hyperkalemia, volume overload, acute kidney injury, and uremia.
  - Kidney transplantation: When a subject receives a kidney transplant, an SAE should be reported using the verbatim term "Progression of CKD", with the outcome denoted as recovered with sequelae of "kidney transplant."
- The following situations will be **reported as SAEs if they meet seriousness criteria** (see Section 10.1.2, Serious Adverse Events); 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

Each AE is to 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.

In addition to the above criteria for classifying AEs as serious, the following situations will also be classified as serious for purposes of this study:

- **Dialysis or Transplantation** - Events requiring transition to chronic, ongoing dialysis, or requiring an acute transient course of dialysis, or requiring an immediate kidney transplantation (ie, not pre-planned) will be classified as serious. Guidance for the reporting of these events is provided in Section 10.1.1, Adverse Events.
- **Malignancies** – Newly diagnosed malignancies or a recurrence of a malignancy should be reported as an SAE with the seriousness criterion "medically important" if no other seriousness criteria are met. If a subject develops basal cell carcinoma of skin, squamous cell carcinoma, or cervical carcinoma in situ during the study, or has worsening of these events from Baseline, the Investigator will determine if the event is reported as an AE or SAE.

- **Designated Medical Events** - The sponsor maintains a list of designated medical events (DME) that they will always classify as serious adverse events. If an event on the DME list is reported as an AE additional information on the event (e.g. investigator confirmation of seriousness, causality) will be requested from the Investigator.

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.

The Sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

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

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

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

10.2 Eliciting Adverse Event Information

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

10.3 Reporting

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

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

10.3.1 Reporting Period

The AE reporting period for this study begins from time of randomization through global study completion.

In addition, any AE that occurs subsequent to the AE reporting period that the Investigator assesses as related to the study medication should also be reported as an AE.

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

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

The Investigator must report follow-up information relating to an SAE to the Sponsor's Medical Monitor or CRO designee within 24 hours of awareness by the Investigator by updating the electronic CRF with the new information or by submitting a paper SAE Report Form in the event that the EDC is not available. When the EDC system becomes available, the SAE information must be entered within 24 hours. The subject should be observed and monitored carefully until the condition resolves or stabilizes.

All deaths are to be thoroughly investigated and reported. Autopsy reports and death certificates are to be obtained, if possible.

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) as 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 Reporting Study Endpoints

Investigators will be counseled to report any event that they assess as potentially being a study endpoint requiring adjudication (death, myocardial infarction, stroke, thromboembolic events, and hospitalization for HF). All study endpoint events will be submitted blinded to the EAC for

adjudication. To protect the integrity of the trial, already adjudicated events will not be unblinded or reported to either Health Authorities (HAs) or Investigators as safety reports unless otherwise requested by HAs or Ethics Committees. After study completion, these events will be included in the final analysis which will be unblinded and submitted to HAs with the study report.

10.3.5 Relationship to Study Medication

The causal relationship of the AE to study medication (vadadustat or darbepoetin alfa) will be assessed by both the Investigator and the Sponsor.

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

Examples of evidence that would suggest a causal relationship between the study medication 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, and 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 medication 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 medication, other treatment (concomitant or previous), withdrawal of study medication, administration error, protocol-related procedure, and others (specify).

10.3.6 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.

10.3.7 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 (ie, until a final report is completed for that subject).

In addition, all SAEs and those nonserious events assessed by the Investigator as possibly or probably 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.

10.4 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 (vadadustat or darbepoetin alfa) or within 30 days of discontinuing the study medication, the pregnancy must be recorded on the Pregnancy Reporting Form/Exposure in Utero Form in the EDC within 24 hours of awareness of the pregnancy or the Investigator will call the CRO SAE hotline within 24 hours of being made aware of the pregnancy.

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 classification as a SAE (ie, spontaneous abortion, stillbirth, neonatal death within 1 month of birth, or congenital anomaly [including that in an aborted fetus]), the Investigator will also follow the procedures for reporting a 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 to the in utero exposure to the study medication should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

10.5 Special Situations

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

- Overdose of the medicinal product
  - Darbepoetin alfa Overdose: The PI or SmPC should be referenced for information on darbepoetin alfa overdosing.
  - Vadadustat Overdose: There is no known antidote for vadadustat. In cases of suspected overdose, Subjects should be treated per standard medical practice based on the Investigator's judgment and dose delays and reductions may be implemented as necessary.

    Chronic overdosage with vadadustat may result in excessive production of red blood cells and polycythemia. Polycythemia can be potentially life threatening and may result in severe thrombosis and death (known as hyperviscosity syndrome). If hyperviscosity syndrome is observed, vadadustat should be discontinued and standard treatment for polycythemic hyperviscosity syndrome should be initiated (i.e., phlebotomy).
- 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 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.

11 DATA ANALYSIS

Data collected throughout the study will be summarized using descriptive statistics and listed in by-subject listings. Continuous variables will be summarized using number of subjects with

data, mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated. Summaries will be provided by treatment group within appropriate analysis populations (as defined in Section 11.2, Study Analysis Populations) and by time point/time period as appropriate.

For Hb, Baseline will be calculated as the average of the central laboratory Hb measurements of samples taken at the screening visit closest to the date of randomization and the measurement taken at randomization. For other parameters, unless otherwise specified, Baseline will be defined as the last available value prior to the first dose of study medication.

Hemoglobin values as assessed through the central laboratory will be used for efficacy and safety evaluations; local HemoCue Hb values will be used only for dose adjustments.

11.1 Sample Size Determination

The goal of this study is to demonstrate the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with anemia secondary to NDD-CKD after conversion from current ESA therapy. The sample size is calculated to ensure sufficient power for testing both efficacy in this trial and the primary safety endpoints as part of a pooled analysis.

11.1.1 Sample Size for the Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the mean change in Hb from Baseline (mean pretreatment Hb) to the average Hb over the primary evaluation period (mean Hb from Weeks 24-36).

The primary efficacy objective of this study is to show that vadadustat is noninferior to darbepoetin alfa within the noninferiority margin. Noninferiority will be established based on a margin of -0.75 g/dL (for vadadustat minus darbepoetin alfa).

For the primary efficacy analysis in this study, it is assumed that the mean change from Baseline in Hb for vadadustat will be the same as for darbepoetin alfa, and the common standard deviation for the mean change from Baseline is assumed to be 1.5 g/dL. Noninferiority will be established based on a 2-sided 95% confidence interval for the difference between the vadadustat group and darbepoetin alfa and using a noninferiority margin of -0.75 g/dL. With these assumptions and approximately 925 subjects per treatment group for the primary efficacy analysis, the noninferiority assessment will have > 90% power.

11.1.2 Sample Size for the Primary Safety Endpoint

The primary safety endpoint is the time from randomization date to the first (adjudicated) MACE +1.

The primary safety analysis will be based upon all events that accrue across the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015). The sample size with respect to the MACE endpoint has been determined based on the number of events needed to demonstrate noninferiority of the 2-sided 95% confidence interval for the hazard ratio (vadadustat/darbepoetin alfa). It has been calculated that 631 events will be required overall to have 80% power to establish noninferiority with a margin of 1.25, and >90% power to establish noninferiority with a margin of 1.3, assuming no difference between treatment groups. The

power is >90% to establish a noninferiority margin of 1.25 if the hazard ratio is 0.95 favoring vadadustat. A MACE rate of 10% annually is anticipated in both treatment arms based on a comprehensive review of available epidemiology and prospective clinical studies in the field. The number of MACE in each study will be a function of the actual pattern and size of enrollment as well as the duration of follow-up.

11.2 Study Analysis Populations

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects
- Full analysis population: defined as randomized subjects receiving 1 or more doses of study medication and had at least one Hb assessment during the primary efficacy evaluation period. This population will be analyzed based upon the randomized treatment.
- Per protocol (PP) population: defined as all randomized subjects who received study medication (vadadustat or darbepoetin alfa) during the primary evaluation period, had at least 2 Hb assessments during the primary evaluation period, received no rescue therapy (with ESA or RBC transfusion) in the 8 weeks prior to the evaluation period, and have no protocol deviations affecting the primary endpoint analyses. Protocol deviations leading to exclusion from the per protocol population will be specified prior to database lock on a blinded basis and recorded in a separate document.
- Safety population: defined as all subjects who received at least 1 dose of study medication. This population will be analyzed based upon the actual treatment received.

Efficacy analyses will utilize the randomized, full analysis, and PP populations while safety analyses (including MACE) will utilize the randomized population.

11.3 Analysis of Demographic and Pretreatment Variables

Descriptive statistics will be generated for demographic and pretreatment variables for each analysis population defined in Section 11.2, Study Analysis Populations.

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

11.4 Disposition of Subjects

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

The number of randomized subjects who completed each period of study medication treatment (maintenance and long-term treatment), discontinued from study medication early, and completed or discontinued from the study and reasons for discontinuation will be summarized by treatment group and overall.

11.5 Missing Data

Subjects who stop study medication treatment after randomization and prior to completion of the study should continue with planned study visits and assessments unless they withdraw consent for participation in the study. Similarly, subjects will continue with study medication and study procedures following the initiation of rescue therapy, with the exception that the subjects must discontinue taking study medication while receiving an ESA rescue therapy. Treatment with study medication should be resumed after an appropriate interval following the ESA rescue therapy as described in Section 8.4.7, Rescue Therapy. Data will continue to be collected following initiation of the rescue therapy as per the study Schedule of Activities.

All data collected during the study, including at any point after the initiation of rescue therapy as well as after early discontinuation of study medication treatment, will be used for the primary analysis as well as main analyses of all efficacy endpoints. Sensitivity analyses will be performed to assess an impact of rescue therapy on study conclusions.

In the primary analysis of the primary efficacy endpoint, all available qualifying Hb measurements during the pretreatment period and during the primary evaluation period (Weeks 24-36) will be used to calculate an average Hb during each period respectively, for each subject. For any subject with no available Hb measurements during the primary evaluation period, multiple imputation will be used to impute a change from Baseline value (details are provided in the SAP). In an analogous manner, an average Hb will be calculated for the secondary evaluation period (Weeks 40-52) for each subject. Given the design of this study where the subjects will continue to be assessed after early study medication discontinuation, it is expected that there will be only a minimal amount of missing data and the primary analysis should not be substantially affected by the imputation.

