CLINICAL PROTOCOL

PHASE 2, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS STUDY OF ORAL VADADUSTAT FOR THE TREATMENT OF ANEMIA IN HEMODIALYSIS SUBJECTS CONVERTING FROM EPOETIN ALFA

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0025
US IND Number:	102,465
Phase:	Phase 2
Original Protocol:	27 JUNE 2018
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Cambridge, MA 02142 United States of America

NCT Number: NCT03799627

1 SIGNATURE PAGES

1.1 Protocol Approval

[redacted]

Signature Date

[redacted]

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Signature Date

[redacted]

[redacted]

[redacted]

[redacted]

Signature

[redacted]

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Phone Number

Full Address

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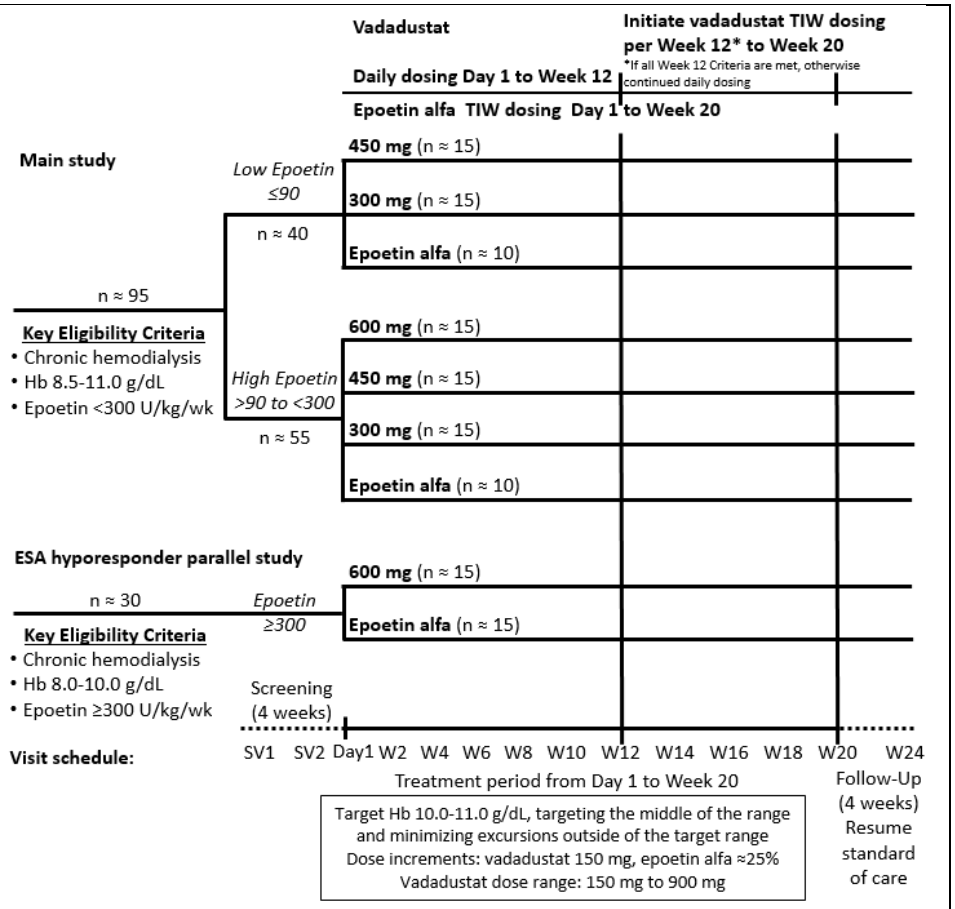
2 PROTOCOL SYNOPSIS

Study Title	Phase 2, Randomized, Open-Label, Active-Controlled, Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics Study of Oral Vadadustat for the Treatment of Anemia in Hemodialysis Subjects Converting from Epoetin Alfa
Protocol Number	AKB-6548-CI-0025
Study Phase	Phase 2
Investigational Product	Vadadustat; 150 mg tablets
Reference Medicinal Product	Epoetin alfa solution for intravenous (IV) injection in multi-dose vials or in single-dose vials
Study Population	The Main study population will consist of adult subjects receiving chronic, outpatient in-center hemodialysis three times weekly (TIW), with 2 screening hemoglobin (Hb) values between 8.5 and 11.0 g/dL (inclusive) and on maintenance treatment with epoetin alfa <300 U/kg/week. The erythropoiesis stimulating agent (ESA) hyporesponder parallel study will consist of adult subjects receiving chronic, outpatient in-center hemodialysis TIW, with 2 screening Hb values between 8.0 and 10.0 g/dL (inclusive) and on maintenance treatment with epoetin alfa ≥300 U/kg/week.
Study Sites	Approximately 40 study sites in the United States
Planned Number of Subjects	Approximately 125 subjects • Main study: ~95 subjects • ESA hyporesponder parallel study: ~30 subjects
Primary Objective	To assess the efficacy and safety of daily dosing of vadadustat compared to epoetin alfa for 12 weeks in hemodialysis subjects
Secondary Objectives	• To assess the efficacy and safety of TIW dosing of vadadustat in selected hemodialysis subjects who have been successfully managed with daily dosing of vadadustat through Week 12 • To evaluate the pharmacokinetics (PK)/pharmacodynamics (PD) of daily and TIW dosing of vadadustat in hemodialysis subjects compared to epoetin alfa • To assess the efficacy and safety of several dosing strategies of vadadustat compared to epoetin alfa during a 20-week Treatment Period in hemodialysis subjects
Overview of Study Design	This is a Phase 2, randomized, open-label study to evaluate vadadustat for the treatment of anemia in hemodialysis subjects converting from epoetin alfa therapy. For all subjects (Main and ESA hyporesponder parallel study), the study will include a Screening Period, a Treatment Period, and a Safety Follow-Up Period as described below. PK and PD sampling will be done throughout the study (see PK and PD Sampling sections for details). The aim is to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Screening Period (up to 28 days; Day -28 to Baseline/Day 1) For all subjects (Main and ESA hyporesponder parallel study) the Screening Period starts at the time the informed consent is signed and will be a maximum of 28 days in duration. Baseline/Day 1 will be performed within 28 days of the start of Screening. Subjects who meet all eligibility criteria will be randomized to a vadadustat treatment arm or an epoetin alfa treatment arm. Subjects will be required to stop epoetin alfa treatment for a minimum duration of 5 days before Baseline/Day 1 in the Main study and for a minimum of 2 days before Baseline/Day 1 in the ESA hyporesponder parallel

	study. In the Main study, randomization will be stratified by the mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to Screening Visit 2 (SV2). • Low epoetin alfa dose group (≤90 units [U]/kg/week) or • High epoetin alfa dose group (>90 to <300 U/kg/week) **Study Treatment Period (Baseline/Day 1 to Week 20)** For all subjects (Main and ESA hyporesponder parallel study), the Treatment Period will run from Baseline/Day 1 to Week 20. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/L, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range. Subjects in the Main study randomized to vadadustat: • Subjects in the low epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300 mg or 450 mg daily. • Subjects in the high epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300 mg, 450 mg, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat: • Subjects will receive a starting dose of vadadustat 600 mg daily. Transition to TIW for all subjects randomized to vadadustat: All subjects randomized to vadadustat (Main and ESA hyporesponder parallel study) who complete the 12-week once daily dosing regimen and who meet all the Week 12 transition criteria for switching from daily to TIW dosing, will initiate TIW dosing at a starting dose one tablet greater (+150 mg) than the final dose in the daily dosing period. Subjects who do not meet criteria for switching from daily to TIW dosing will remain on daily dosing. Subjects in both the Main and ESA hyporesponder parallel study randomized to epoetin alfa: All subjects randomized to epoetin alfa will receive TIW dosing for the entire Treatment Period based on the subject's central laboratory Hb value and the approved epoetin alfa United States (US) Package Insert (PI) for adult patients with chronic kidney disease (CKD) on dialysis. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range. **Safety Follow-Up Period (Weeks 20 to 24)** For all subjects (Main and ESA hyporesponder parallel study), the 4-week Safety Follow-Up Period starting at Week 20 will be followed by a post-treatment safety assessment conducted at the beginning of Week 24.

Study Schematic	
Study Duration	Individual subjects will participate in the study for up to 28 weeks, including a Screening Period of up to 4 weeks, a 20-week Treatment Period and a 4-week Safety Follow-Up Period.
Inclusion Criteria	Subjects must meet the following inclusion criteria: 1. ≥18 years of age 2. Receiving chronic, outpatient in-center hemodialysis (TIW) for end-stage renal disease for at least 12 weeks prior to Screening 3. Maintained on IV epoetin alfa therapy for 8 weeks prior to and including Screening through SV2 4. Eligibility in the Main study and ESA hyporesponder parallel study is based on the following mean weekly epoetin alfa doses: • Main study: Mean weekly epoetin alfa dose <300 U/kg/week for 8 weeks prior to SV2 • ESA hyporesponder parallel study: Mean weekly epoetin alfa dose ≥300 U/kg/week for 8 weeks prior to SV2 5. Two Hb values measured at least 4 days apart by the central laboratory during Screening as indicated below • Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive • ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive 6. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening

	7. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening 8. Hemodialysis adequacy as indicated by single-pool Kt/V_{urea} ≥1.2 using the most recent historical measurement within 8 weeks prior to or during Screening 9. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.
Exclusion Criteria	Subjects must not meet any of the following exclusion criteria: 1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia) 2. Active bleeding or recent blood loss within 8 weeks prior to randomization 3. Red blood cell (RBC) transfusion within 8 weeks prior to randomization 4. Anticipated to discontinue hemodialysis during the study 5. Judged by the Investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study 6. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver) 7. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >1.5 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded. 8. Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of epoetin alfa 9. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening 10. History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Subjects with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded. 11. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening 12. History of hemosiderosis or hemochromatosis 13. History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded) 14. Scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months 15. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded) 16. Known hypersensitivity to vadadustat, epoetin alfa, or any of their excipients 17. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to Screening (subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation) 18. Previous participation in this study, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor other than vadadustat

	19. For female subjects: a. Of non-childbearing potential i. Inability to confirm surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or ii. Not considered post-menopausal (no menses for >1 year with follicle stimulating hormone >40 U/L at Screening) b. Or, if of childbearing potential i. Lack of confirmation of the use of acceptable forms of contraception* for a minimum of one complete menstrual cycle prior to Screening ii. Positive serum pregnancy test at SV2 iii. Unwilling to use two acceptable forms of contraception* (at least one of which must be a barrier method) starting Baseline/Day 1, throughout the Treatment Period and for 30 days after the final study drug administration 20. Breastfeeding during Screening or throughout the Treatment Period and for 30 days after the final study drug administration. 21. Donation of ova starting at Screening, throughout the Treatment Period, and for 30 days after the final study drug administration. 22. Male subjects who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception* during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat. 23. Any other reason, which in the opinion of the Investigator, would make the subject not suitable for participation in the study. * *Acceptable forms of contraception include:* • *Established use of oral, injected or implanted hormonal methods of contraception.* • *Placement of an intrauterine device or intrauterine system.* • *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.*
Retesting/Rescreening	**Retesting** Retesting is defined as repeating laboratory tests within the same Screening Period. Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 4-week Screening Period, per Investigator discretion. **Rescreening** Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the Investigator if it is considered that the subject status has changed, and the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on inclusion criteria values for 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). A new informed consent is required to be signed prior to every rescreening.