All data pertaining to the MACE endpoint collected at any point during the study, both during study medication treatment and post study medication treatment discontinuation, and regardless of the rescue therapy, will be used for the primary analysis of the MACE endpoint and its individual components.

Unless stated otherwise in the SAP, missing data for all other secondary efficacy and safety endpoints will not be imputed and the analysis will be based on observed data. For certain responder-type binary endpoints, subjects with no available data will be classified into one of the categories as described in the relevant sections of the SAP

11.6 Efficacy Analyses

The primary efficacy endpoint as well as all key and other secondary endpoints will be summarized using descriptive statistics by treatment group, as well as by study visit and/or analysis period as appropriate. Mean values of Hb as well as selected other efficacy parameters will be plotted across study visits/periods by treatment group.

11.6.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the mean Hb change from Baseline (mean pretreatment Hb) to the mean Hb from Weeks 24-36 (inclusive).

11.6.1.1 Primary Analysis of Primary Efficacy Endpoint

The primary analysis will use an analysis of covariance (ANCOVA) with multiple imputation, stratified by the randomization strata and using Baseline Hb as the covariate.

A 2-sided 95% confidence interval (CI) will be calculated for the difference between treatment groups (vadadustat minus darbepoetin alfa).

Noninferiority of vadadustat will be established if the lower limit of this CI is ≥-0.75g/dL.

The primary analysis will be performed using the randomized population and the assigned treatment as described in Section 11.2, Study Analysis Populations. All data collected during the study for subjects included in the randomized population at the time of analysis, including data collected at any point after the initiation of rescue therapy as well as after early discontinuation of study medication treatment, will be used for the primary analysis. Missing data will be handled using multiple imputation methodology as described in the SAP.

11.6.1.2 Sensitivity Analyses of Primary Efficacy Endpoint

- The following sensitivity analyses will be conducted: Primary analysis will be repeated using the full analysis population.
- Primary analysis will be repeated using only subjects with available Hb data during the primary evaluation period, ie, excluding subjects with no available data during the primary evaluation period.
- Primary analysis will be repeated using the PP population with the actual treatment received.
- Primary analysis will be repeated with alternate approaches to imputation of missing data as described in the SAP.
- Primary analysis will be repeated with imputation of data which may have been affected by a subject's having received any form of rescue (transfusion of ESA). Details are provided in the SAP.

11.6.2 Secondary Efficacy Analyses

Secondary efficacy endpoints analyses will be performed using the randomized and full analysis populations and the assigned treatment as described in Section 11.2, Study Analysis Populations. Analysis for the key secondary efficacy endpoints will be repeated using the PP population with the actual treatment received.

11.6.2.1 Key Secondary Efficacy Analyses

Mean change in Hb value between Baseline and the secondary evaluation period (Weeks 40-52) will be analyzed using the same methodology as specified for the primary efficacy endpoint. Sensitivity analyses similar to those of the primary efficacy endpoint will be performed and details will be provided in the SAP.

11.6.3 Subgroups

Analyses of the primary efficacy endpoint and key secondary efficacy endpoints will also be performed using the randomized and full analysis populations, using the assigned treatment, for subgroups based on the following:

- Hb stratification level
- NYHA CHF stratification level
- Due to use of different target Hb levels in the U.S. vs. non-US, the endpoints will also be analyzed for subsets based on the target Hb level:
  - the U.S. subset will be assessed due to the target Hb range being 10.0-11.0 g/dL in the U.S.
  - the combined EU and ROW (non-US) subset will be assessed since the target Hb range is 10.0-12.0 g/dL in these two Regions
- Geographic region (U.S., EU, ROW)
- Age
- Gender
- Race

11.7 Safety Analyses

All analyses of safety data will use the randomized population.

11.7.1 Analysis of MACE and Expanded MACE Components

The primary safety endpoint, time to the first adjudicated MACE, will be analyzed as [date of the first MACE minus the date of randomization +1]. A MACE is defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke. Subjects who have not experienced a MACE by study closure will be censored on the date of their last study assessment. The hazard ratio (vadadustat/darbepoetin alfa) and its 95% confidence interval will be obtained from a stratified Cox proportional hazards model. As this study has not been designed to provide a stand-alone assessment of MACE, this analysis will be considered a descriptive analysis. A similar analysis as described for the primary analysis of the MACE endpoint will be performed with censoring of subjects 4 weeks following discontinuation of study medication if they did not have a MACE prior to that time.

An additional analysis as described for the primary analysis of the MACE endpoint will be performed with censoring at time of chronic dialysis initiation for subjects who have progressed to chronic dialysis and who did not have a MACE prior to that time.

The following safety endpoints will also be summarized using time to event methods as for MACE:

1) Individual components (all-cause mortality, non-fatal myocardial infarction, non-fatal stroke) of MACE
2) Thromboembolic events (defined as arterial thrombosis, DVT, PE, or vascular access thrombosis)
3) Hospitalization for heart failure

4) Expanded MACE, defined as all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, hospitalization for HF, or thromboembolic event

For these endpoints the incidence ("yes"/"no") of the endpoint will be presented for each treatment arm. Kaplan-Meier curves will be presented for each endpoint as the time of endpoint free survival (ie, time until endpoint or death).

The primary MACE analysis will be based upon all events that accrue over the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015) (see Section 11.1.2,Sample Size for the Primary Safety Endpoint).

The SAP for this pooled MACE assessment in NDD-CKD subjects provides details of the primary analyses for MACE, for individual components of MACE, and for an expanded version of MACE. Details of sensitivity analyses and subgroup analyses are also provided in the MACE SAP.

11.7.2 Analysis of Adverse Events

Adverse events will be summarized using the number and percentage of subjects with AEs for all subjects in the safety population. Summaries will also be provided for subgroups including Region, Age, Gender and Race.

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

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

- SAEs
- Related AEs (including all categories for relationship to study medication other than "Unrelated", as determined by the Investigator)
- AEs leading to early discontinuation of study medication.

11.7.3 Remaining Safety Endpoints

The analysis of the following safety endpoints will be detailed in the SAP:

The analysis of proportion of subjects with Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL post-Baseline will classify a subject as a "yes" if:

- Any value Hb >12.0 g/dL at any time after Day 1
- Any confirmed value Hb >12.0 g/dL at any time after Day 1
- Any value Hb >13.0 g/dL at any time after Day 1
- Any confirmed value Hb >13.0 g/dL at any time after Day 1
- Any value Hb >14.0 g/dL at any time after Day 1
- Any confirmed value Hb >14.0 g/dL at any time after Day 1.

A Hb value above a set threshold will be considered as confirmed if there are 2 consecutive values above that threshold. The second of the 2 consecutive assessments should be done at

most 12 weeks after the first assessment. Subjects with no available data post-Baseline will be excluded from this analysis. All other subjects will be classified to the "no" category.

The analysis of proportion of subjects with any Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval post-Baseline will classify a subject as a "yes" if at least 1 of the following criteria at any point after Day 1 is met:

- Hb increase >1.0 g/dL within any 2-week interval
- Hb increase >2.0 g/dL within any 4-week interval.

Subjects with no available data post-Baseline will be excluded from this analysis. All other subjects will be classified to the "no" category.

Observed values of continuous and categorical parameters and changes from Baseline for continuous parameters to each study visit will be summarized descriptively for vital signs and clinical laboratory results. Graphical displays of selected laboratory parameters will also be provided.

11.8 Additional Assessments

11.8.1 Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug dictionary.

Prior medications will be defined as any medications that were taken before the date of the first dose of study medication. Concomitant medications will be defined as any medications taken at any time from the date of the first dose of study medication through the date of the last dose of the study medication.

11.8.2 Biomarkers

Biomarkers (including but not limited to, hepcidin and VEGF) will be summarized descriptively at Baseline and by visit post-Baseline.

11.8.3 Pharmacokinetics

Descriptive and graphical summaries will be generated for PK measurements.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms/Electronic Data Capture

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. Case report forms 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 Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

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

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

13.1 Investigative Site Monitoring Visits

During study conduct, the Sponsor or its agent 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 the 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 investigative site may also be subject to QA audits performed by the Sponsor or companies working with or on behalf of the Sponsor, 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 will 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 will consult with the Sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action.

The investigative site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the investigative site should notify the Sponsor or its designee (and IRB or IEC, as required). Significant 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 study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the study.

14.1 Criteria for Premature Termination or Suspension of the Study

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

- New information regarding the safety or efficacy of the study 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
- Significant 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 study for other valid administrative reasons.

14.2 Criteria for Premature Termination or Suspension of Investigational Study Sites

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

14.3 Procedures for Premature Termination or Suspension of the Study or Investigational Sites

In the event that the Sponsor elects to terminate or suspend the study or the participation of an investigational study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational study 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/Independent Ethics Committee

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 or its designee.

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

The only circumstance in which an amendment may be initiated prior to IRB/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

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

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

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

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

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

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP, defined as a breach that will likely affect the safety or physical or mental integrity of subjects or the scientific value of the trial, 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, 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 (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

16 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator 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

Study Period	Optional Pre-Screen	Screening		Treatment Period																									Post Treatment	
				BL/ rand. [a]	Year 1																	Year 2				Year 3/Year 4					
Visit	**PS**	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22/ 26**	**23/ 27**	**24/ 28**	**25/ 29**	**End of Trtmt**	**Follow-up [b]**
Week		**-8 to 0**		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**104**	**116/ 168**	**128/ 180**	**140/ 192**	**156/ 208**	**EOT [c]**	**EOT +4 wks [dd]**
Visit Window (Days)					±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±10	±10	±10	±10	±10	±10	±10	±10	±7	±7
Procedures/Assessments																														
Informed Consent	X [d]	X [d]																												
Pre-Screening Local Hb [e]	X																													
I/E Criteria [f]	X	X	X																											
Vital Signs [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Demographics, Med History			X																											
Physical Exam [h]			X																											
12-Lead ECG [i]				X																										
Randomization				X																										
Laboratory Procedures																														
Pregnancy Test [j]			X																											
Folate and Vitamin B_{12}		X[k]																												
Coagulation Tests [l]				X																										
C-Reactive Protein				X										X						X				X				X	X	
Urine Albumin/Creatinine (uACR)				X										X						X				X				X	X	
CBC [m] with periodic diff		X [k,]	X [k,n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Iron Indices [o]		X[k]		X		X		X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	
Serum Chem and eGFR [p]		X[k]		X		X		X		X		X		X		X		X		X		X		X		X		X	X	

Study Period	Optional Pre-Screen	Screening		Treatment Period																								Post Treatment	
				BL/ rand. [a]	Year 1																	Year 2				Year 3/Year 4					
Visit	**PS**	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22/ 26**	**23/ 27**	**24/ 28**	**25/ 29**	**End of Trtmt**	**Follow-up [b]**
Week		**-8 to 0**		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**104**	**116/ 168**	**128/ 180**	**140/ 192**	**156/ 208**	**EOT [c]**	**EOT +4 wks [dd]**
Visit Window (Days)					±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±10	±10	±10	±10	±10	±10	±10	±10	±7	±7
Liver Function Tests [q]		X[k]		X		X		X		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X	
Lipid Panel [r]				X										X						X										
Biomarkers [s]				X						X				X						X				X				X	X	
Reticulocyte Count				X		X				X				X						X										
Erythropoietin				X		X				X				X						X										
PK [t]				X		X				X				X						X										
Exploratory Samples [u]				X										X						X				X				X	X	
Safety Assessments																														
MACE Endpoint Questionnaire [v]					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment [w]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusions and ESA Rescue					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Therapeutic Phlebotomy					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Assessments and Procedures																														
Concomitant Med Review [x]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vadadustat Medication Dispensing [y]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug Reconciliation					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visit Registration in IWR		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hb via HemoCue for Dose Adjustment [z]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Monthly Hb Monitoring [z]																					X	X	X	X	X	X	X	X			
Darbepoetin Alfa				Dosing according to Dose Adjustment Algorithms [aa]																												

Study Period	Optional Pre-Screen	Screening		Treatment Period																								Post Treatment	
				BL/ rand. [a]	Year 1																Year 2				Year 3/Year 4					
Visit	**PS**	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22/ 26**	**23/ 27**	**24/ 28**	**25/ 29**	**End of Trtmt**	**Follow-up [b]**
Week		**-8 to 0**		**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**104**	**116/ 168**	**128/ 180**	**140/ 192**	**156/ 208**	**EOT [c]**	**EOT +4 wks [dd]**
Visit Window (Days)					±3	±3	±3	±3	±3	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±10	±10	±10	±10	±10	±10	±10	±10	±7	±7
Vadadustat Dose Adjustments [bb]				Start at 300 mg once daily, then adjust dose as per Dose Adjustment Algorithms																										
Oral or IV Iron Supplementation [cc]				As needed to maintain ferritin ≥100 ng/mL or TSAT ≥20%																										

Abbreviations: AE = adverse event; ALT/SGPT = alanine aminotransferase/serum glutamic-pyruvic transaminase; AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BUN = blood urea nitrogen; CBC = complete blood count; CPK = creatine phosphokinase; CRF = case report form; diff = differential; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOT = end of treatment; ESA = erythropoiesis-stimulating agent; HDL = high density lipoprotein; Hb = hemoglobin; HIF = hypoxia inducible factor; ICF = informed consent form; I/E = inclusion/exclusion; INR = international normalized ratio; IWR = interactive web response; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MACE = major adverse cardiovascular event; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; med = medication; PK = pharmacokinetic; PS = Pre-Screening; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RDW = red cell distribution width; SV1 = Screening visit 1; SV2 = Screening visit 2; TIBC = total iron binding capacity; Trtmt = treatment; TSAT = transferrin saturation; uACR = urine albumin to creatinine ratio; VEGF = vascular endothelial growth factor; WBC = white blood cell; wks = weeks.

[a] The Screening period is a maximum of 8 weeks in duration. The Baseline visit must be performed at a minimum of 4 days from the last Screening visit (SV2), or date of last re-test.

[b] The Follow-up visit can be performed either in person OR via the telephone.

[c] The EOT visit will be performed at the time a subject permanently discontinues study medication (vadadustat or darbepoetin alfa) or for subjects on study medication at the time of notification of global study completion. It is important to continue to follow subjects that discontinue study medication through global study completion at a frequency and approach that is agreed to between the Investigator and subject. Visit schedule and assessments are flexible and at the discretion of the investigator and subject and will be clearly documented in the medical chart.

[d] An abbreviated ICF will be used for Pre-Screening. If the subject is eligible for Screening, a separate full ICF will be used, which may be signed in advance of the SV1 pocedures. The Screening period starts at the time the informed consent is signed and will be a maximum of 8 weeks in duration. An optional consent form for collection of blood samples for future genetic analysis will be provided at SV1. An additional optional consent form for participation in an adrenal function substudy in 200 subjects in the EU will also be provided at SV1.

[e] If the Pre-Screen HemoCue Hb is between 8.0 and 11.0 g/dL (inclusive) within the US or between 9.0 and 12.0 g/dL (inclusive) outside of the US, the investigative site may proceed with Screening Visit 1 (SV1), preferably on the same day as Pre-Screening.

[f] Inclusion/Exclusion criteria will be reviewed at the Pre-Screening and Screening visits (SV1 and SV2). Final eligibility determination will occur following the Screening visits when all data are available.

[g] Vitals: Heart rate and blood pressure to be assessed in the seated position after 5 minutes of rest. Height (SV2 only) and weight (SV2, Weeks 12, 24, 36, and 52, yearly thereafter, and at the EOT visit) will also be measured.

[h] Physical exam: a physical exam is required at SV2 as outlined in the protocol. Thereafter, an abbreviated symptom-directed physical exam should be performed at the discretion of the Investigator as clinically indicated.

[i] ECG should be performed prior to blood draws when possible and obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes.

[j] Serum pregnancy will be tested in women of childbearing potential at SV2. (Eligible subjects will be advised to use an adequate contraceptive method.) Additional serum or local urine pregnancy tests should be conducted throughout the study in sufficient number, as determined by the Investigator or required by local regulations, to establish the absence of pregnancy during the study. If positive at SV2, the subject is not eligible to enter the study. If a subject becomes pregnant during the study, the subject must permanently discontinue study medication and should attend all subsequent study visits and be continually monitored according to the Schedule of Activities for the duration of the study.

[k] Subjects may be retested and/or rescreened as detailed in Section 7.4 Retesting and Rescreening

[l] Coagulation tests: prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).

[m] A CBC with differential will be performed at Baseline and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208. At all other noted visits, a CBC without differential will be performed.

CBC: hemoglobin, hematocrit, red blood cells (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

[n] Mean Screening Hb between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) outside of the US, as determined by the average of 2 Hb values measured by the central laboratory during Screening. If the subject's Hb does not qualify after SV1, SV2, or retest, the subject should be considered a Screen Failure.

[o] Iron indices: ferritin, iron, total iron binding capacity (TIBC), and transferrin saturation (TSAT).

[p] A full serum chemistry panel will be performed at SV1, Baseline, and twice annually at Weeks 28, 52, 76, 104, 128, 156, 180, 208. At all other noted visits, serum creatinine and eGFR will be performed. Serum chemistry: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen (BUN)/urea, creatine phosphokinase (CPK), uric acid, albumin, total protein, and eGFR.

[q] Liver function tests: total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), and lactate dehydrogenase (LDH).

[r] Lipids: total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides.

[s] The biomarkers include, but are not limited to, hepcidin and VEGF.

[t] PK samples are to be drawn only for subjects randomized to vadadustat. Subjects will be questioned regarding the timing of their last dose of vadadustat.

[u] Additional blood and urine samples will be collected at Baseline, Weeks 28, 52, 104, 156, and EOT which may be used for exploratory measurement of biomarkers (eg, factors relating to the activation of the HIF pathway). Subjects will also be asked to provide optional consent to obtain a blood sample at Baseline and EOT to be stored for future genetic analyses (eg, DNA, mRNA).

[v] At each post-randomization study visit, the subject must specifically be questioned regarding the occurrence of any potential MACE endpoint events since the last study visit. If a potential endpoint event is reported, the date of the event should be recorded and the appropriate source documents should be collected according to the endpoint packet checklist.

[w] Adverse events should be documented and recorded at each visit. The AE reporting period for this study begins upon randomization through global study completion. All adverse events (serious and non-serious, and related and non-related) will be documented and recorded through the follow-up visit. Subjects must be followed for adverse events until the final required protocol visit or until all drug-related toxicities and serious adverse events have resolved (or are considered chronic/stable).

[x] Concomitant medications should be collected and recorded at each visit as noted. All concomitant medications received during the screening window (minimum of 30 days prior to the start of study medication) through the EOT visit will be recorded.

[y] Subjects will be provided with a supply of vadadustat at the Baseline visit and will be resupplied at subsequent visits as needed. Subjects will be instructed to complete 1 bottle prior to opening the next bottle. The dose should be taken at approximately the same time each day.

[z] Hemoglobin will be monitored via local HemoCue throughout the study to determine if the dose of study medication will be adjusted, interrupted, or maintained. From Week 53, Hb will be monitored monthly as part of local standard of care labs or at unscheduled visits for dose adjustment.

[aa] Refer to the Dosing Algorithm adult patients with CKD not on dialysis. If the subject progresses to DD-CKD during the study and is able to continue study medication, use the Appendix Dosing Algorithms for adult patients with DD-CKD. Vital signs and weight should be obtained prior to dosing . Darbepoetin alfa dosing is independent of the visit schedule, thus, the dosing schedule may shift per local standard of care and Investigator discretion. .

[bb] The dose will be adjusted in accordance with the Dose Adjustment Algorithms. Changes to dose will be accomplished by changing the number of tablets to be taken per day.

[cc] Iron supplementation will be prescribed during the study to maintain ferritin ≥100 ng/mL or TSAT ≥20%. In general, only oral iron should be considered before initiating IV iron for therapy. Subjects who fail to qualify for the study based on low TSAT, ferritin, folate, or B_{12} values may receive replacement therapy based on the investigative sites' standard of care during the screening period and retest the laboratory parameter(s). Subjects who receive iron replacement may retest screening Hb a minimum of 3 weeks after completion of iron replacement therapy. Vadadustat is not to be administered concurrently with the oral iron supplement (including multivitamins containing iron), iron containing phosphate binders or any medications containing iron. Oral iron supplement should be taken at least 2 hours before or 2 hours after the dose of study medication. (See study protocol for further details regarding iron administration and potential intravenous therapy).