Efficacy Endpoints	**Primary Endpoint** Mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 10 to 12) **Key Secondary Endpoints** • Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) • For subjects who transitioned to TIW vadadustat dosing, mean change in Hb from primary evaluation period (average Hb from Weeks 10 to 12) to the secondary evaluation period (average Hb from Weeks 18 to 20) **Other Secondary Endpoints** • Mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 18 to 20) • Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • For subjects who transitioned to TIW vadadustat dosing, proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • Proportion of subjects with a mean increase in Hb from Baseline to the primary evaluation period ≥0.5 g/dL (average Hb from Weeks 10 to 12) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) • Proportion of subjects with a mean increase in Hb from Baseline to the secondary evaluation period ≥0.5 g/dL (average Hb from Weeks 18 to 20) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • IV iron supplementation • ESA rescue • RBC transfusion **Exploratory Endpoints** [redacted]
PK/PD Endpoints	An exposure-response analysis of vadadustat and PD measures will be conducted as deemed appropriate. The PK parameters will include (but are not limited to) the following: • AUC_{last} • AUC_{inf} • Time to reach C_{max} (T_{max}) • Apparent total body clearance (CL/F) • Apparent volume of distribution (V_d/F) • Terminal half-life ($t_{1/2}$)

	The PD parameters will include (but are not limited to) the following: • Erythropoietin (EPO) • Reticulocytes • Iron • Ferritin • Total iron binding capacity (TIBC) • Hepcidin
Safety Endpoints	• Adverse events (AEs) • Vital sign measurements and clinical laboratory values • Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL • Hb <8.0 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (Main Study); Hb <7.5 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (ESA hyporesponder parallel study) • Hb increase >1.0 g/dL within any 2-week interval
Dosage and Regimens	The aim is to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Dosing will be initiated at Baseline/Day 1 and the first dose of vadadustat will be administered at the study site after other Baseline/Day 1 procedures have been completed. Thereafter, vadadustat will be taken once daily on an outpatient basis. Subjects may take vadadustat with or without food and will be instructed to swallow the tablet(s) whole. Subjects will be instructed to take vadadustat at roughly the same time each day. Epoetin alfa dose will be administered intravenously at the hemodialysis clinic, based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis. **Note:** For all subjects, no epoetin alfa will be administered after SV2 after the subject has met all eligibility criteria and before Baseline/Day 1, for a minimum duration of 5 days in the Main study and 2 days in the ESA hyporesponder parallel study. <u>Main Study:</u> Subjects will be randomized to either a vadadustat treatment arm or epoetin alfa treatment arm. Randomization will be stratified by mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to SV2: • Low epoetin alfa dose group (≤90 U/kg/week) or • High epoetin alfa dose group (>90 to <300 U/kg/week) In the low epoetin alfa dose group, subjects will be randomized in a 3:3:2 ratio to receive either an initial vadadustat daily dose of 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa. In the high epoetin alfa dose group, subjects will be randomized in a 3:3:3:2 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets), 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa. <u>ESA Hyporesponder Parallel Study</u> Subjects will be randomized in a 1:1 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets) or epoetin alfa.

Epoetin alfa arm in both the Main study and ESA hyporesponder parallel study:

For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.

Study Drug Guidelines for Dose Adjustment

Dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment (see below). Hb will be monitored via central laboratory throughout the study to determine if the dose of study drug (vadadustat or epoetin alfa) will be adjusted, interrupted, or maintained as follows:

- Dose adjustments are based on the Investigator's clinical discretion, incorporating the protocol guidance below as well as the subject's current Hb level, trajectory, and variability; symptoms; cardiovascular risk; and other features of his/her clinical condition(s).
- If a dose increase or decrease is required to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for epoetin alfa approximately 25%).
- In general, do not increase the dose more frequently than once every 4 weeks. A one-time dose increase after 2 weeks is allowed on only two occasions.
    - A subject's dose may be increased by 1 dose level if the subject has a decline in Hb ≥0.5 g/dL from Baseline/Day 1 in the first 2-week period (the initial period from Baseline/Day 1 to Week 2 following conversion from prior epoetin alfa therapy).
    - A subject's dose may also be increased by 1 dose level in the first 2-week period after initiation of TIW dosing (from Week 12 to Week 14) for subjects that meet criteria for transitioning from daily to TIW dosing.
- Reduce or interrupt the dose in the setting of a rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Reduce or interrupt the dose in the setting of Hb >11.0 g/dL
- Interrupt the dose in the setting of a Hb >12.0 g/dL until Hb value falls below 11.0 g/dL. After Hb falls below 11.0 g/dL, restart study drug and consider restarting at a lower dose.

The minimum dose of vadadustat will be 150 mg daily or TIW (1 tablet daily/TIW) and the maximum dose will be 900 mg daily or TIW (6 tablets daily/TIW).

Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen

All subjects randomized to vadadustat who complete 12 weeks of once daily dosing regimen **and** who meet all the Week 12 criteria below will be transitioned to a TIW vadadustat dosing regimen. Subjects who meet all of the Week 12 criteria will transition to TIW dosing.

Week 12 Transition criteria:

- Vadadustat daily dose of 600 mg or lower at Week 12
- Hb within target range of 10.0 to 11.0 g/dL, inclusive, at Week 12 confirmed by central laboratory Hb value from Week 11 (11 weeks of treatment completed)
- No receipt of rescue therapy (ESA or RBC transfusion) for worsening of anemia due to CKD from Baseline to Week 12.
    - ESA or RBC transfusion prior to Week 12 for reasons unrelated to worsening of anemia due to CKD (e.g., surgery, gastrointestinal bleed, or inadvertent administration) is not considered rescue therapy

	• No other reason, based on the Investigator's clinical discretion, that would make the subject not suitable for TIW dosing. Selected subjects who meet Week 12 transition criteria will transition to the TIW vadadustat dosing regimen at the Week 12 visit. Subjects on 150 mg, 300 mg, 450 mg, or 600 mg of vadadustat daily at the Week 12 visit will transition to an initial vadadustat TIW dose one tablet greater (+150 mg), i.e., 300 mg, 450 mg, 600 mg, or 750 mg vadadustat TIW, respectively. Subjects will be instructed to take vadadustat on dialysis days. After 2 weeks of treatment in the TIW vadadustat dosing regimen (at Week 14), subjects in any vadadustat TIW dosing arms who have a decline in Hb ≥0.5 g/dL will be eligible for a dose increase by 1 tablet, based on the Investigator's clinical discretion. Subjects who are not eligible to switch from daily vadadustat to TIW dosing at Week 12 will remain on daily dosing for the remainder of the study. Subjects on TIW dosing may be converted back to vadadustat once daily dosing at the discretion of the Investigator in the setting of inadequate Hb response. The starting daily dose after the switch from TIW to daily dosing will be based on the Investigator's discretion after review of the subject's clinical status and dosing history, in particular, the daily dose previously administered to the subject prior to the transition to TIW dosing (Week 12). Subjects who switch from vadadustat TIW to daily dosing will continue once daily vadadustat until the end of the Treatment Period. Subjects in the vadadustat arm will be guided for dosing compliance using an electronic diary (eDiary).
PK/PD Sampling - vadadustat arm	Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below (see Appendix B). Preferably, PK/PD samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week). At Baseline/Day 1, PK/PD samples will be collected prior to dialysis and administration of vadadustat. At Week 1 (after at least a full week of vadadustat treatment), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose On the following non-dialysis day, blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes post-dose At Week 11, vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

<table>
<tr><td></td><td>At Week 13 (after at least one week on TIW vadadustat dosing regimen), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:
15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes hours post-dose
From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose
Note: Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Week 13 PK/PD sampling.</td></tr>
<tr><td>PK Sampling - epoetin alfa arm</td><td>Blood for measurement of EPO level in the epoetin alfa arm in both the Main study and ESA hyporesponder parallel study will be collected as outlined below (see Appendix B). Preferably, PK samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).
At Baseline/Day 1, a sample will be collected prior to dialysis and administration of epoetin alfa.
At Week 1 (after at least a full week of study epoetin alfa treatment), epoetin alfa will be administered within 1 hour after start of dialysis. Blood samples will be collected as follows:
15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose
On the following dialysis day, one blood sample will be collected 15 minutes prior to administration of epoetin alfa.</td></tr>
<tr><td>Iron Supplementation</td><td>IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol below:
<table>
<tr><th></th><th>Ferritin
<200 ng/mL</th><th>Ferritin
200-500 ng/mL</th><th>Ferritin
>500 ng/mL</th></tr>
<tr><td>TSAT
<20%</td><td>IV Iron 100 mg every treatment (max 400 mg/month)</td><td>IV Iron 50 mg weekly</td><td>Hold</td></tr>
<tr><td>TSAT
20-50%</td><td>IV Iron 100 mg every week</td><td>IV Iron 50 mg weekly</td><td>Hold</td></tr>
<tr><td>TSAT
>50%</td><td>Hold</td><td>Hold</td><td>Hold</td></tr>
</table>
Intra-dialytic iron preparations (e.g., Triferic) and oral iron supplementation including iron-containing phosphate binders are prohibited during the study.
Important: As the study will be assessing PK/PD parameters, and as there are no empirical data on concurrent administration of vadadustat and phosphate binders, vadadustat will not be administered concurrently with a phosphate binder. Subjects will be instructed to take phosphate binders at least 3 hours before or at least 2 hours after the dose of vadadustat based on the guidance in the phosphate binder package inserts.</td></tr>
</table>

Rescue Therapy Guidelines	To ensure the safety of subjects and to standardize the use of rescue in the study, rescue therapy guidelines are provided. 1. 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 will 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 medical necessity. Study drug (vadadustat or epoetin alfa) may be continued during the transfusion period. Reasons for RBC transfusion will be captured in the appropriate CRF. 2. ESA Use: ESA administration will be allowed when medically necessary at the discretion of the Investigator. In general, ESA will not be administered in subjects with Hb ≥8.5 g/dL, and ESA rescue will be stopped when Hb ≥9.0 g/dL. ESA therapy will be administered using an approved ESA and dosing as per the local institution's guidelines and per the approved product label. While receiving ESA therapy, subjects randomized to vadadustat must temporarily interrupt vadadustat. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA, and treatment will be resumed after the following intervals: • 2 days after last dose of epoetin alfa • 7 days after last dose of darbepoetin alfa • 14 days after last dose of methoxy polyethylene glycol-epoetin beta Following ESA administration, vadadustat will be resumed at the same dose as previously used or with one additional tablet (+150 mg) at the discretion of the Investigator. Reasons for ESA use will be captured in the appropriate CRF.
Phlebotomy	If a subject's Hb exceeds 14.0 g/dL or the rate of rise of Hb raises concern to the Investigator, the subject may be phlebotomized based on the Investigator's clinical judgment. The method of phlebotomy will be in accordance with the study site's standard clinical practice.
Concomitant Medications	1. ESA Co-administration of any ESA with vadadustat is 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 ESA Rescue) if deemed medically necessary at the discretion of the Investigator. Guidelines for ESA administration as rescue therapy are provided above. All efforts will be made to avoid inadvertent administration of ESAs resulting from adherence to ESA hemodialysis center protocols (e.g., DaVita ESA protocols for patients 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. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA. Vadadustat treatment may be resumed after the following intervals: • 2 days after last dose of epoetin alfa • 7 days after last dose of darbepoetin alfa • 14 days after last dose of methoxy polyethylene glycol-epoetin beta 2. Iron See guidance above (Iron Supplementation).

Study Completion, Subject Completion, Temporary Interruption of Study Drug, Early Discontinuation from Study (Early Termination)	**Study Completion** The study will be considered completed after all randomized subjects have completed their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination). **Subject Completion** A subject will be considered as having completed the study after completion of their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination). **Temporary Interruption of Study Drug** During the study, a subject may interrupt study drug (vadadustat or epoetin alfa) for any of the following reasons: • AE • Missed dialysis visit (epoetin alfa arm) • Investigator's discretion • Rapid rise in Hb (defined as >1.0 g/dL in any 2-week period) • Hb above 11.0 g/dL • ESA use (vadadustat arm) Unless contraindicated, treatment will be resumed whenever possible and assessed at every visit following study drug interruption. **Early Discontinuation from Study (Early Termination)** Subjects who discontinue prematurely from the study will complete the End-of-Treatment visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14. Subjects may discontinue for any of the following reasons: • AE • Investigator's discretion • Subject withdrawal of consent • Lack of efficacy • Lost to follow up despite reasonable efforts by the Investigator to locate the subject • Death • Other reasons (pregnancy, kidney transplantation, specific reasons to be documented by the Investigator)
Study Termination/ Individual Study Site Termination	The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advanced notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator and subsequently provide written instructions for study termination. If the study has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.
Statistical Considerations	Efficacy and safety endpoint analysis will be descriptive in nature. Continuous variables will be summarized using number of subjects with mean, standard deviation (SD), median, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated. PK and PD parameters will be summarized using descriptive statistics: number of subjects, mean, median, SD, minimum, maximum, and coefficient of variation,

	geometric mean and geometric mean SD. Mean and individual plasma concentration-time profiles will be presented graphically in both linear scale and log-linear scale. The ESA hyporesponder parallel study will be analyzed separately from the main study.
PK Analysis	A population PK analysis will be conducted to describe vadadustat PK and determine the covariates that impact the PK profile (i.e., demographics, laboratory values, concomitant iron, dosing relative to dialysis, etc). PK analysis will be reported separately.
PD Analysis	An exposure-response analysis of vadadustat, EPO and other PD measures will be conducted as deemed appropriate. PD analysis will be reported separately.
Sample Size Estimation	Approximately 95 subjects are planned for enrollment in the Main study with 40 and 55 subjects randomized to the low epoetin alfa dose group and the high epoetin alfa dose group respectively. Approximately 30 subjects are planned for enrollment in the ESA hyporesponder parallel study. Sample size reflects the exploratory nature of this study. Enrollment may be increased by up to 20 additional subjects in the Main study, and by up to 30 additional subjects in the ESA hyporesponder parallel study to ensure adequate data is captured for the primary, PK/PD, and safety endpoints.
Safety Monitoring	This is an open label study allowing the study team full access to safety data which will be reviewed on a regular basis, throughout the course of the study. Safety monitoring will be performed as described in the Medical Monitor Plan.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC_{inf}	area under concentration-time curve from dosing to infinity
AUC_{last}	area under concentration-time curve from dosing to last measurable concentration
BP	blood pressure
CBC	complete blood count
CKD	chronic kidney disease
CL/F	apparent total body clearance
C_{max}	maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
DD-CKD	dialysis dependent chronic kidney disease
ECG	electrocardiogram
EDC	electronic data capture
eDiary	electronic diary
EOT	end-of-treatment
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FAS	Full Analysis Population
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Hb	hemoglobin
HF	heart failure
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl-hydroxylase
HIF-PHI	hypoxia-inducible factor prolyl-hydroxylase inhibitor
HR	heart rate
HRQOL	health-related quality of life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web Response System
LFT	liver function test
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid

NDD-CKD	non-dialysis dependent chronic kidney disease
PGI-C	patient global impression of change
PGI-S	patient global impression of severity
PHD	prolyl 4-hydroxylase domains
PI	Package Insert
PK	pharmacokinetic(s)
PD	pharmacodynamics(s)
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SF-36	36-Item Short-Form General Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SO_2	oxygen saturation
TIW	three times a week
T_{max}	time to reach C_{max}
TSAT	transferrin saturation
U	unit
ULN	upper limit of normal
US	United States
V_d/F	apparent volume of distribution
VEGF	vascular endothelial growth factor

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% to 16% of the population (Jha 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, infection, cancer, and mortality (Iseki 2007).

The prevalence and severity of renal anemia in CKD increases as renal function deteriorates (Di Iorio 2007; Stauffer 2014). As CKD progresses, the combined effect of decreased red blood cell (RBC) production from lower erythropoietin (EPO) signaling, increased rate of RBC destruction, and reduced iron availability to the bone marrow results in the increased prevalence and severity of anemia (Pergola 2016). Anemia generally exists when hemoglobin (Hb) is less than 13.0 g/dL in men or less than 12.0 g/dL in women (KDIGO 2012). Three principal factors contribute to the development of anemia as CKD progresses:

- Peritubular fibroblasts, a type of cell in the kidney, are designed to sense the amount of oxygen carried by the blood. These cells secrete EPO to adjust the production of RBCs by the bone marrow and maintain circulating oxygen levels at normal physiologic levels. As kidney disease progresses, the number of peritubular fibroblasts is reduced and EPO secretion is significantly decreased, leading to a reduction in RBC production (Iseki 2007; Nurko 2006).
- On average, the RBCs in CKD patients have a shorter lifespan (approximate lifespan of 70 days) compared with the RBCs in healthy people (approximate lifespan of 90 to 120 days) (Ly 2004; Nurko 2006). Such a condition leads to increased RBC production in CKD patients to maintain normal physiologic levels.
- The availability of iron to the bone marrow is impaired. Iron is a required component in the formation of Hb, and is essential for the transport of oxygen to the tissues of the body.

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

The risks associated with erythropoiesis-stimulating agents (ESAs), including an increased risk of death and cardiovascular events (Besarab 1998; Drueke 2006; Pfeffer 2009a; Pfeffer 2009b; Singh 2006), 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 dialysis dependent CKD (DD-CKD) patients remains high. To fulfill this unmet need, the vadadustat clinical program is focused on developing an orally active therapeutic agent 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 (HIF-PHs) for the treatment of anemia associated with CKD. HIF-PH enzymes are also referred to as prolyl 4-hydroxylase domains (PHDs), of which the 2 most commonly expressed isoforms 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.

The efficacy, safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of vadadustat have been characterized in 10 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 non-dialysis dependent CKD (NDD-CKD) subjects, 1 completed Phase 2b study in NDD-CKD subjects, and 1 completed Phase 2 study in DD-CKD subjects. The United States (US) 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, double-blind, placebo-controlled study with 5 different dose groups dosed for 42 days. The US Phase 2b, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 20 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 16 weeks. The US Phase 2 open-label study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. In the studies completed to date, a total of 630 subjects have received vadadustat, including 200 healthy volunteers and 430 subjects with CKD.

Vadadustat has shown 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 and Hb 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 consistent bioavailability with area under concentration-time curve (AUC) and C_{max} 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 for 10 days. The plasma half-life of vadadustat was about 4 to 6 hours, 7 to 8 hours, and 9 to 10 hours in healthy subjects, NDD-CKD patients, and DD-CKD patients, respectively.

Vadadustat is extensively metabolized and its metabolites are eliminated from the body by dual routes of excretion (both 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.

Multiple doses of 700 mg and 900 mg daily for up to 10 days (Study AKB-6548-CI-0002 [CI-0002]) and single doses of 1200 mg (Study AKB-6548-CI-0001 [CI-0001], Study AKB-6548-CI-0010 [CI-0010]) have been examined in healthy volunteers. Vadadustat demonstrated dose-proportional PK and achieved serum EPO concentrations up to 34.4 mIU/mL, levels considered physiologic and below exposures achieved with injectable ESAs (Besarb 1992). A higher incidence of adverse events (AEs) in the gastrointestinal System Organ Class (SOC) – nausea, diarrhea, abdominal pain, dyspepsia – was observed in groups treated with 700 mg, 900 mg, or 1200 mg compared with lower vadadustat doses or placebo. Most AEs were mild to moderate, short-lived (1 or 2 days), and assessed as unrelated by investigators. No AEs led to study withdrawal, and no serious adverse events (SAEs) were reported. No clinically meaningful changes or abnormalities in vital signs, safety laboratory studies, or ECG parameters were reported.

A 16-week, open-label, multicenter, Phase 2 trial evaluated vadadustat in 94 subjects receiving chronic hemodialysis previously maintained on epoetin alfa and IV iron form the 3 months prior to Screening (Study AKB-6548-CI-0011 [CI-0011]). Subjects were assigned to one of three vadadustat dose cohorts: 300 mg daily, 450 mg daily, or 450 mg three times a week (TIW). Dosing was fixed for the first 8 weeks; for the subsequent 8 weeks dose was adjusted according to Hb response based upon a dose adjustment algorithm. Sixty-nine of the 94 subjects completed the study. The primary endpoint was the mean Hb concentration change from pre-treatment average (Screening Visit 1, Screening Visit 2, and Baseline Visit) to mid-study (Weeks 7 to 8) and end-of-study (Weeks 15 to 16) and was analyzed using observed Hb values (no imputation for missing data). No statistically significant mean change in Hb from pre-treatment average was observed for either of the two time points for any of the three treatment groups.

Among subjects randomized to an initial dose of 300 mg daily, 450 mg daily, or 450 mg TIW, 0% (0 of 30), 3% (1 of 33), and 19% (6 of 31) of subjects withdrew from the study due to worsening anemia, respectively. In a sensitivity analysis using last observation carried forward (LOCF) for the primary efficacy endpoint, no significant mean change in Hb from pre-treatment levels was observed in the 300 mg daily dosing group. At Weeks 15 to 16, modest, statistically significant mean decreases were observed in the 450 mg daily and 450 mg TIW dosing groups.

In a post-hoc univariate analysis of baseline characteristics, higher pre-baseline epoetin alfa dose was associated with a decrease in mean Hb at Weeks 7 to 8 and Weeks 15 to 16 in the dosing cohorts. Subjects who discontinued the study due to worsening anemia had a higher mean pre-baseline epoetin alfa dose compared with subjects who discontinued due to other reasons or subjects who completed the study.

Based on 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.

In the ongoing global Phase 3 and Japanese Phase 3 clinical studies, over 7000 subjects are planned to be treated with vadadustat or comparator.

This study will evaluate efficacy, safety and PK/PD with different vadadustat dosing strategies in hemodialysis subjects converting from epoetin alfa to further characterize the optimal vadadustat regimen.

4.3 Potential Benefits and Risks

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

Trials of injectable 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 2009a). Post-hoc analyses performed by the Food and Drug Administration (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 2007). Potential clinical benefits include enhanced erythropoiesis and decreased exogenous iron requirements.

In nonclinical safety studies, the main findings originated from an exaggerated pharmacological response that results in increased erythropoiesis, polycythemia, blood hyperviscosity, and the formation of fibrin thrombi in multiple organs. Early mortality noted in the mouse and rat and moribundity in the dog were due to the sequelae associated with polycythemia. These findings were reproducible across species and studies, dose-dependent and showed reversibility. Dose-limiting toxicity in the exploratory toxicology studies was due to hemoglobinuric nephropathy (rat) and emesis associated with body weight loss (dog).

In completed Phase 1 clinical studies of vadadustat in healthy volunteers, there were low numbers of treatment-emergent AEs. The most frequently reported AEs were in the gastrointestinal disorders (i.e., nausea, diarrhea, abdominal pain, flatulence, dyspepsia) and nervous system disorders (i.e., headache, dizziness) SOC. The majority of AEs were mild to moderate in severity.

The most frequently reported AEs in completed Phase 2 studies of NDD- and DD-CKD subjects were in the following SOCs: gastrointestinal disorders (nausea, diarrhea, vomiting), cardiovascular disorders (hypertension, hypotension, coronary artery disease), renal (renal failure chronic, renal failure acute), infections and infestations (gastroenteritis, urinary tract infection,

pneumonia), and metabolism and nutrition disorders (hyperkalemia, fluid overload). Four deaths occurred in the completed Phase 2 clinical studies.

Identified risks include nausea, diarrhea, vomiting, headache, abdominal pain, and uric acid elevations. Hypersensitivity, hyperkalemia and hypertension have been identified as potential risks associated with vadadustat therapy.

Review of safety data from completed Phase 1 and 2 clinical studies, as well as review of accumulating data from ongoing studies, continue to support further development of the vadadustat program.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

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

5.2 Secondary Objectives

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

5.3 Efficacy Endpoints

5.3.1 Primary Endpoints

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

5.3.2 Key Secondary Endpoints

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

5.3.2.1 Other Secondary Endpoints

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

- Intravenous (IV) iron supplementation
- ESA rescue
- RBC transfusion

5.3.2.2 Exploratory Endpoints

[redacted]

5.4 PK/PD Endpoints

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

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

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

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

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

5.5 Safety Endpoints

Safety endpoints in this study include the following:

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

6 STUDY DESIGN

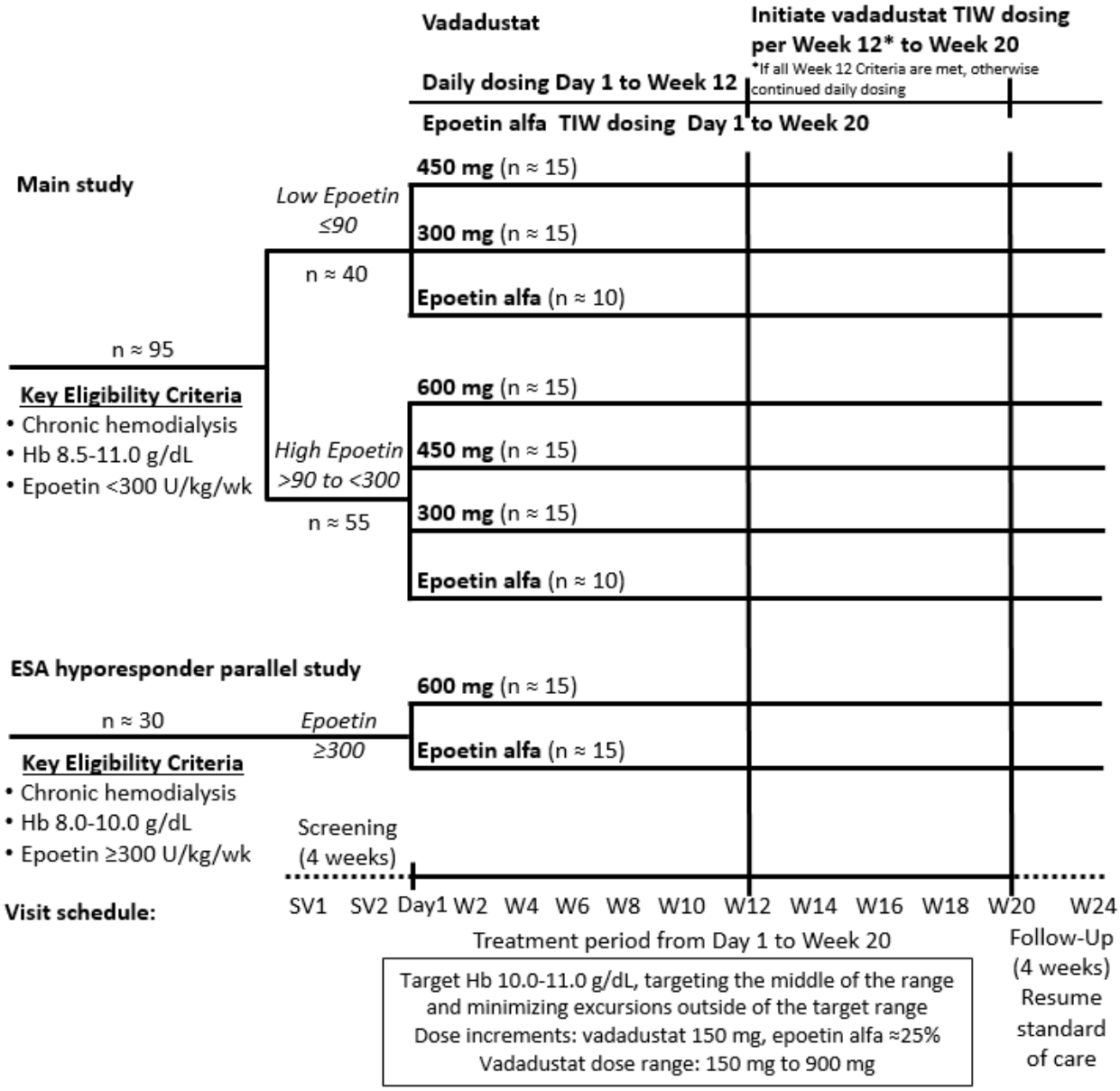
6.1 Study Design

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

For all subjects (Main and ESA hyporesponder parallel study), the study (as shown in Figure 1) will include a Screening Period, a study Treatment Period, and a Safety Follow-Up Period as described below. PK and PD sampling will be done throughout the study (see PK and PD Sampling Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa, respectively, for details).

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

Figure 1: Overview of Study Design



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

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

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

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

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

6.1.2.1 Vadadustat Treatment

Subjects in the Main study randomized to vadadustat:

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

Subjects in the ESA hyporesponder parallel study randomized to vadadustat:

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

Transition to TIW for all subjects randomized to vadadustat:

All subjects randomized to vadadustat (Main and ESA hyporesponder parallel study), who complete the 12-week once daily dosing regimen and who meet all the Week 12 transition criteria for switching from daily to TIW dosing, will initiate TIW dosing at a starting dose one tablet greater (+150 mg) than the final dose in the daily dosing period (see Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen).

Note: Subjects who are not eligible to switch from daily vadadustat to TIW dosing at Week 12 will remain on daily dosing from the remainder of the study (see Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment).

6.1.2.2 Epoetin Alfa Treatment

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

All subjects randomized to epoetin alfa will receive TIW dosing for the entire Treatment Period based on the subject's central laboratory Hb value and the approved epoetin alfa United States (US) Package Insert (PI) for adult patients with CKD on dialysis. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range (see Section 8.4.4, Epoetin Alfa Dosing Regimen).

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

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

6.2 Rationale for Study Design

The Main Study and the ESA hyporesponder parallel study will evaluate different starting doses of vadadustat based on pre-baseline ESA doses. Numerous studies have demonstrated that hemodialysis patients requiring higher ESA doses to treat their anemia have a higher burden of comorbidities, a more inflammatory state, and a greater risk of adverse outcomes (Besarb 1998; Parfrey 2005; Unger 2010). As described above (Section 4.2, Summary of Clinical Experience) in a Phase 2 hemodialysis study (CI-0011), a post-hoc analysis suggested higher pre-baseline ESA doses were associated with lower observed mean Hb levels. Subjects on higher pre-baseline ESA doses may benefit from a higher starting dose of vadadustat after initial conversion from ESAs.

Three levels of pre-baseline ESA dose will be evaluated. In the Main Study subjects will be randomized to one of two cohorts based on pre-baseline ESA dose (≤90 U/kg/week and >90 to <300 U/kg/week). The ESA threshold of 90 U/kg/week was based on the median ESA doses reported in the US Renal Data System and US Dialysis Outcomes and Practice Patterns Study, which ranged from approximately 90 to 110 U/kg/week.

The ESA hyporesponder parallel study will evaluate subjects with Hb levels below the target range despite receiving ≥300 U/kg/week of epoetin alfa. This ESA threshold was based on the definition of resistance to ESAs proposed in the ERA-EDTA 2004 guidelines (Locatelli 2004).

The Main study and the ESA hyporesponder parallel study incorporate an approach to vadadustat dose adjustment designed to maximize the probability that Hb can be maintained within the target range of 10.0 to 11.0 g/dL, inclusive (see Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment). The approach to vadadustat dose adjustment in this Phase 2 study includes several modifications as compared to the vadadustat dosing algorithms used in previously completed Phase 2 studies and the dosing algorithm used in the ongoing Phase 3 studies.

During this study, dose increases for vadadustat will be allowed at 4-week intervals, with the exception of the initial 2 weeks of treatment, in the daily and TIW dosing periods of the study. Dose increases will be permitted in the initial 2 weeks of treatment, in the daily and TIW dosing periods, in subjects with a Hb decline ≥0.5 g/dL from baseline and Week 12, respectively. This approach is commonly used in clinical practice to treat patients with declining or low Hb values (Pfeffer 2009a; Singh 2006). Risk of abrupt or excessive increases in Hb is minimized due to the underlying Hb trajectory and is further mitigated by close Hb monitoring.

In the present study, the safety and efficacy of a vadadustat TIW dosing regimen is being evaluated as a potential alternative treatment regimen to a once daily dosing regimen in hemodialysis subjects. Specifically, this study will evaluate conversion from once daily dosing to TIW dosing. As described above (Section 4.2, Summary of Clinical Experience), the 16-week Phase 2 hemodialysis study evaluated hemodialysis subjects switching from ESA to vadadustat 450 mg TIW for an 8-week fixed-dose period followed by 8 weeks of dose adjustment according to Hb response. The primary efficacy analysis in CI-0011 using observed data showed stable mean Hb levels in this group. Six of 31 (19%) subjects withdrew due to worsening anemia, and a sensitivity analysis imputing missing Hb values using LOCF demonstrated a decline in mean Hb levels. To maximize the probability that subjects treated with vadadustat TIW will maintain Hb levels within the target range, this study will: examine subjects successfully treated with

daily dosing converting to TIW dosing; allow for earlier dose increase after 2 weeks of initial treatment; and permit dose increases up to 900 mg TIW.

6.3 Dose Justification

In this study, vadadustat starting daily doses will be determined by pre-baseline ESA dose (Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment). In the Main study starting doses of vadadustat will be 300 mg and 450 mg daily in subjects converting from epoetin alfa doses ≤90 U/kg/week and 300 mg, 450 mg, and 600 mg daily in subjects converting from epoetin alfa doses >90 to <300 U/kg/week. For the ESA hyporesponder parallel study, the starting doses will be 600 mg daily. As described above (Section 4.2, Summary of Clinical Experience), the maximum vadadustat starting dose evaluated in completed Phase 2 NDD-CKD studies was 630 mg or 600 mg daily, in Study AKB-6548-CI-0005 (CI-0005) and Study AKB-6548-CI-0021 (CI-0021) respectively, and in completed Phase 2 DD-CKD studies was 450 mg or 600 mg in Study AKB-6548-CI-0011 (CI-0011) and Study AKB-6548-CI-0022 (CI-0022), respectively.

Based on the dosing algorithm, vadadustat will be titrated to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive. The dose range for titration is 150 mg to 900 mg daily or TIW. Doses of 150 mg to 630 mg daily have been evaluated in studies evaluating subjects with NDD-CKD and DD-CKD. The maximum vadadustat dose evaluated in healthy volunteers was 1200 mg in a single dose study (CI-0001 and CI-0010) and 900 mg daily in a 10-day multiple dose study (CI-0002), as described in Section 4.2, Summary of Clinical Experience.

The rationale to evaluate higher maximum doses for titration is that to date, dose-ranging clinical studies have not identified a vadadustat dose at which a plateau in exposure or effect has been observed. In Phase 1 studies in healthy volunteers, dose-proportional increases in AUC and C_{max} and dose-related increases in serum EPO were observed up to the maximum doses studied, single doses of 1200 mg and multiple doses of 900 mg daily for 10 days (CI-0001, CI-0002). In Phase 2 studies in anemic NDD-CKD and DD-CKD subjects, dose-dependent increases in Hb were observed up to the maximum dose studied of 600 mg or 630 mg daily (CI-0005, CI-0021, CI-0022). It is anticipated that daily doses of vadadustat at 750 mg or 900 mg would yield an incremental erythropoietic effect greater than 600 mg for the treatment of renal anemia.

This study design mitigates the risk of vadadustat doses of 750 mg or 900 mg. Intensive Hb monitoring, a strict dose adjustment algorithm, and phlebotomy will be implemented to mitigate the potential risk of a rapid Hb rise, as follows:

- Hb measurements are scheduled at least every 2 weeks to Week 20
- The dose adjustment algorithm will target a narrow Hb range, 10.0 to 11.0 g/dL, inclusive
- The protocol specifies that phlebotomy may be considered in the setting of high Hb levels (>14.0 g/dL) or a high Hb rate of rise, based on the Investigator's judgment

Importantly, the Phase 2 studies demonstrated that cessation of treatment resulted in prompt reduction in mean Hb to baseline values.

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 the subject must meet all eligibility criteria. No study procedures (including Screening tests) may be performed until after the informed consent has been legally signed.

7.2 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. ≥18 years of age
2. Receiving chronic, outpatient in-center hemodialysis (TIW) for ESRD for at least 12 weeks prior to Screening
3. Maintained on IV epoetin alfa therapy for 8 weeks prior to and including Screening through SV2
4. Eligibility in the Main study and ESA hyporesponder parallel study is based on the following mean weekly epoetin alfa doses:
    - Main study: Mean weekly epoetin alfa dose <300 U/kg/week for 8 weeks prior to SV2
    - ESA hyporesponder parallel study: Mean weekly epoetin alfa dose ≥300 U/kg/week for 8 weeks prior to SV2
5. Two Hb values measured at least 4 days apart by the central laboratory during Screening as indicated below
    - Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive
    - ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive
6. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening
7. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening
8. Hemodialysis adequacy as indicated by single-pool Kt/V_{urea} ≥1.2 using the most recent historical measurement within 8 weeks prior to or during Screening
9. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.

7.3 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia)
2. Active bleeding or recent blood loss within 8 weeks prior to randomization
3. RBC transfusion within 8 weeks prior to randomization
4. Anticipated to discontinue hemodialysis during the study
5. Judged by the Investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study
6. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver)

7. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >1.5 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded.
8. Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of epoetin alfa
9. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening
10. History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Subjects with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded.
11. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening
12. History of hemosiderosis or hemochromatosis
13. History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded)
14. Scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months
15. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded)
16. Known hypersensitivity to vadadustat, epoetin alfa, or any of their excipients
17. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to Screening (subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation)
18. Previous participation in this study, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) other than vadadustat
19. For female subjects:
    - Of non-childbearing potential
      - Inability to confirm surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or
      - Not considered post-menopausal (no menses for >1 year with follicle stimulating hormone [FSH] >40 U/L at Screening)
    - Or, if of childbearing potential,
      - Lack of confirmation of the use of acceptable forms of contraception* for a minimum of one complete menstrual cycle prior to Screening
      - Positive serum pregnancy test at SV2
      - Unwilling to use two acceptable forms of contraception* (at least one of which must be a barrier method) starting Baseline/Day 1, throughout the Treatment Period and for 30 days after the final study drug administration
        (refer to Section 9.1.5, Contraception and Pregnancy Avoidance Measures)

20. Breastfeeding during Screening or throughout the Treatment Period and for 30 days after the final study drug administration.
21. Donation of ova starting at Screening, throughout the Treatment Period, and for 30 days after the final study drug administration.
22. Male subjects who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception* (refer to Section 9.1.5, Contraception and Pregnancy Avoidance Measures) during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat.
23. Any other reason, which in the opinion of the Investigator, would make the subject not suitable for participation in the study.