[dd] End of Study status will be done to capture subject status at the global completion of the study or time of withdrawal of consent or when subject deemed LTFU or death. Subjects active on the study (including those permanently discontinued from study medication and are being followed) will complete the Follow-up visit. For subjects active on the study medication at global study completion, the EOS status will be collected at the at the Follow-up visit. For subjects that have permanently discontinued study medication and are being followed until global study completion, the EOS status will be as collected, which includes activities outlined at the Follow-up visit.

APPENDIX B: CKD-EPI CREATININE EQUATION

The estimated glomerular filtration rate (eGFR) will be calculated from serum creatinine (isotope dilution mass spectrometry [IDMS] calibrated in mg/dL) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Levey et al. 2009).

The CKD-EPI creatinine equation is:

$eGFR = 141 \times \min(SCr/k,1)^{\alpha} \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018 \text{ if female}] \times [1.159 \text{ if black}]$

where:

SCr is serum creatinine (in mg/dL)

k = 0.7 for females

k = 0.9 for males

α = -0.329 for females

α = -0.411 for males

min = the minimum of SCr/k or 1

max = the maximum of SCr/k or 1

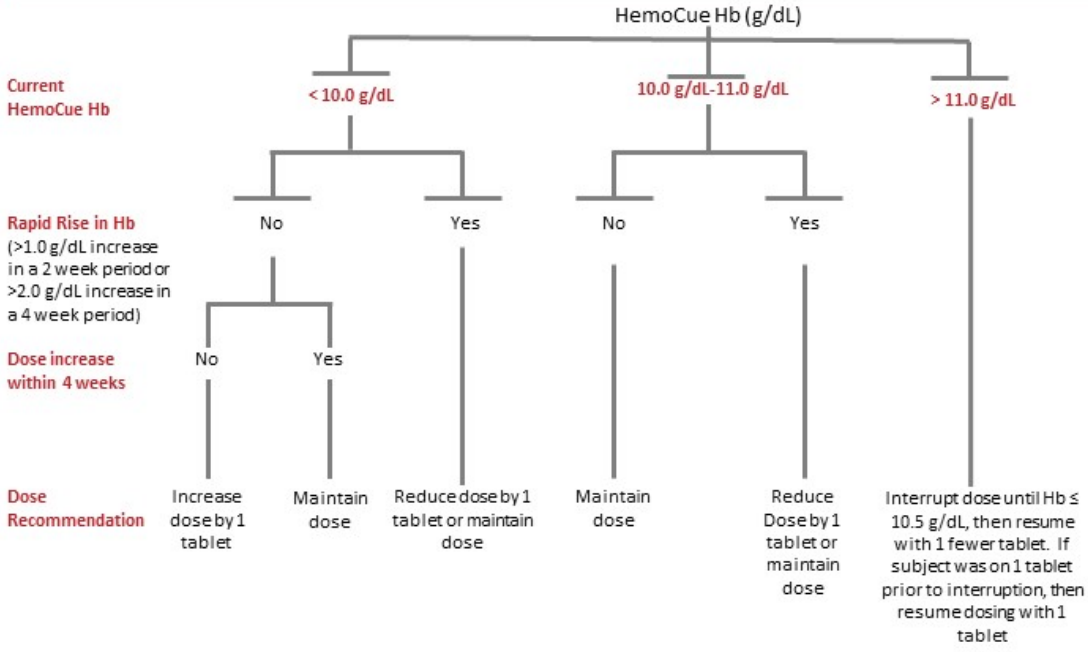
APPENDIX C: VADADUSTAT DOSING AND DOSE ADJUSTMENT ALGORITHMS

PRO$_2$TECT-CONVERSION (CI-0015)

Vadadustat Dose Adjustment – **United States**

Target Hb: 10.0 g/dL - 11.0 g/dL

- Do not increase the dose more frequently than once every 4 weeks.
- Decreases in dose can occur more frequently.
- If a dose adjustment is required to achieve or maintain Hb at the desired level, the vadadustat dose is adjusted by 1 tablet (150 mg.)
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, and Hb variability.
- Dose options are 150, 300, 450, or 600 mg.

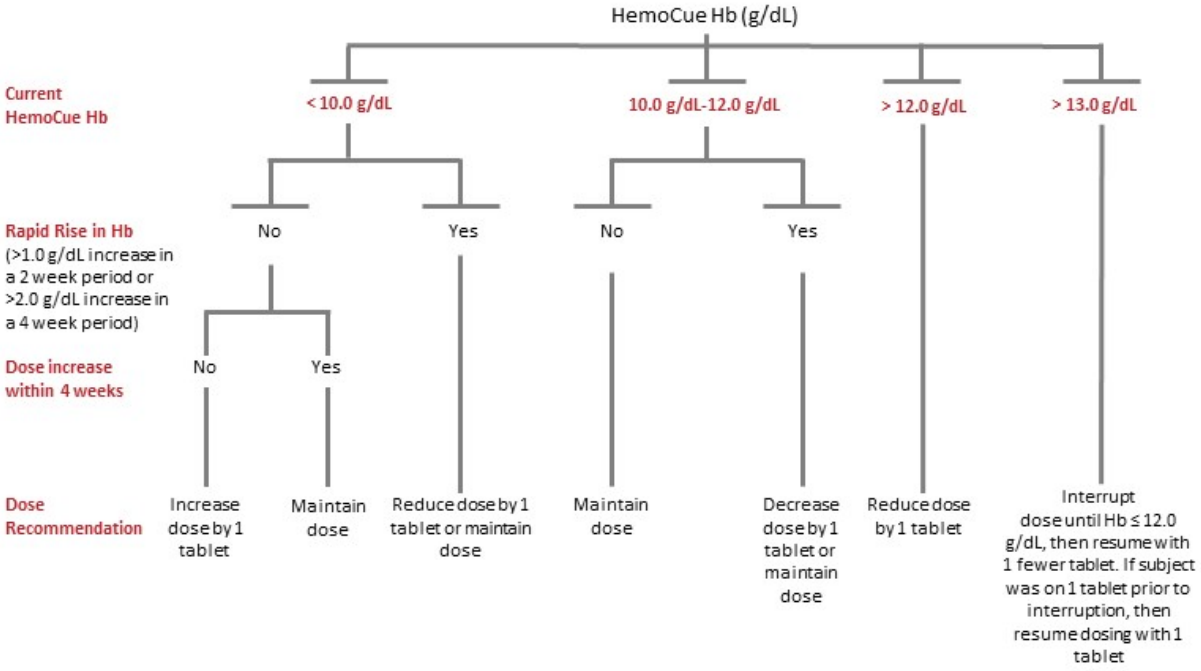


PRO$_2$TECT-CONVERSION (CI-0015)

Vadadustat Dose Adjustment – **Outside United States**

Target Hb: 10.0 g/dL - 12.0 g/dL

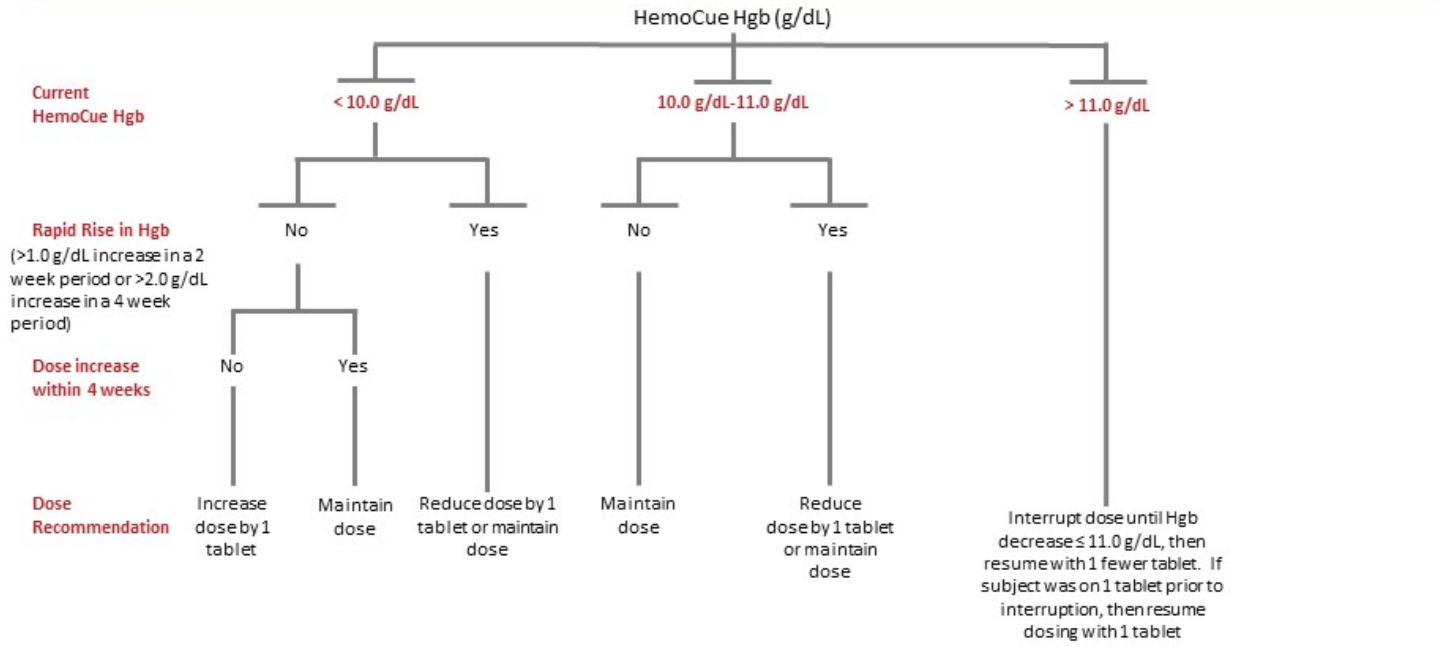
- Do not increase the dose more frequently than once every 4 weeks.
- Decreases in dose can occur more frequently.
- If a dose adjustment is required to achieve or maintain Hb at the desired level, the vadadustat dose is adjusted by 1 tablet (150 mg).
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, and Hb variability.
- Dose options are 150, 300, 450, or 600 mg.