7.4 Retesting and Rescreening

7.4.1 Retesting

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

Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 4-week Screening Period, per Investigator discretion.

7.4.2 Rescreening

Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the Investigator if it is considered that the subject status has changed, and the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on inclusion criteria values for 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). A new informed consent is required to be signed prior to every rescreening.

7.5 Study Completion, Study Termination, and Individual Site Termination

7.5.1 Study Completion

The study will be considered completed after all randomized subjects have completed their final study visit (Visit 15/Week 24), Safety Follow-Up or Early Termination).

7.5.2 Study Termination

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advanced notice is not required if the study is stopped due to safety concerns. If a study site has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements. Criteria and procedures 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 study site for various reasons. Criteria and procedures for premature termination or suspension of an study site are detailed in Section 14.2, Criteria for Premature Termination or Suspension of Study Sites and Section 14.3, Procedures for Premature Termination or Suspension of the Study or Study Sites. If a study site has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

7.6 Subject Completion and Subject Discontinuation

7.6.1 Subject Completion

A subject will be considered as having completed the study after completion of their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination).

7.6.2 Temporary Interruption of Study Drug

Subjects who temporarily interrupt their study drug (vadadustat or epoetin alfa) after receiving the first dose and prior to completion of the study, will continue with the study visits, safety assessments, and other activities as deemed applicable through Week 20, and will complete the 4-week Safety Follow-Up Period and the Visit 15/Week 24 assessments (see Appendix A: Schedule of Activities.

During the study, a subject may interrupt study drug (vadadustat or epoetin alfa) for any of the following reasons:

- AE
- Missed dialysis visit (epoetin alfa arm)
- Investigator's discretion
- Rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Hb above 11.0 g/dL
- ESA use (vadadustat arm)

Unless contraindicated, treatment will be resumed whenever possible and assessed at every visit following study drug interruption.

7.6.3 Early Discontinuation from Study (Early Termination)

Subjects who discontinue prematurely from the study will complete the End-of-Treatment (EOT) visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14.

Subjects may discontinue for any of the following reasons:

- AE
- Investigator's discretion
- Subject withdrawal of consent

- Lack of efficacy, defined as inadequate response to vadadustat or epoetin alfa in the Investigator's opinion
- Lost to follow-up despite reasonable efforts by the Investigator to locate the subject. Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.
- Death
- Others reasons (pregnancy, kidney transplantation, specific reasons to be documented by the Investigator)

8 STUDY DRUG AND TREATMENT OF SUBJECTS

Subjects will receive either vadadustat or epoetin alfa according to the randomization assignments provided via the Interactive Web Response System (IWRS) (see Section 8.4.1, Randomization).

Both vadadustat and epoetin alfa will be used as open-label supplies. All study drug supplies will 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 drug for dispensing to the subject (Section 8.1, Epoetin Alfa and Section 8.2.2, Dispensing of Vadadustat) and for study drug supply accountability (Section 8.3, Vadadustat Accountability and Destruction).

8.1 Epoetin Alfa

Epoetin alfa solution for IV injection in multi-dose vials (e.g., 20,000 Units/2 mL and 20,000 Units/1 mL) or in single-dose vials (e.g., 2,000 Units/mL, 3,000 Units/mL, 4,000 Units/mL, and 10,000 Units/mL) will be provided by the sites in commercially-approved primary packaging and stored per the approved label.

8.2 Vadadustat

8.2.1 Supplies and Storage

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 and local regulatory requirements.

Dose levels utilized in this study will include: 150 mg (1 tablet), 300 mg (2 tablets), 450 mg (3 tablets), 600 mg (4 tablets), 750 mg (5 tablets), and 900 mg (6 tablets) per day or TIW.

Vadadustat will be stored per the product label.

8.2.2 Dispensing of Vadadustat

At Baseline/Day 1, subjects who are randomized to vadadustat treatment will be administered the first dose of vadadustat at the study site.

Thereafter, vadadustat will be taken once daily from Baseline/Day 1 to Week 12 and TIW from Weeks 12 to 20 **if** Week 12 criteria are met (Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen). If the Investigator determined criteria for Week 12 is not met, daily dosing will continue on an outpatient basis. Subjects who are randomized to the vadadustat treatment arm will be provided with up to 2 bottles of vadadustat. Each bottle of vadadustat will contain 100 tablets of vadadustat (150 mg/tablet). Subjects may take vadadustat with or without food and will be instructed to swallow the tablet(s) whole. Subjects will be instructed to take vadadustat at approximately the same time each day.

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

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

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

8.3 Vadadustat Accountability and Destruction

Drug accountability will be an ongoing process throughout the study. All vadadustat will 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 study site, and study drug dispensed to or returned from each subject. Records will be maintained that accurately reflect the drug accountability of vadadustat at all times. An electronic Diary (eDiary) will be utilized throughout the study to guide dosing for subjects in the vadadustat arm (see Section 9.1.2, eDiary).

Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for all vadadustat received and that all required fields are complete, accurate, and legible.

If any dispensing errors or discrepancies are discovered, the Sponsor will 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 study site will complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the Sponsor or its designee for destruction as specified by the Sponsor.

Prior to study 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 other study materials will be returned to the Sponsor or destroyed at the study site, as specified by the Sponsor. Appropriate records of the disposal will be documented and maintained. No unused vadadustat 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

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

8.4.1 Randomization

Main Study:

Subjects will be randomized to either a vadadustat treatment arm or epoetin alfa treatment arm. Randomization will be stratified by mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to SV2:

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

In the low epoetin alfa dose group, subjects will be randomized in a 3:3:2 ratio to receive either an initial vadadustat daily dose of 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa.

In the high epoetin alfa dose group, subjects will be randomized in a 3:3:3:2 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets), 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa.

ESA Hyporesponder Parallel Study:

Subjects will be randomized in a 1:1 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets) or epoetin alfa.

Note: No epoetin alfa will be administered after SV2 after the subject has met all eligibility criteria and before Baseline/Day 1, for a minimum duration of 5 days in the Main study and 2 days in the ESA hyporesponder parallel study.

8.4.2 Blinding

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

8.4.3 Measurement of Hb Levels for Dose Adjustment Consideration

Hb values will be measured by a central laboratory. Study drug treatment will aim to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Hb will be monitored throughout the study to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive (see Section 8.4.6, Guidelines for Dose Adjustments). Hb levels can be measured more frequently based on Investigator's clinical judgment.

In both the vadadustat and epoetin alfa arm, if dose adjustment is recommended based on Hb value and protocol-specified guidelines, dosing instructions can be provided to the subject over the telephone or at the next dialysis session at the study site (or dialysis center) or during an unscheduled site visit within 3 business days after receiving the Hb result from the central laboratory.

8.4.4 Epoetin Alfa Dosing Regimen

Epoetin alfa arm in both the Main study and ESA hyporesponder parallel study:

For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.

Epoetin alfa dose will be administered based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis.

From Baseline/Day 1 to Week 20, dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 and 11.0 g/dL, inclusive.

8.4.5 Vadadustat Dosing Regimen and Guidelines for Dose Adjustment

8.4.5.1 Dosing Regimen for the Vadadustat Treatment Arm

Subjects in the low epoetin alfa dose group randomized to vadadustat treatment will start at an initial dose of vadadustat 300 mg or 450 mg daily. Subjects in the high epoetin alfa dose group randomized to vadadustat treatment will receive an initial dose of 300 mg, 450 mg, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat treatment will receive a starting dose of vadadustat 600 mg daily.

After completing the 12-week once daily dosing regimen, subjects randomized to vadadustat who meet criteria for switching from daily to TIW dosing will initiate TIW dosing at a starting dose 1 tablet greater (+150 mg) than the final dose in the daily dosing period (see Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen). Subjects who do not meet criteria for switching from daily to TIW dosing will remain on daily dosing. From Baseline/Day 1 to Week 20, dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive.

8.4.5.2 Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen

All subjects randomized to vadadustat who complete 12 weeks of once daily dosing regimen **and** who meet all the Week 12 criteria below will be transitioned to a TIW vadadustat dosing regimen.

Week 12 Transition criteria:

- Vadadustat daily dose of 600 mg or lower at Week 12
- Hb within target range of 10.0 to 11.0 g/dL, inclusive, at Week 12 confirmed by central laboratory Hb value from Week 11 (11 weeks of treatment completed)
- No receipt of rescue therapy (ESA or RBC transfusion) for worsening of anemia due to CKD from Baseline/Day 1 to Week 12.
    - ESA or RBC transfusion prior to Week 12 for reasons unrelated to worsening of anemia due to CKD (e.g., surgery, gastrointestinal bleed, or inadvertent administration) is not considered rescue therapy
- No other reason, based on the Investigator's clinical discretion, that would make the subject not suitable for TIW dosing.

Selected subjects who meet Week 12 transition criteria will transition to the TIW vadadustat dosing regimen at the Week 12 visit. Subjects on 150 mg, 300 mg, 450 mg, or 600 mg of vadadustat daily at the Week 12 visit will transition to an initial vadadustat TIW dose one tablet greater (+150 mg), i.e., 300 mg, 450 mg, 600 mg, or 750 mg vadadustat TIW, respectively. Subjects will be instructed to take vadadustat on dialysis days.

After 2 weeks of treatment in the TIW vadadustat dosing regimen (at Week 14), subjects in any vadadustat TIW dosing arms who have a decline in Hb ≥0.5 g/dL will be eligible for a dose increase by 1 tablet, based on the Investigator's clinical discretion.

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

Subjects on TIW dosing may be converted back to vadadustat once daily dosing at the discretion of the Investigator in the setting of inadequate Hb response. The starting daily dose after the switch from TIW to daily dosing will be based on the Investigator's discretion after review of the subject's clinical status and dosing history, in particular, the daily dose previously administered to the subject prior to the transition to TIW dosing (Week 12). Subjects who switch from vadadustat TIW to daily dosing will continue once daily vadadustat until the end of the Treatment Period.

Subjects in the vadadustat arm will be guided for dosing compliance using an eDiary (see Section 9.1.2, eDiary).

8.4.6 Guidelines for Dose Adjustments

Dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment (see below). Hb will be monitored via central laboratory throughout the study to determine if the dose of study drug (vadadustat or epoetin alfa) will be adjusted, interrupted, or maintained as follows:

- Dose adjustments are based on the Investigator's clinical discretion, incorporating the protocol guidance below as well as the subject's current Hb level, trajectory, and variability; symptoms; cardiovascular risk; and other features of his/her clinical condition(s).
- If a dose increase or decrease is required to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for epoetin alfa approximately 25%).
- In general, do not increase the dose more frequently than once every 4 weeks. A one-time dose increase after 2 weeks is allowed on only two occasions.
    - A subject's dose may be increased by 1 dose level if the subject has a decline in Hb ≥0.5 g/dL from Baseline/Day 1 in the first 2-week period (the initial period from Baseline/Day 1 to Week 2 following conversion from prior epoetin alfa therapy).
    - A subject's dose may also be increased by 1 dose level in the first 2-week period after initiation of TIW dosing (from Week 12 to Week 14) for subjects that meet criteria for transitioning from daily to TIW dosing.
- Reduce or interrupt the dose in the setting of a rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Reduce or interrupt the dose in the setting of Hb >11.0 g/dL
- Interrupt the dose in the setting of a Hb >12.0 g/dL until Hb value falls below 11.0 g/dL. After Hb falls below 11.0 g/dL, restart study drug and consider restarting at a lower dose.

Note: The minimum dose of vadadustat will be 150 mg daily or TIW (1 tablet daily/TIW) and the maximum dose will be 900 mg daily or TIW (6 tablets daily/TIW).

8.4.7 Late or Missed Doses

Subjects on vadadustat will be instructed to take the study drug at approximately the same time each day. If a dose is forgotten, subjects will be instructed to take the dose as soon as they remember during the same day.