PRO$_2$TECT-CONVERSION (CI-0015)
Vadadustat Arm **Initiating Dialysis** to Follow Vadadustat Dose Adjustment Algorithm for DD-CKD – **United States**

Target Hgb: 10.0 g/dL - 11.0 g/dL

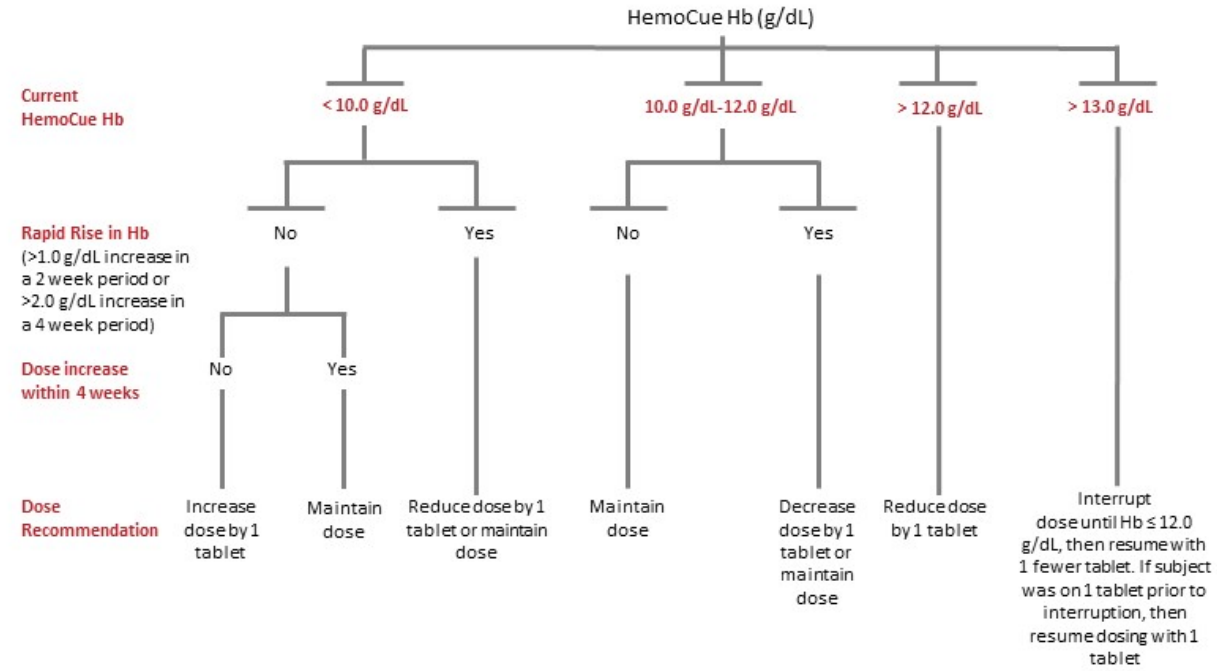
- Do not increase the dose more frequently than once every 4 weeks
- Decreases in dose can occur more frequently
- If a dose adjustment is required to achieve or maintain Hgb at the desired level, the vadadustat dose is adjusted by 1 tablet (150 mg)
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hgb rate of rise, Hgb rate of decline, and Hgb variability
- Dose options are 150, 300, 450, or 600 mg



PRO$_2$TECT-CONVERSION (CI-0015)
Vadadustat Arm **Initiating Dialysis** to Follow Vadadustat Dose Adjustment Algorithm for DD-CKD – **Outside United States**

Target Hb: 10.0 g/dL - 12.0 g/dL

- Do not increase the dose more frequently than once every 4 weeks.
- Decreases in dose can occur more frequently.
- If a dose adjustment is required to achieve or maintain Hb at the desired level, the vadadustat dose is adjusted by 1 tablet (150 mg).
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, and Hb variability.
- Dose options are 150, 300, 450, or 600 mg.



Note: Dosing Algorithm for NDD-CKD and DD-CKD populations are the same for outside United States.

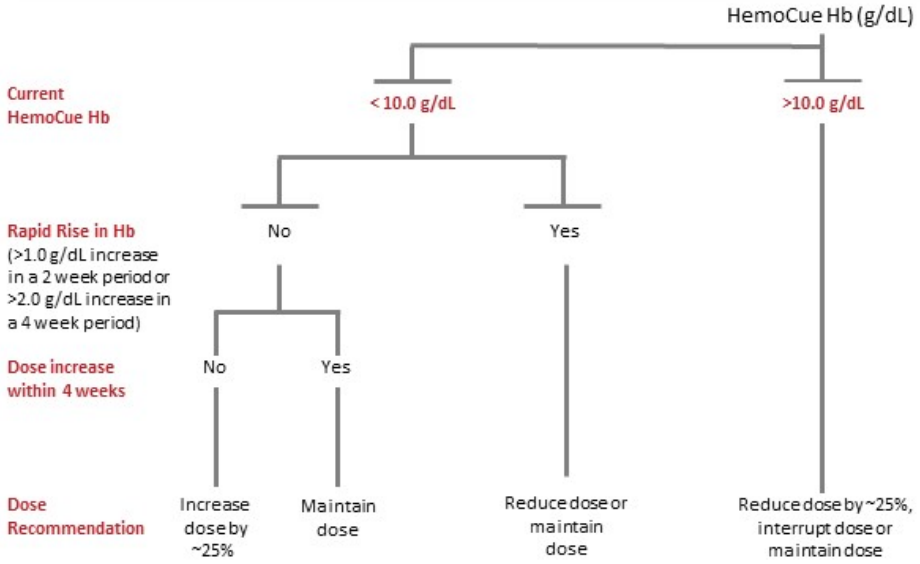
APPENDIX D: DARBEPOETIN ALFA DOSING AND DOSE ADJUSTMENT ALGORITHMS

PRO$_2$TECT-CONVERSION (CI-0015)

Darbepoetin Alfa Dose Adjustment – **United States**

Target Hb: 10.0 g/dL - 11.0 g/dL

- Do not increase the dose more frequently than once every 4 weeks.
- Decreases in dose can occur more frequently.
- If a dose adjustment is required to achieve or maintain Hb at the desired level, the darbepoetin dose is adjusted by ~25%.
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, and Hb variability.

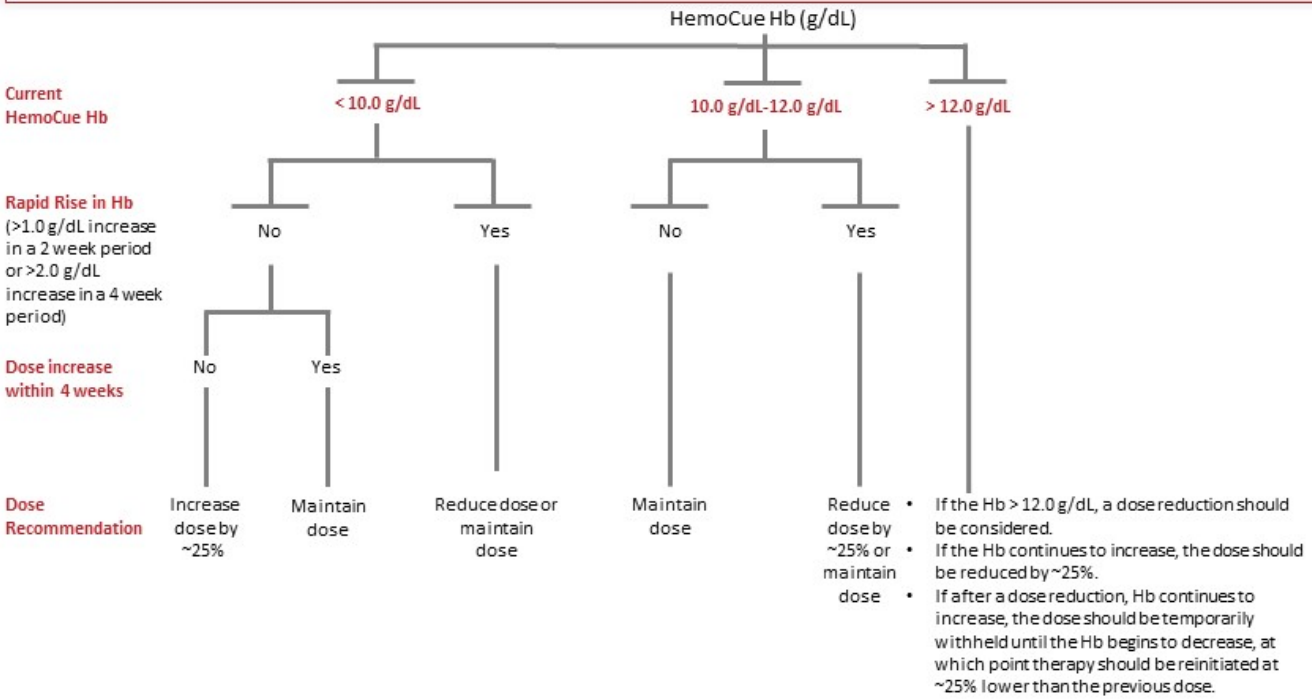


PRO$_2$TECT-CONVERSION (CI-0015)

Darbepoetin Alfa Dose Adjustment – **Outside United States**

Target Hb: 10.0 g/dL - 12.0 g/dL

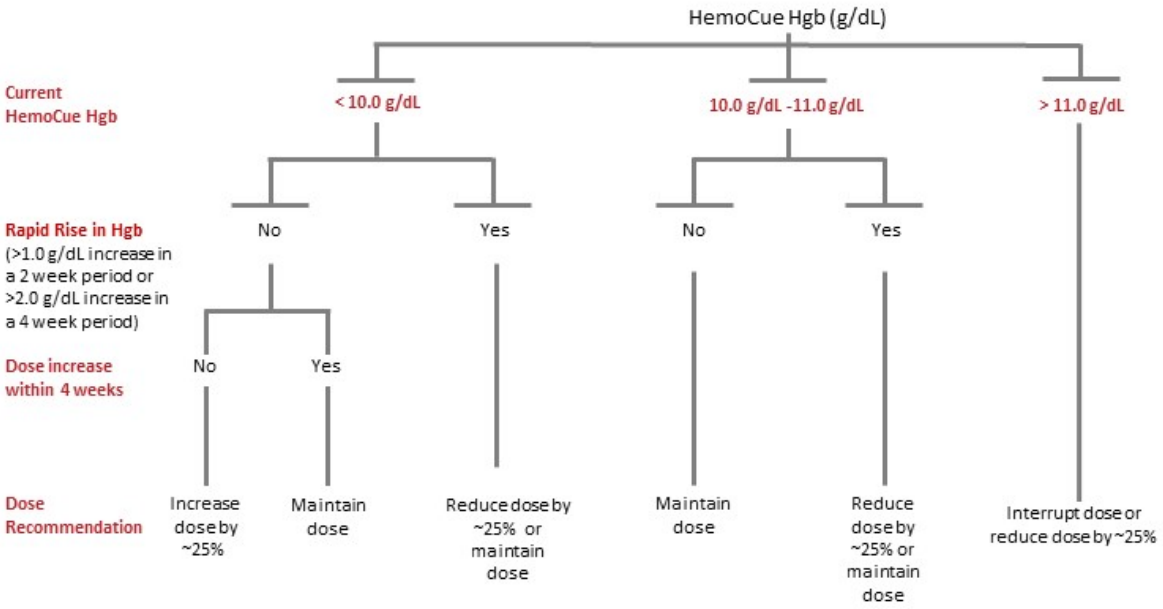
- Do not increase the dose more frequently than once every 4 weeks.
- Decreases in dose can occur more frequently.
- If a dose adjustment is required to achieve or maintain Hb at the desired level, the darbepoetin dose is adjusted by ~25%.
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, and Hb variability.