- Daily dosing regimen: If a forgotten dose is not remembered on the same day, the subject will skip the dose and resume the normal dosing schedule the following day.
- TIW dosing regimen: If a forgotten dose is not remembered on the same day, the subject will take the dose on the following day (a non-dialysis day). If a forgotten dose is not remembered on the same day or the following day of a long interdialytic gap, the subject will take the dose on the subsequent day (the second non-dialysis day). Thereafter, the subject should resume the normal dosing schedule.
- Subjects will not double-up on missed doses.

Epoetin alfa dose (including handling of late or missed dose) will be administered at the site and titrated based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis.

8.4.8 Iron Supplementation

IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol in Table 1.

Table 1: Iron Supplementation Protocol

	Ferritin <200 ng/mL	**Ferritin 200-500 ng/mL**	**Ferritin >500 ng/mL**
TSAT <20%	IV Iron 100 mg every treatment (max 400 mg/month)	IV Iron 50 mg weekly	Hold
TSAT 20-50%	IV Iron 100 mg every week	IV Iron 50 mg weekly	Hold
TSAT >50%	Hold	Hold	Hold

Intra-dialytic iron preparations (e.g., Triferic) and oral iron supplementation including iron-containing phosphate binders are prohibited during the study.

Important: As the study will be assessing PK/PD parameters, and as there are no empirical data on concurrent administration of vadadustat and phosphate binders, vadadustat will not be administered concurrently with a phosphate binder. Subjects will be instructed to take phosphate binders at least 3 hours before or at least 2 hours after the dose of vadadustat based on the guidance in the phosphate binder package inserts.

8.4.9 Rescue Therapy

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

8.4.9.1 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 will 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 medical necessity. Study drug (vadadustat or epoetin alfa) may be continued during the transfusion period.

Reasons for RBC transfusion will be captured in the appropriate CRF.

8.4.9.2 ESA Use

ESA administration will be allowed when medically necessary at the discretion of the Investigator. In general, ESA will not be administered in subjects with Hb ≥8.5 g/dL, and ESA will be stopped when Hb ≥9.0 g/dL. ESA therapy will be administered using an approved ESA and dosing as per the local institution's guidelines and per the approved product label.

While receiving ESA therapy, subjects randomized to vadadustat must temporarily interrupt vadadustat. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA, and treatment will be resumed after the following intervals:

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

Following ESA administration, vadadustat will be resumed at the same dose as previously used or with one additional tablet (+150 mg) at the discretion of the Investigator.

Reasons for ESA use will be captured in the appropriate CRF.

8.4.10 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 clinical judgment. The method of phlebotomy will be in accordance with the study site's standard clinical practice.

8.4.11 Treatment Compliance

Throughout the study, subjects in the vadadustat arm will be guided regarding dosing compliance using an eDiary. The focus of the vadadustat eDiary is to guide subjects to remind them of the dose, instruct them to hold their dose for the PK/PD sample dates and guide them if they have transitioned from daily dosing to TIW dosing. Subjects will also be questioned at study visits on whether they have questions or have experienced any problems related to the dosing of vadadustat. Subject compliance with eDiary data entry will be routinely monitored to identify potential issues that may impact or prevent data entry. The Investigator will also maintain drug accountability logs itemizing all study drugs dispensed to and returned from each subject during

the study. Treatment compliance will be determined from these logs, subject questioning, and the study drug Case Report Form (CRF)

For epoetin alfa, the dose that is administered is required to be entered in the electronic data capture (EDC) system, and the EDC system will be used to determine dosing compliance.

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

8.4.12 Continuation of Treatment

Subjects in the vadadustat dosing groups will not receive vadadustat beyond the Treatment Period of approximately 20 weeks. However, enrollment may be increased by up to 20 additional subjects on the Main study and up to 30 additional subjects on the ESA hyporesponder parallel study to ensure adequate data is captured for the primary, PK/PD, and safety endpoints. Subjects in the vadadustat dosing groups who complete Visit 14 (Week 20), or discontinue early, will resume dosing with epoetin alfa (or another ESA) as per standard of care after all EOT procedures are completed.

8.5 Prior and Concomitant Therapy

8.5.1 General

Any medicinal product, prescribed or non-prescribed (including vitamins, minerals, natural and herbal remedies, topicals, inhaled, intranasal and dietary supplements) taken before entering the study is considered prior medication. All medicinal products other than the study drug, including prescribed or non-prescribed treatments used during the Treatment Period will be considered concomitant medication.

8.5.2 ESAs

Co-administration of any ESA with vadadustat is 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 8.4.9.2, ESA Use) if deemed medically necessary at the discretion of the Investigator. Guidelines for ESA administration as rescue therapy are provided in Section 8.4.9.2, ESA Use. All efforts will be made to avoid inadvertent administration of ESAs resulting from adherence to ESA hemodialysis center protocols (e.g., DaVita ESA protocols for patients 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. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA. Vadadustat treatment may be resumed after the following intervals:

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

8.5.3 Dialysis Treatment and Renal Replacement Therapy

Information on dialysis treatment including dialysis vascular access type, dialysis adequacy, and history of and changes in renal replacement therapies will be collected as described in Section 9, Study Procedures and Schedule of Activities and Appendix A: Schedule of Activities.

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 had previous participation in a study with another HIF-PHI other than vadadustat.

Additionally, subjects should not take another investigational medication while participating in this study. Subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation.

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:

- Eligibility Screening Period (from Day -28 to Baseline/Day 1)

  The Screening Period starts at the time the informed consent is signed and will be a maximum of 28-days in duration. Two Screening visits (SV1 and SV2) must be performed within the Screening Period and prior to dosing (Baseline/Day 1).

  - Screening Visit 1 (SV1)
  - Screening Visit 2 (SV2)
- Study Treatment Period will consist of study visits from Baseline/Day 1 through Week 20 visit. In weeks where there is no schedule study visit a subject will have a status check performed during one of their dialysis treatment appointments.
  - Baseline/Day 1, Visit 1
  - Visit 2, Week 1 +5 days
  - Visit 3, Week 2 ± 3 days
  - Visit 4, Week 4 ± 3 days
  - Visit 5, Week 6 ± 3 days
  - Visit 6, Week 8 ± 3 days
  - Visit 7, Week 10 ± 3 days
  - Visit 8, Week 11 ± 3 days
  - Visit 9, Week 12 ± 3 days (Transition to TIW dosing if all Week 12 criteria are met)
  - Visit 10, Week 13 +5 days
  - Visit 11, Week 14 ± 3 days
  - Visit 12, Week 16 ± 3 days
  - Visit 13, Week 18 ± 3 days
  - Visit 14, Week 20 ± 3 days (EOT visit)
- Safety Follow-Up Period (from Week 20 to 24)
  - Visit 15, Week 24 visit ± 5 days

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

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent will be obtained and legally signed prior to the subject entering into the study and before any protocol-directed procedures (including Screening activities) are performed (see Section 15.3, Subject Information and Consent). After providing informed consent and receiving a unique subject identification number, subjects will undergo various Screening activities.

9.1.2 eDiary

An eDiary will be utilized throughout the study for completion of SF-36 and PGI assessments. In addition, the eDiary will guide dosing for subjects in the vadadustat arm. The focus of the vadadustat eDiary is to guide subjects to remind them of the dose, instruct them to hold their dose for the PK/PD sample dates and guide them if they have transitioned from daily dosing to TIW dosing. At SV2, subjects will be instructed on data entry procedures for the eDiary. Subject compliance with eDiary data entry will be routinely monitored to identify potential issues that may impact or prevent data entry.

9.1.3 Documentation of Screen Failures

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

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

9.1.4 Status Check

In weeks where there is no scheduled study visit, a subject will have a status check performed during one of their dialysis treatment appointments in the week. It will include a review of the subject's vital signs and a review of current health status for identification of any issues that may require follow-up by the Investigator or delegated staff personnel. Documentation of the review must be done in the subject's source documentation. No data will be captured on the status checks in the EDC system. If an AE is identified at the status check or other actions result from the status check, these will be captured per the protocol.

9.1.5 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 of vadadustat in the rat are ongoing, and there are no data on the transmission of vadadustat in breast milk or the effect of vadadustat on infants.

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 drug.

Adequate contraception for subjects is defined as follows:

- For females of non-childbearing potential
    - Confirmation of surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or
    - Post-menopausal (no menses for >1 year with FSH >40 U/L at Screening)
- For females of childbearing potential
    - Subjects must confirm the use of acceptable forms of contraception*, for a minimum of one complete menstrual cycle prior to Screening.

- Must have a negative serum pregnancy test at SV2.
- Starting Baseline/Day 1, subjects must use two acceptable forms of contraception* (at least one of which must be a barrier method) throughout the Treatment Period and for 30 days after the final study drug administration

- For males subjects who have not had a vasectomy must agree to the following: use of an acceptable form of contraception* during the study and for 30 days after the last dose of the study drug; to not donate sperm during the study and for at least 30 days after the last dose of vadadustat.

* *Acceptable forms of contraception include:*

- *Established use of oral, injected or implanted hormonal methods of contraception.*
- *Placement of an intrauterine device or intrauterine system.*
- *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.*

9.1.6 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. If the evaluations occur on a hemodialysis day, the evaluations will be completed before dialysis, if applicable.

- 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 will be documented. After SV2, an abbreviated, symptom-directed physical examination will be performed at the discretion of the Investigator, as clinically indicated.
- Dialysis Adequacy: Dialysis adequacy, as available from local collection, will be recorded in the CRF at SV1 and Visits 9 and 14 (EOT).
- SF-36 HRQOL and PGI-S: The SF-36, a patient-reported survey of patient health, and PGI-S will be completed at SV2, Visits 9, 14 (EOT) and 15. Assessments will be completed by subjects using the eDiary. The PGI assessment will be completed after the other assessments.
- PGI-C: The PGI-C will be completed at the Safety Follow-Up (Visit 15). The assessment will be completed by subjects using the eDiary. The PGI assessment will be completed after the other assessments.
- Vital Sign Measurements: Vital signs will include temperature, heart rate (HR), BP, respiratory rate (RR), oxygen saturation (SO_2), and dry weight. Temperature, HR, BP,

RR, and SO_2 will be assessed in the seated position after 5 minutes of rest. For BP, a total of two measurements at intervals of at least 2 minutes should be performed. Temperature, HR, BP, RR, and SO_2 will be collected at SV1, SV2, Baseline/Day 1, during all study visits, and Visit 14 (EOT). Measurements will be taken prior to blood draws when possible.

Dry weight will be collected for all subjects at SV2, Baseline/Day 1, Visit 9 and 14 (EOT). For subjects on epoetin 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/Day 1, which may be obtained up to 3 days prior to Baseline/Day 1. The ECG will be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and will be taken prior to vital sign assessments and blood draws when possible. 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.
- AE Assessments: Beginning with the first dose of study drug (vadadustat or epoetin alfa) at Baseline/Day 1 and through 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 (study end date) or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
- Prior and Concomitant Medication Recording: All prior and concomitant medications (except those routinely administered as part of the hemodialysis procedures, such as heparin or saline flushes used for routine catheter maintenance, unless relevant for an AE or SAE) taken within 30 days prior to Baseline/Day 1 and through the final study visit will be recorded on the appropriate CRF.

  Iron treatment regimen 30 days prior to Baseline/Day 1 and through the final study visit will be recorded on the appropriate CRF. In addition, to ensure adequate collection of prior ESA dosing history, a minimum of 8 weeks of ESA therapy prior to start of study drug will be recorded on the appropriate CRF page.

  At each study visit, subjects will be asked whether they have started, changed or discontinued any medication since their previous study visit. This includes single use or as needed medication use. All medications and changes in dosage and frequency will be recorded on the appropriate CRF Page. Documentation for all medicinal products will include the medication name, indication, dose, dosing frequency and dates of administration.

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. If blood is collected on a dialysis day, blood draws

will be done prior to dialysis, if applicable. The Investigator is responsible for reviewing laboratory results for clinical significance.

For eligibility purposes, one retest for each parameter may be performed during the Screening window. Refer to Section 7.4.1, Retesting and Section 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening Period.

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 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 drug. A FSH test will be performed at SV2 for post-menopausal females.
- Complete Blood Count (CBC): A CBC with differential will be performed at Baseline/Day 1 and at Visit 14 (EOT). At all other noted visits in Appendix A: Schedule of Activities, including SV1 and SV2, a CBC without differential will be performed. The CBC without differential will include: Hb, hematocrit, RBCs, mean corpuscular Hb, mean corpuscular Hb concentration, red cell width distribution, white blood cell count and platelets. The CBC with differential will include the same parameters as CBC without differential with the addition of white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

  Hb will be monitored throughout the study via central laboratory to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive. Refer to Section 8.4.3, Measurement of Hb Levels for Dose Adjustment Consideration. Hb levels can be measured more frequently based on Investigator's clinical judgment.
- Reticulocyte Count: An automated reticulocyte count (both absolute and percent) will be performed at Baseline/Day 1 and at Visits 2, 4, 6, 8, 9, 10, 12, and 14 (EOT).
- Folate and Vitamin B_{12}: A blood sample will be drawn at SV1 to assess the folate and Vitamin B_{12} levels.
- CRP: A blood sample for CRP will be collected at the Baseline/Day 1, Visit 9 and 14 (EOT).
- Serum Chemistry: Blood samples to assess serum chemistry will be collected at SV1, Baseline/Day 1, Visit 9 and 14 (EOT). The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen, creatine phosphokinase, uric acid, albumin, and total protein.
- Liver Function Tests (LFTs): Blood samples to assess liver function will be collected at SV1, Baseline/Day 1, Visit 4, 6, 9, 12 and 14 (EOT). LFTs will include: total bilirubin, alkaline phosphatase (ALP), ALT/SGPT, AST/SGOT, and lactate dehydrogenase.
- Iron Indices: Blood samples to assess the iron indices will be collected at SV1, Baseline/Day 1, Visit 4, 6, 9, 12 and 14 (EOT). Assessments will include the following indices: ferritin, iron, transferrin, TIBC, and TSAT.

- Lipid Profile: Blood samples will be collected at the Baseline/Day 1 and Visit 14 (EOT) to assess the cholesterol levels and will be tested for the following types of lipids: total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides.
- Biomarkers (including, but not limited to, vascular endothelial growth factor [VEGF], and hepcidin): Samples for VEGF and hepcidin biomarker analyses will be drawn at the Baseline/Day 1, Visit 9 and 14 (EOT).

9.2.2.1 PK/PD Sampling for Subjects Randomized to Vadadustat

Refer to Appendix B for a schematic overview of the PK/PD samples for the vadadustat arm.

Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below. Preferably, PK/PD samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).

At Baseline/Day 1, PK/PD samples will be collected prior to dialysis and administration of vadadustat.

At Week 1 (after at least a full week of vadadustat treatment), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

On the following non-dialysis day, blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes post-dose

At Week 11, vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

At Week 13 (after at least one week on TIW vadadustat dosing regimen), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

Note: Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Week 13 PK/PD sampling.

9.2.2.2 PK Sampling for Subjects Randomized to Epoetin Alfa

Refer to Appendix B for a schematic overview of the PK samples for the epoetin alfa arm.

Blood for measurement of EPO level in the epoetin alfa arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below. Preferably, PK samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).

At Baseline/Day 1, a sample will be collected prior to dialysis and administration of epoetin alfa.

At Week 1 (after at least a full week of study epoetin alfa treatment), epoetin alfa will be administered within 1 hour after start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

On the following **dialysis day**, one blood sample will be collected 15 minutes prior to administration of epoetin alfa.

9.2.2.3 PK/PD Sampling

For all PK and PD sampling the time of the previous dose of study drug (vadadustat or epoetin alfa) is to be collected for the pre-dose sample and the timing of administration of study drug (epoetin alfa and vadadustat) and the start and stop time of the dialysis session will be recorded.

9.3 Schedule of Activities

The Schedule of Activities (see Appendix A: Schedule of Activities) shows the timing of planned study procedures. Every effort will be made to adhere to this procedure schedule and all assessments will be completed at each study visit. Where possible, study visits will be performed and scheduled as part of a patients regularly scheduled dialysis session.

9.3.1 Screening Visits

Subjects will need to sign a full consent form prior to SV1 procedures. The consent form may be signed in advance of the SV1 procedures. The Screening Period starts at the time the informed consent is signed and will be a maximum of 28-days in duration. Two Screening visits (SV1 and SV2) must be performed within the Screening Period and prior to dosing (Baseline/Day 1).

The Investigator will arrange for sufficient time (a minimum 4 days) between SV1 and SV2 and between SV2 or last retest (if applicable) and Baseline/Day 1 to allow for all laboratory results to be available that are required to assess eligibility for the next study visit.

In addition, subjects will be required to stop epoetin alfa treatment for a minimum duration of 5 days before Baseline/Day 1 in the Main study and for a minimum of 2 days before Baseline/Day 1 in the ESA hyporesponder parallel study.

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

9.3.1.1 SV1

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

- Informed consent
- Review of eligibility criteria
- Review of acceptable methods of contraception
- Vital signs including temperature, HR, BP, RR and SO_2 (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Dialysis adequacy
- Laboratory procedures:
  - CBC (without differential)
  - Folate and vitamin B_{12} levels
  - Serum Chemistry
  - LFTs
  - Iron indices

  Refer to Section 7.4.1, Retesting and Section 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening Period.
- Visit registration in IWRS
- Review of prior medication
- Epoetin alfa dosing will continue

9.3.1.2 SV2

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

- Review of eligibility criteria
- Review of acceptable methods of contraception
- SF-36 and PGI-S assessments
- Physical examination (including height)
- Demographics and medical history
- Vital signs including temperature, HR, BP, RR and SO_2 (assessed in seated position after 5 minutes of rest and prior to blood draws), and dry weight
- Laboratory procedures:
  - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method see Section 9.2.2, Laboratory Evaluations for additional information). A FSH test will be performed at SV2 for post-menopausal females.
  - CBC (without differential)

  Subjects must have 2 Hb values measured by the central laboratory during Screening as indicated below:
  - Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive
  - ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive

  If the subject's Hb does not qualify after SV1, SV2, or retest Hb, the subject will be considered a screen failure

- Visit registration in IWRS
- Introduction to and instruction on the use of the eDiary
- Prior and current medication use
- Epoetin alfa dosing will stop for a minimum of 5 days in the Main study or 2 days in the ESA hyporesponder parallel study until Baseline/Day 1

9.3.2 Baseline/Day 1 (Visit 1)

Epoetin alfa dosing will have been stopped for a minimum of 5 days in the Main study or 2 days in the ESA hyporesponder parallel study until Baseline/Day 1.

On Baseline/Day 1, blood sample collection and other Baseline/Day 1 procedures will be completed prior to dosing with study drug (vadadustat or epoetin alfa). On Baseline/Day 1, study drug will be administered at the study site, and will be administered after the PK sample is collected and prior to the dialysis session.

At Baseline/Day 1, the following activities/procedures will be performed:

- Review of study eligibility criteria
- Review acceptable methods of contraception
- Abbreviated, symptom-directed physical examination, at the discretion of the Investigator, as clinically indicated
- 12-lead ECG. ECGs will be completed prior to blood draws when possible and will be obtained after the subject has been resting supine comfortably for approximately 5 minutes; ECG may be completed and reviewed by the Investigator on Baseline/Day 1 or if needed for scheduling reasons (e.g., dialysis treatment is scheduled for early morning of Baseline/Day 1), the ECG can be completed and reviewed up to 1-3 days prior to Baseline/Day 1.
- Randomization
- Vital signs including temperature, HR, BP, RR and SO_2 (assessed in seated position after 5 minutes of rest and prior to blood draws), and dry weight
- Laboratory Procedures:
  - CBC (including differential)
  - Reticulocyte count
  - CRP
  - Serum chemistry
  - LFTs
  - Iron indices
  - Lipid profile
  - Biomarkers (VEGF, and Hepcidin)
  - PK prior to vadadustat or epoetin alfa dosing (see Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa) and prior to the dialysis session
- Review of medical history for new conditions since SV2
- Review of medication use since SV2
- Study drug assessments and procedures:
  - Subject will take/receive their first dose of study drug at the study site during Baseline/Day 1

  - For subjects in the vadadustat treatment arm only:
    - Initiate vadadustat dosing
    - Vadadustat drug dispensation
    - Review vadadustat dosing instructions
  - Epoetin alfa dosing will continue for the subjects in the epoetin alfa arm
  - Iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation
  - Visit registration in IWRS
- Safety assessments:
  - AE review as needed (after receiving the first dose of study drug)
  - Review use of rescue therapy

9.3.3 Visit 2 to Visit 13 (Weeks 1 to 20)

At the Baseline/Day 1, Visit 7 and Visit 9, subjects in the vadadustat treatment arm will be reminded and instructed to hold their vadadustat dose on the day of Visit 2, Visit 8, and if applicable Visit 10, respectively, as blood sample for PK analysis will be collected on the day of Visit 2, Visit 8, and Visit 10 prior to vadadustat administration at the study site.

The following activities/procedures will be performed at Visit 2 to Visit 13, unless noted otherwise:

- Abbreviated, symptom-directed physical examination, at the discretion of the Investigator, as clinically indicated
- Vital signs including temperature, HR, BP, RR and SO_2 (assessed in seated position after 5 minutes of rest and prior to blood draws). Dry weight will be collected at Visit 9 only.
  - A status check (BP, vital signs, and review of current health status) will be performed during weeks with no scheduled study visit.
- Dialysis adequacy, as available from local information (Visit 9 only)
- SF-36 and PGI-S assessments (Visit 9 only)
- Safety assessments:
  - AE review
  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws will be done prior to dialysis, if applicable):
  - CBC
  - Reticulocyte count (Visit 2, 4, 6, 8, 9, 10 and 12 only)
  - CRP (Visit 9 only)
  - Serum chemistry (Visit 9 only)
  - LFTs (Visit 4, 6, 9 and 12 only)
  - Iron indices (Visit 4, 6, 9 and 12 only)
  - Biomarkers (VEGF and Hepcidin, Visit 9 only)
  - Vadadustat PK/PD sampling (Visit 2, 8 and 10 only) for details, see Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.3, PK/PD Sampling)

    - Epoetin alfa PK sampling (Visit 2 only) for details, see Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa and Section 9.2.2.3, PK/PD Sampling)
- Medication assessments and procedures:
    - Review of concomitant medications
    - Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa
    - For subjects in the vadadustat treatment arm only:
        - Visit registration in IWRS (for bottle dispensing only)
        - Vadadustat drug dispensation (scheduled Visits 4, 6, 9 and 12)
        - Review vadadustat dosing instructions
        - Review of vadadustat dosing compliance
        - Vadadustat reconciliation
    - Review of iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation)

9.3.4 EOT Visit 14 (Week 20)

EOT evaluations will be performed when the Treatment Period (Baseline/Day 1 to Visit 13) is completed. Subjects who prematurely discontinue study drug for any reason will also attend this visit.

At Visit 14 (EOT), the following activities/procedures will be performed:

- Vital signs including, HR, BP, RR and SO_2 (assessed in seated position after 5 minutes of rest and prior to blood draws), as well as temperature and dry weight
- Dialysis adequacy, as available from local information
- SF-36 and PGI-S assessments
- Safety assessments:
    - AE review
    - RBC transfusions and ESA rescue
    - Therapeutic phlebotomy
- Laboratory Procedures:
    - CBC (with differential)
    - Reticulocyte count
    - CRP
    - Serum chemistry
    - LFTs
    - Iron indices
    - Lipid panel
    - Biomarkers (VEGF and Hepcidin)
- Medication assessments and procedures:
    - Review of concomitant medications
    - Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa.
    - For subjects in the vadadustat treatment arm only:
        - Review of vadadustat dosing compliance
        - Vadadustat reconciliation
        - Resume dosing with epoetin alfa (or another ESA): After the end of vadadustat treatment at Visit 14 (or following early discontinuation of

vadadustat), subjects may resume dosing with epoetin alfa (or another ESA), based on standard of care.
- Visit registration in IWRS
- Review of iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation)

9.3.5 Safety Follow-Up Visit 15 (Week 24)

At the Visit 15, the following activities/procedures will be performed:

- SF-36 HRQOL, PGI-S, and PGI-C assessments
- AE review
- Review use of rescue therapy (RBC transfusions and ESA rescue therapy)
- Review use of therapeutic phlebotomy
- Concomitant medication review

9.3.6 Unscheduled Visits

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

- Safety assessments:
  - AE review
  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
- Medication assessments and procedures:
  - Review of concomitant medications
- Any other procedures that are medically warranted at the discretion of the Investigator.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

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.