PRO$_2$TECT-CONVERSION (CI-0015)
Darbepoetin Alfa Arm **Initiating Dialysis** to Follow Darbepoetin Alfa Dose Adjustment Algorithm for DD-CKD – **United States**

Target Hgb: 10.0 g/dL - 11.0 g/dL

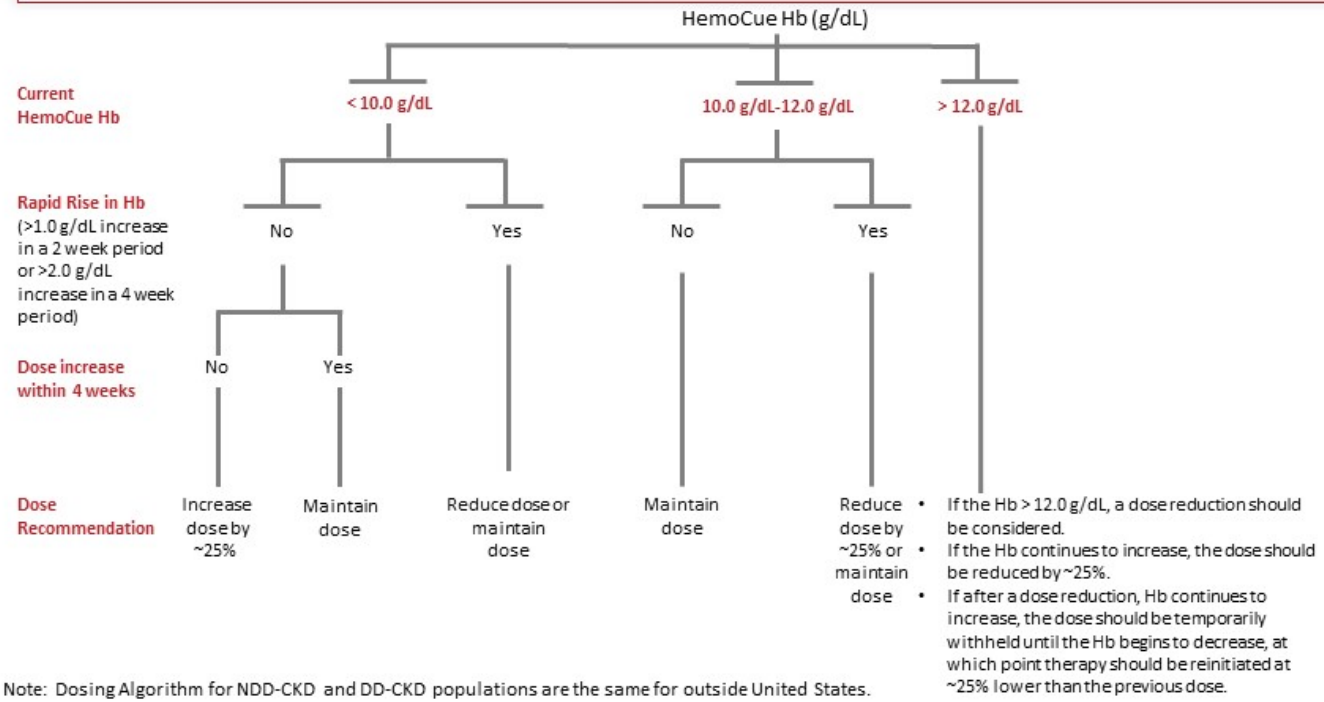
- Do not increase the dose more frequently than once every 4 weeks
- Decreases in dose can occur more frequently
- If a dose adjustment is required to achieve or maintain Hgb at the desired level, the darbepoetin dose is adjusted by ~25%
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hgb levels within the target Hgb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hgb rate of rise, Hgb rate of decline, and Hgb variability.



PRO$_2$TECT-CONVERSION (CI-0015)
Darbepoetin Alfa Arm **Initiating Dialysis** to Follow Darbepoetin Alfa Dose Adjustment Algorithm for DD-CKD – **Outside United States**

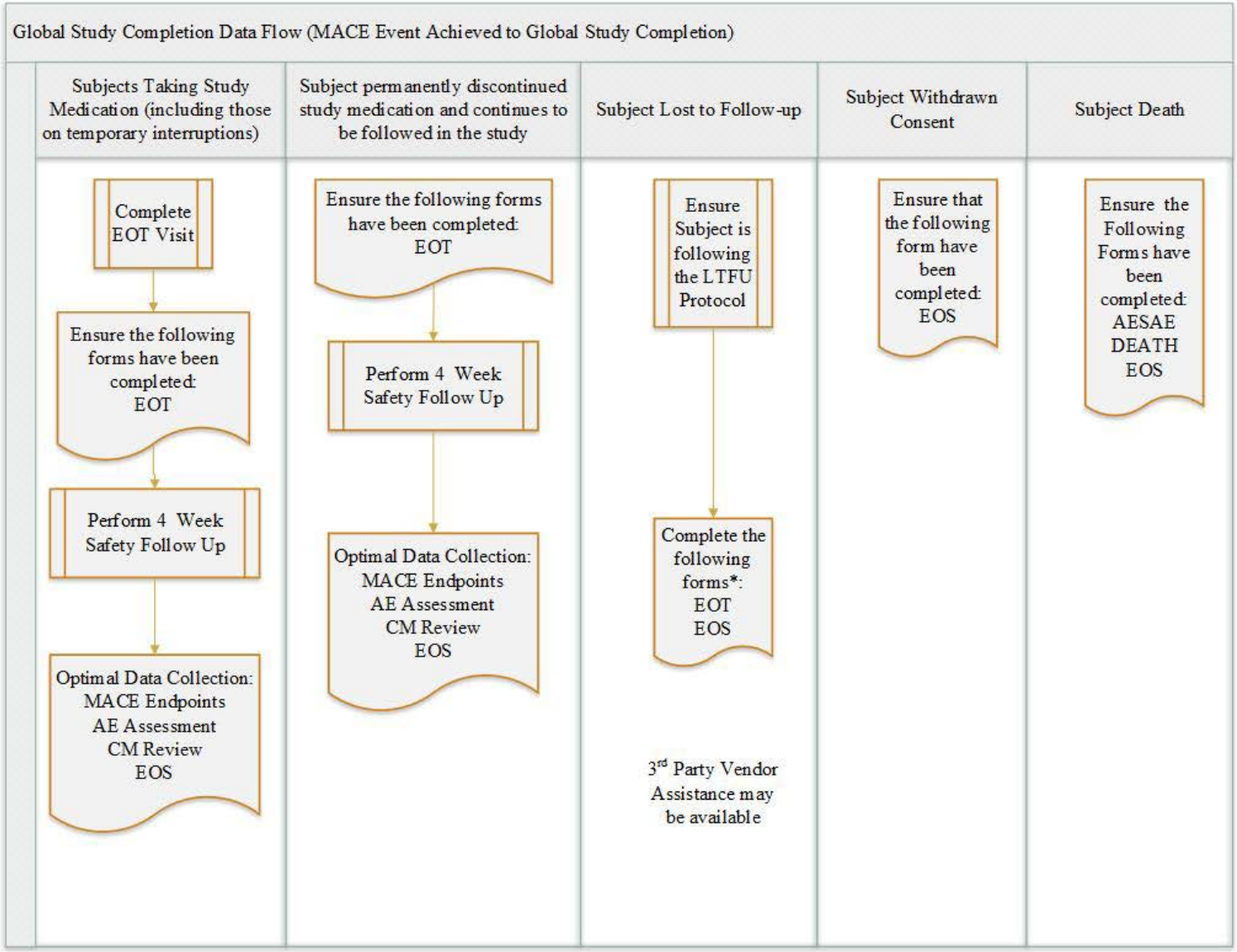
Target Hb: 10.0 g/dL - 12.0 g/dL

- Do not increase the dose more frequently than once every 4 weeks.
- Decreases in dose can occur more frequently.
- If a dose adjustment is required to achieve or maintain Hb at the desired level, the darbepoetin dose is adjusted by ~25%.
- The protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, and Hb variability.



Note: Dosing Algorithm for NDD-CKD and DD-CKD populations are the same for outside United States.

APPENDIX E: END OF TREATMENT AND GLOBAL STUDY COMPLETION SUBJECT FLOW



APPENDIX F: HISTORY OF AMENDMENTS TO THE PROTOCOL

Amendment 1 (Version 2; [redacted])

Amendment 1 was issued based on requests from health authorities during review of the protocol under the European Voluntary Harmonisation Procedures (VHP).

Amendment 1 was issued to a limited number of sites.

The major changes introduced in the amendment are summarized below:

- Added Exclusion Criterion No. 19: "Hypersensitivity to darbepoetin or vadadustat, or to any of their excipients."
- Clarified that the adrenal function assessment (adrenocorticotropic hormone [ACTH] stimulation test) will be conducted in a subset of 200 subjects in the European Union (100 subjects from the vadadustat treatment arm and 100 subjects from the darbepoetin alfa treatment arm) across the 2 non-dialysis dependent chronic kidney disease (NDD-CKD) studies AKB-6548-CI-0014 and AKB-6548-CI-0015.
- Defined that the study completion date (end of trial) will take place when 631 major adverse cardiovascular events (MACE) events have accrued over the 2 NDD-CKD studies (Studies AKB-6548-CI-0014 and AKB-6548-CI-0015).
- Clarified that the double-barrier method should be practiced starting at Screening Visit 1, throughout the study, and for 30 days after the last dose of study medication.
- Added that "In case of substantial protocol amendment, the sponsor will obtain approval from responsible Regulatory Authorities before implementation."

Amendment 2 (Version 3; [redacted])

Amendment 2 was issued based on feedback from regulatory authorities and a Clinical Expert Advisory Board, as well as requests from study sites for additional clarification.

All protocol changes present in Amendment 1 have also been included in Amendment 2.

The major changes introduced in the amendment are summarized below:

- To update the following exclusion criteria:
    - Exclusion Criterion No. 7: Additional clarification of exclusionary cardiovascular events within 12 weeks prior to screening
    - Exclusion Criterion No. 8: To not exclude subjects with basal cell carcinoma who have been successfully treated with cryotherapy instead of surgical resection
    - Exclusion Criterion No. 11: To specifically exclude subjects with a history of hematopoietic stem cell transplant
    - Exclusion Criterion No. 13: Considering the short half-life of vadadustat and clinical experience in previous Phase 1 and Phase 2 studies in NDD-CKD and DD-CKD subjects, it could be beneficial for subjects who participated in previous

vadadustat studies to be considered for this global Phase 3 study, provided the subject meets all eligibility criteria

- To add hospitalization for heart failure (HF) as an adjudicated safety endpoint in addition to MACE and thromboembolic events
- To clarify that the darbepoetin alfa dosing adjustment guidelines is based on the approved local product label for adult patients with CKD not on dialysis
- To allow subjects who transition to hemodialysis or peritoneal dialysis during the study to continue to receive study medication (vadadustat or darbepoetin alfa). This is supported by acceptable safety data from a recently-completed Phase 2 trial of vadadustat in subjects with dialysis-dependent chronic kidney disease (DD-CKD).
- To introduce a binary causality system (ie, "related" or "unrelated") for clinical trial investigators to assign causality of adverse events to study drugs in accordance with recommendations from the Council for International Organizations of Medical Sciences (CIOMS) VI Working Group
- Following discussions with the United States Food and Drug Administration (US FDA), it was requested that the sparse pharmacokinetic (PK) sampling scheme be described and justified. The results of PK simulations indicated that collection of a sample between 0.25 to 1 hour after administration of the first dose along with sparse samples collected during Weeks 4, 12, 28 and 52 will provide additional information to help characterize the population PK and PK/PD relationships
- Adverse event reporting related to critically increased liver function test results were aligned with the US FDA Drug-Induced Liver Injury (DILI) guidelines to provide instructions to study sites regarding reporting for improved consistency and case quality
- To add visit windows to provide flexibility to the subjects and the study sites during scheduling of study visits
- To clarify definitions for renal events to improve understanding and site compliance

Amendment 2-COL ([redacted] Colombia-specific protocol amendment)

Amendment 2-COL was issued based on requests from the Instituto Nacional de Vigilancia de Medicamentos y Alimentos (Invima) during review of the protocol. This amendment is country-specific and will only be issued to investigative sites in Colombia.

Following is a list of the changes in Amendment 2-COL compared with the original protocol:

- All changes to the original protocol that were included in Amendment 1 and Amendment 2 have also been included in Amendment 2-COL.
- The protocol language specifying that site investigators should encourage patients (who wish to discontinue study medication or withdraw from the study) to continue study participation has been removed.
- The protocol language describing procedures to encourage patients to continue study participation has been removed.

Amendment 3-COL (Version 4; [redacted]

Amendment 3 was issued based on a Clinical Expert Advisory Board, and requests from study sites for additional clarification.

The major changes introduced in the amendment are summarized below:

- To update the study design from the current screening period of up to 4 weeks to up to 8 weeks and allow iron, vitamin B12, and folate supplementation as needed during the screening period.
    - Screening period changed from up to 4 weeks to up to 8 weeks
    - One retest will be allowed for each laboratory parameter, within the screening period.
    - Subjects who receive iron replacement may retest screening Hb a minimum of 3 weeks after completion of iron replacement therapy.
- Inclusion Criterion No. 3 adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks.
- To update the following exclusion criterion:
    - Exclusion Criterion No. 3: Adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks.
    - Exclusion Criterion No. 8: To clarify that benign colonic polyps is not a malignancy, therefore removed to correct the error
    - Exclusion Criterion No. 9: Adjusted due to increase of screening period from up to 4 weeks to up to 8 weeks, and to clarify that chronic treatment with anticoagulants for a history of DVT or PE over 12 weeks prior to randomization is not exclusionary.
- The number of total sites has been increased in efforts to increase enrollment.
- Vadadustat dosing and dose adjustment guidelines were updated to clarify that patients receiving 1 tablet of dosing prior to interruption will resume treatment with 1 tablet after interruption.
- Section 4.2 Summary of Clinical Experiences was updated to reflect information from recently completed trials.
- Section 6.4.1 Executive Steering Committee has been added.
- To clarify Darbeopoetin alfa administration and accountability
    - Darbepoetin alfa should be administered per the label.
    - Darbepoetin alfa doses may be self-administered or administered by health care professionals at the clinics, site facility, or at home according to the investigator's determination and local practice.
    - Added additional information on return of darbepoetin for drug accountability and compliance assessment.

- 9.2.2 Laboratory Evaluations was revised to reflect the following:
    - Modification to the frequency of protocol specified Biomarker sample collection
    - Additional exploratory sample collection
- A clarification of the study analysis populations has been provided.

Amendment 4-COL (Version 5; [redacted]

Amendment 4 was issued based on sponsor internal assessment, external input from nephrology experts, and investigative sites.

The major changes introduced in the amendment are summarized below:

- Section 4.2 Summary of Clinical Experiences was updated to reflect information from recently completed trials and for alignment with vadadustat Investigator's Brochure.
- Section 4.3 Secondary Efficacy Endpoints was updated to reflect addition of several key secondary, other secondary efficacy endpoints and Safety Endpoints to align with the Statistical Analysis Plan (SAP)
- Section 7.4.1 Retesting was updated for simplification
- Section 7.5.1 Study Completion was revised to clarify that all enrolled subjects in this study will have the opportunity to complete (at least) the week 36 visit.
- Section 7.5.5 Individual Subject Discontinuation was updated to add Lack of Efficacy as a reason for discontinuation for accurate data capture.
- Section 8.4.4 Dosing and Dose Adjustment Guidelines was revised to guide Investigators to follow printed dose adjustment algorithms in lieu of IWRS-programmed dosing recommendations due to some aspects of IWRS-programmed dosing instructions not operating as planned. Also, updated guidance to Investigators to use clinical judgement and other Hb data to appropriately dose subjects in cases of clinical concern regarding HemoCue value. Another clarification was added that after a subject completes ESA rescue, the Investigator has the option to resume study drug at the same dose as previously used or with one dose higher. Monthly Hb monitoring for dosing oversight in Year 2-4 was also added to this section.
- Section 8.4.6 Iron Supplementation was updated to align with published guidelines to prescribe iron supplementation during the study when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%
- Section 8.4.7.1 ESA Rescue (Optional) was updated to align with published guidelines and to permit Investigator initiation of rescue when medically necessary even if protocol defined criteria are not met.
- Section 8.4.9 Dosing Compliance was updated to specify a range of 80% to 120% which is commonly used in clinical trials with oral products.

- Section 8.5 Prior and Concomitant Therapy was updated to include text clarifying that if the duration of the screening period is less than 30 days, all medications taken within 30 days prior to first dose of study medication will be recorded.
- Section 9.3.6 Year 2- 4 Monthly Hb monitoring was added, with the requirement for monthly monitoring of Hgb drawn as part of local standard of care labs or via an unscheduled visit.
- Section 10.1.1 was updated to add text defining overdose of study drugs.
- Section 10.1.2 Serious Adverse Events was updated to require all new and recurrent malignancies (with a few exceptions) to be reported as a Serious Adverse Events (SAEs) to standardize reporting. If a subject develops basal cell carcinoma of skin, squamous cell carcinoma, or cervical carcinoma in situ during the study, or has worsening of these events from Baseline, the Investigator will determine if the event is reported as an AE or SAE.
- Section 10.5 Special Situations was updated to add text defining overdose of study drugs.
- Section 11.1.1 Sample Size for Primary Efficacy Endpoint was updated to reflect a change in the non-inferiority margin from -0.5 g/dl to -1.0 g/dl
- Section 11.1.2 Sample Size for the Primary Safety Endpoint was updated with enrollment projections as well as median study drug exposure times.
- Section 11.5 Missing Data was updated to align with Statistical Analysis Plan (SAP)
- Section 11.6.3 Subgroups is updated to pre-specify key subgroups for subsequent analysis
- Section 11.7.2 Analysis of Adverse Events was updated and AE summaries will be provided for specific sub groups.

Amendment 5 (Version 6; XX [redacted])

Amendment 5 was issued based on sponsor assessment, external input, regulatory authority engagement and investigative sites feedback.

The major changes introduced in the amendment are summarized below:

- Section 6.1 Study Design was updated with revised subject number
- Section 7.5.1 Study Completion was updated to clarify that all enrolled subjects will be allowed to complete the primary evaluation period (Weeks 24-36) prior to global study completion.
- Section 7.5.2 Subject Completion was updated to clarify procedures at time of global study completion.
- Section 7.5.5 Individual Subject Discontinuation was updated to emphasize the importance of continuing to follow subjects through global study completion.

- Section 7.5.5.1 Temporary Interruption of Study Medication was updated to state that if study medication is temporarily interrupted for more than 60 days, Medical Monitor should be contacted before resuming study medication.
- Section 7.5.5.2 Permanent Discontinuation of Study Medication was updated to have the EOT visit and Follow up visit performed at the time of permanent discontinuation of study medication. Emphasized importance of continuing to follow subjects through global study completion.
- Section 7.5.5.3 Complete Withdrawal from Further Study Visits/Assessments is updated to reflect all options that must be considered by the Investigator before a subject withdraws consent.
- Section 7.5.5.4 Procedures to Support Continued Study Participation is added to include all options available to the Investigator to follow subjects that permanently discontinue study medication.
- Section 7.5.5.5 Procedures to Prevent "Lost to Follow-up" details steps to support sites in efforts to identify subjects lost to follow-up.
- Section 8.4.3 Blinding was updated to reflect information for which the Sponsor and CRO study teams will remain blinded.
- Section 8.4.7 Rescue Therapy was clarified reflect restarting of study medication after ESA Rescue and RBC Transfusion.
- Section 8.5.2 Erythropoiesis-stimulating Agents was updated to provide clarity on study medication dosing following ESA administration.
- Section 8.5.5 Rosuvastatin, Pravastatin, and Other HMG-CoA Reductase Inhibitors (Statins) was added to provide guidance on how to manage concomitant use of statins with vadadustat.
- Section 9.2.1 Clinical Evaluations was updated to include collection of AEs from the time of randomization through global study completion.
- Section 9.3.9 EOT Visit was updated to include detail on managing subjects that permanently stop study medication during the study and managing subjects on study medication at global study completion.
- Section 9.3.12 End of Study Subject Status is added to define the end of study assessments that document subject status at the global study completion or at the time of subject withdrawal or when subject is deemed LTFU or upon death.
- Section 10.1.1 Adverse Events is updated by adding guidance on managing subjects who develop malignancy while on study medication.
- Section 10.1.2 Serious Adverse Events is updated to indicate that Sponsor has defined events that will be classified as serious regardless of their assessment.
- Section 10.3.1 Reporting Period is updated to clarify that the AE reporting period begins at the time of randomization and continues through global study completion.
- Section 11 Data Analysis was updated to reflect how Baseline will be calculated for Hb.
- Section 11.1.1 Sample Size for Primary Efficacy Endpoint was updated to reflect a change in the non-inferiority margin from -1.0 g/dL to -0.75g/dL.
- Section 11.1.2 Sample Size for the Primary Safety Endpoint was modified to include updated definition for primary safety endpoint and how noninferiority is established between treatment groups.

- Section 11.2 Study Analysis Populations is updated with definition of full analysis population.
- Section 11.6.1.1 Primary Analysis of Primary Efficacy Endpoint is updated with use of ANCOVA with multiple imputation, stratified by the randomization strata and using Baseline Hb as the covariate.

Amendment 6-COL (Version 7.0; [redacted]

Amendment 6-COL was issued based on preliminary results of a drug-drug interaction study.

The major changes are summarized below:

- Section 8.1.1 Vadadustat was updated to include reference to the Pharmacy Manual which provides further details on storage and managing temperature excursions.
- Section 8.5.5 HMG-CoA Reductase Inhibitors (Statins) was updated to provide further guidance regarding concomitant use of simvastatin drug interactions with vadadustat.
- Section 8.5.6 Sulfasalazine and Other BCRP Substrates was added to provide guidance regarding concomitant use of BCRP substrates with vadadustat.
- Section 10.5 Special Situations was updated to reflect recent results of investigative toxicology studies.
- Liver function tests were increased in Year 2, 3, and 4 to include Week 64, 88, 116, 140, 168, and 192 for gathering data to better understand the hepatic profile of vadadustat. This change is reflected in Section 9.2.2 Laboratory Evaluations, Section 9.3.7 Year 2 Treatment Period Visits (Weeks 53 through 104), Section 9.3.8 Year 3/4 Treatment Period Visits (Weeks 116 through 208), and Appendix A: Schedule of Activities.

Amendment 7-COL (Version 8.0; [redacted]

Amendment 7-COL was issued based on FDA guidance regarding potential drug-induced liver injury.

- Section 7.5.5 Individual Subject Discontinuation was updated to include a reference to Study Medication Stopping Rules for management of subjects with ALT and AST abnormalities.
- Section 9.4 Study Medication Stopping Rules was added to include a table of liver function test results that would require permanent discontinuation of vadadustat.
- Section 10.1.1 Adverse events was updated to exclude elevations in ALT or AST >3 times ULN with an elevation of total serum bilirubin >2 times ULN from conditions of temporary discontinuation, as this is now a condition for permanent discontinuation.
- Section 10.1.2 Serious adverse events was updated to include information defining designated medical events.

1. IDENTIYFING INFORMATION FOR AMENDMENT

Protocol Title:	Phase 3, Randomized, Open-Label, Active-Controlled Study Evaluating the Efficacy And Safety Of Oral Vadadustat For The Maintenance Treatment Of Anemia In Subjects With Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD) (PRO2TECT – CONVERSION)
Protocol Number:	AKB-6548-CI-0015
Compound:	Vadadustat (AKB-6548)
Status / Date:	Original Protocol; [redacted] Amendment 1; [redacted] Amendment 2; [redacted] Amendment 2-COL; [redacted] (Colombia-specific protocol amendment) Amendment 3-COL; [redacted] (Colombia-specific protocol amendment) Amendment 4-COL; [redacted] (Colombia-specific protocol amendment) Amendment 5-COL; [redacted] (Colombia-specific protocol amendment) Amendment 6-COL; [redacted] (Colombia-specific protocol amendment) Amendment 7-COL; [redacted] (Colombia-specific protocol amendment)

2. PROTOCOL CHANGES DETAILS

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

Protocol Section	Text in Version 7.0 (Amendment 6-COL)	Changes through Version 8.0 (Amendment 7-COL)	Rationale for Change
Section 7.5.5	(Paragraph 3) Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or darbepoetin alfa) permanently discontinued.	(Paragraph 3) Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or darbepoetin alfa) permanently discontinued. See Section 9.4, Study Medication Stopping Rules for additional details on the management of subjects with ALT and AST abnormalities.	To include a reference to Study Medication Stopping Rules for management of subjects with ALT and AST abnormalities.
Section 9.4 (added)		Study Medication Stopping Rules Study medication must be permanently discontinued if a subject meets one of the criteria in Table 2 below **Table 1. Study Medication Stopping Rules** See Section 10.1.1, Adverse Events for reporting requirements related to a subject being permanently discontinued based on meeting the laboratory abnormalities list above in Table 2.	To include a table of liver function test results that would require permanent discontinuation of vadadustat.

<table>
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<tr><td>ALT or AST >3x ULN and total bilirubin >2x ULN</td><td>Permanently Discontinue Treatment</td></tr>
<tr><td>ALT or AST >3x ULN and INR >1.5</td><td>Permanently Discontinue Treatment</td></tr>
<tr><td>ALT or AST >8x ULN</td><td>Permanently Discontinue Treatment</td></tr>
<tr><td>ALT or AST remains >5x ULN over 2 weeks*</td><td>Permanently Discontinue Treatment</td></tr>
<tr><td>ALT or AST >3x ULN with symptoms including e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia</td><td>Permanently Discontinue Treatment</td></tr>
</table>
*Re-challenge generally should be avoided with ALT or AST >5 times ULN unless there are no other good therapeutic options.
ALT: alanine transferase; AST: asparagine transferase; INR: international normalized ratio; ULN: upper limit of normal
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<td>Section 10.1.1</td>
<td>(paragraph 8)

Abnormalities in ALT, AST and Total Bilirubin - Abnormalities in ALT, AST and Total Bilirubin should be reported to the Sponsor’s Medical Monitor or CRO designee within 24 hours of awareness as SAE with “medical significance” criteria selected, if the following conditions are met:

• New elevation in ALT or AST > 3 times ULN, with or without an elevation of total serum bilirubin > 2 times ULN; AND

• No other reason was identified that explains the increased ALT/AST with or without an increased</td>
<td>(paragraph 8)

Abnormalities in ALT, AST and Total Bilirubin - Abnormalities in ALT, AST and Total Bilirubin should be reported to the Sponsor’s Medical Monitor or CRO designee within 24 hours of awareness as SAE with “medical significance” criteria selected, if the following conditions are met:

• New elevation in ALT or AST > 3 times ULN, with or without an elevation of total serum bilirubin > 2 times ULN; AND

• ~~No other reason was identified that explains the increased ALT/AST with or without an increased bilirubin (eg, viral hepatitis, acute liver disease).~~</td>
<td>To include language for elevations in ALT or AST >3 times ULN.</td>
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</table>

	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 Investigational Medicinal Product (IMP); • 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; • IMP should not be resumed until monitoring indicates abnormalities have resolved or have stabilized.	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 Investigational Medicinal Product (IMP); • Repeat testing of ALT, AST, ALP, and total bilirubin, ~~to~~ should be completed within 48 to 72 hours to confirm the abnormalities and to determine trend; • IMP should not be resumed until monitoring indicates abnormalities have resolved or have stabilized. Details on the management of subjects with other ALT and AST abnormalities are further described in Section 9.4, Study Medication Stopping Rules.	
Section 10.1.2	(paragraph 2) In addition to the above criteria for classifying AEs as serious, the following situations will also be classified as serious for purposes of this study: • **Dialysis or Transplantation**- - Events requiring transition to chronic, ongoing dialysis, or requiring an acute transient course of dialysis, or requiring an immediate kidney transplantation (ie, not pre-planned) will be classified as serious. Guidance for the reporting of these events is provided in Section 10.1.1, Adverse Events. • **Malignancies** – Newly diagnosed malignancies or a recurrence of a	(paragraph 2) In addition to the above criteria for classifying AEs as serious, the following situations will also be classified as serious for purposes of this study: • **Dialysis or Transplantation**- - Events requiring transition to chronic, ongoing dialysis, or requiring an acute transient course of dialysis, or requiring an immediate kidney transplantation (ie, not pre-planned) will be classified as serious. Guidance for the reporting of these events is provided in Section 10.1.1, Adverse Events. • **Malignancies** – Newly diagnosed malignancies or a recurrence of a malignancy should be reported as an SAE with the seriousness criterion “medically important” if no other seriousness criteria are met. If a subject develops basal cell carcinoma of skin, squamous cell carcinoma, or cervical carcinoma in situ during the study, or has worsening of these	To define a list of designated medical events that shall always be classified as serious adverse events (SAEs).

	malignancy should be reported as an SAE with the seriousness criterion "medically important" if no other seriousness criteria are met. If a subject develops basal cell carcinoma of skin, squamous cell carcinoma, or cervical carcinoma in situ during the study, or has worsening of these events from Baseline, the Investigator will determine if the event is reported as an AE or SAE.	events from Baseline, the Investigator will determine if the event is reported as an AE or SAE. • **Designated Medical Events** - The sponsor maintains a list of designated medical events (DME) that they will always classify as serious adverse events. If an event on the DME list is reported as an AE additional information on the event (e.g. investigator confirmation of seriousness, causality) will be requested from the Investigator.	