AEs therefore include the following:

- All AEs, whether suspected to be causally related to study drug or otherwise.
- All AEs secondary to any medication overdose, medication error, abuse, withdrawal, sensitivity, or toxicity.
- Illnesses apparently unrelated to study drug, including the worsening of a pre-existing illness (see paragraph below on Pre-existing Conditions).
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) will 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 (e.g., elevated liver enzymes in a subject with jaundice) will 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 will 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 will be the reported AE term, instead of fever and dyspnea, when the diagnosis has been established. Signs and symptoms will 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, will not be reported as AEs. However, the medical condition for which the procedure was performed will be reported if it meets the definition of an AE. For example, an acute

appendicitis that begins during the AE reporting period will 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 will not be reported as AEs.

Pre-existing Conditions – In this study, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) will 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 will 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 will also be reported as AEs. Any abnormal laboratory value which requires treatment or further diagnostic testing and/or results in discontinuation from study will 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 will be reported to the Sponsor's Medical Monitor or Contract Research Organization (CRO) designee within 24 hours of awareness as an SAE with 'other medically important event' 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 (e.g., viral hepatitis, acute liver disease).

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

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

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 will not be considered an AE unless the worsening of anemia is associated with a cause *other than* the subject's CKD.

Transplantation – During this study, it is anticipated that subjects may receive a kidney transplant. These events will not be recorded as AEs. Subjects who discontinue study drug for

receipt of a kidney transplant will complete the EOT visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14 as described in Section 7.6.3, Early Discontinuation from Study.

10.1.2 SAEs

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 situation will also be classified as serious for purposes of this study:

- Malignancies – Newly diagnosed malignancies or a recurrence of a malignancy will 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 of skin, 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.

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

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

Hospitalization – Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the study for a pre-existing condition that has not worsened during the AE reporting period does not constitute an SAE unless an untoward event occurs related to the procedure (e.g., 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 AE 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 study drug.

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 this protocol will be reported, whether or not the event is considered related to study drug (vadadustat or epoetin alfa).

10.3.1 Reporting Period

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

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

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, will 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 will contain, at a minimum items number 1 to 6:

1. Subject number/ID, sex, and age/date of birth
2. The date of report
3. Name of the reporter
4. Name of the suspected medicinal product
5. A description of the event, including event term(s), seriousness criteria, and a clinical summary of the event
6. Causality assessment

If the causality assessment is not provided in the initial report an updated report with the causality must be provided within 24 hours, once assessed.

Information about all SAEs (either initial or follow-up information) will be collected and recorded in English on the electronic SAE Report Form within the EDC system. The Investigator will assess the relationship to each specific component of the study treatment. If the event meets serious criteria and it is not possible to access the EDC system, a paper SAE Report Form will 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 again, the SAE information will be entered within 24 hours of the system becoming available.

The Investigator will report follow-up information relating to an SAE to the Sponsor's Medical Monitor or CRO designee within 24 hours of awareness 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 will be entered within 24 hours. The subject will 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 IRB 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 study site.

10.3.4 Relationship to Study Drug

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

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

Examples of evidence that would suggest a causal relationship between the study drug and the AE include the occurrence of an AE that is uncommon and known to be strongly associated with drug exposure (e.g., 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 drug are generally uninformative and do not contribute meaningfully to the development of the safety profile of the drug or to subject protection.

Investigators are encouraged to choose the most plausible cause for the event(s) from the following list: medical history, lack of efficacy/worsening of treated condition, study treatment,

other treatment (concomitant, or previous), withdrawal of study treatment, administration error, protocol-related procedure, others (specify).

10.3.5 Severity

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

MILD: Does not interfere with subject's usual function

MODERATE: Interferes to some extent with subject's usual function

SEVERE: Interferes significantly with subject's usual function

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

10.3.6 Follow-up of Unresolved Events

All AEs will be followed until they are resolved or the Investigator assesses them as chronic or stable or the subject's participation in the trial ends (i.e., until a final report is completed for that subject).

In addition, all SAEs and those nonserious events assessed by the Investigator as related to the study drug will continue to be followed even after the subject's participation in the trial is over. Such events will 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 will be confirmed by a positive serum β human chorionic gonadotropin test.

The study drug will 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 drug (vadadustat or epoetin alfa) or within 30 days of discontinuing the study drug, the pregnancy will be recorded on the Pregnancy Reporting Form/Exposure in Utero Form in 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 will also be reported.

The Pregnancy Reporting Form/Exposure in Utero Form will be completed with all known information regarding the pregnancy at the time of reporting. Study 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 an SAE (i.e., 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 an SAE within 24 hours of awareness. A pregnancy in and of itself is not considered an AE; however, unexpected complications are considered AEs.

Additional information about pregnancy outcomes follows:

- Note that "spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth will be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as related or unrelated to the in utero exposure to the study drug will also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

10.5 Special Situations

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

- Overdose of the medicinal product
    - Epoetin alfa overdose – The PI or SmPC will be referenced for information on epoetin alfa overdosing.
    - Vadadustat overdose – There is no known antidote for vadadustat. In cases of suspected overdose, subjects will 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 will be discontinued and standard treatment for polycythemic hyperviscosity syndrome will be initiated (i.e., phlebotomy).

      Dose-limiting toxicity in exploratory toxicology studies was due to hemoglobinuric nephropathy in the rat and emesis associated with body weight loss in the dog. In the rat, doses ≥500 mg/kg were not tolerated in two 7-day exploratory toxicology studies. The probable cause of the findings is considered to be intravascular hemolysis leading to hemoglobinuric nephropathy.

      The clinical data from human volunteer subjects and renal study subjects demonstrate that currently there is no evidence of any drug-related hemolysis associated with vadadustat at the doses studied. The highest dose in the majority of subjects exposed to vadadustat was up to 600 mg daily with minimal exposures at doses higher than this (up to 1200 mg single dose and up to 900 mg daily for 10 days). No conclusion concerning the safety profile of vadadustat at doses higher than 600 mg daily can be drawn.

- 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 exposure to the Sponsor's medicinal product [e.g., name confusion])
- Drug-drug interaction.

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

10.6 Safety Monitoring

This is an open label study allowing the study team full access to safety data which will be reviewed on a regular basis, throughout the course of the study. Safety monitoring will be performed as described in the Medical Monitor Plan.

11 DATA ANALYSIS

Data collected throughout the study will be summarized using descriptive statistics and listed in the by-subject listings. Continuous variables will be summarized using number of subjects with mean, standard deviation (SD), 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.

11.1 Sample Size Estimation

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

Sample size reflects the exploratory nature of this study.

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

11.2 Study Analysis Populations

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects. Analyses of this population will be based on the randomized treatment.
- Full Analysis Population (FAS): all subjects in the randomized population who received at least one dose of study drug and had at least one Hb assessment during the primary efficacy evaluation period. Analyses of this population will be based on the randomized treatment.
- Safety Population: all subjects in the randomized population who received at least one dose of study treatment. Analysis of this population will be based on the actual treatment received. Subjects who received in error some vadadustat and some epoetin alfa will be classified by the more frequently received drug.
- Per protocol (PP) population: all randomized subjects who received study drug during the primary evaluation period, had at least one Hb assessment during the primary efficacy evaluation period, received no rescue therapy (with ESA or transfusion) prior to the evaluation period, and had no major protocol deviation affecting the primary endpoint analyses. Major protocol deviations leading to exclusion from the PP population will be specified prior to database lock and recorded in a separate document. Analyses of this population will be based on actual treatment received.

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 Randomized Population and other analysis populations which will be defined in detail in the Statistical Analysis Plan.

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

11.4 Disposition of Subjects

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

The number of randomized subjects who completed the study, discontinued early from study drug, completed or discontinued from the study, and reasons for discontinuation will be summarized by treatment group and overall.

11.5 Missing Data

It is expected that few subjects will discontinue Follow-Up. The reasons for any missing data will be summarized by treatment arm. Missing Hb values will be imputed using last observation carried forward (LOCF).

11.6 Efficacy Analyses

The primary efficacy endpoint as well as all other secondary endpoints will be summarized using descriptive statistics (means or proportions) by treatment groups and in total, 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.

11.7 Safety Analyses

Safety analyses will be descriptive in nature.

All AEs will be coded using MedDRA. Treatment-emergent and post-treatment AEs will be summarized by SOC and PT for each treatment group. AEs will also be summarized by their maximum severity.

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

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

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

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

PK and PD parameters will be summarized using descriptive statistics: number of subjects, mean, median, SD, minimum, maximum, and coefficient of variation, geometric mean and geometric mean SD. Mean and individual plasma concentration-time profiles will be presented graphically in both linear scale and log-linear scale.

11.8.1 PK Assessments

A population PK analysis will be conducted to describe vadadustat PK and determine the covariates that impact the PK profile (i.e., demographics, laboratory values, concomitant iron, dosing relative to dialysis, etc.). PK analysis will be reported separately.

11.8.2 PD Assessments

An exposure-response analysis of vadadustat, EPO and other PD measures will be conducted as deemed appropriate. PD analysis will be reported separately.

11.8.3 Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug dictionary. Refer to Section 8.5, Prior and Concomitant Therapy.

11.8.4 Biomarkers

Biomarkers (including, but not limited to, hepcidin and VEGF) will be summarized descriptively at Baseline/Day 1 and by visit post-Baseline/Day 1.

12 DATA HANDLING AND RECORD KEEPING

12.1 CRFs/EDC

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

Any form of data from the electronic system are the sole property of the Sponsor and will 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 will 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 will 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, e.g., 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 (e.g., letters, meeting minutes, and telephone calls reports). The records will be retained by the Investigator according to the International Council for Harmonisation of Technical Requires for Pharmaceuticals for Human Use (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 (e.g., retirement and relocation), the Sponsor will be prospectively notified. The study records will be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator will obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study 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 study site may also be subject to Quality Assurance audits performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or review by the IRB, 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

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an Investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the Investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File.

Note: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

14 STUDY DISCONTINUATION/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 will contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the study.

14.1 Criteria for Premature Termination or Suspension of the Study

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

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

The Sponsor reserves the right to discontinue the study for other valid administrative reasons.

If the study has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

14.2 Criteria for Premature Termination or Suspension of 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.

The Investigator will notify the Sponsor if the trial is terminated by the Investigator or the IRB at the site. If the Investigator, IRB, or Sponsor decides to terminate or suspend the trial conduct at a particular study site for safety, non-enrollment, non-compliance with the protocol, or other unanticipated reasons, the above parties will be promptly notified.

14.3 Procedures for Premature Termination or Suspension of the Study or Study 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 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 E6 guideline on GCP, and applicable local regulatory requirements and laws.

15.2 IRB

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

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

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

15.3 Subject Information and Consent

The Investigator or designee will explain the nature of the study to the subject or their legally acceptable representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or their legally acceptable representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

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, will be prospectively approved by both the IRB 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 (i.e., clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor will 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 (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

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

16 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor will 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 will 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	**Screening [a]**		**Study Treatment Period**													**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [c]**	**15**
Weeks of study completed Study Day	**Day -28 to 0**		**Baseline/ Day 1 [b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57**	**Week 10 Day 71**	**Week 11 Day 78**	**Week 12 Day 85**	**Week 13 Day 92**	**Week 14 Day 99**	**Week 16 Day 113**	**Week 18 Day 127**	**EOT Week 20 Day 141**	**Week 24 Day 169**
Visit Window (Days)	—		—	+5	±3	±3	±3	±3	±3	±3	±3	+5	±3	±3	±3	±3	±5
Administrative Procedures																	
Informed consent	X																
Eligibility criteria [d]	X	X	X														
Review Contraception methods [e]	X	X	X														
Vital Signs [f]	X	X [g]	X [g]	X	X	X	X	X	X	X	X [g]	X	X	X	X	X [g]	
Demographics, Medical History [h]		X	X [i]														
Physical Exam [j]		X															
12-Lead ECG [k]			X														
Dialysis Adequacy (Kt/V)	X										X					X	
SF-36		X									X					X	X
PGI-S		X									X					X	X
PGI-C																	X
Randomization			X														
Assessment for meeting criteria to switch from daily to TIW dosing (vadadustat arm)											X						
Status check [l]																	
Safety Assessments																	
AE review [m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Screening [a]**		**Study Treatment Period**													**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [c]**	**15**
Weeks of study completed Study Day	**Day -28 to 0**		**Baseline/ Day 1 [b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57**	**Week 10 Day 71**	**Week 11 Day 78**	**Week 12 Day 85**	**Week 13 Day 92**	**Week 14 Day 99**	**Week 16 Day 113**	**Week 18 Day 127**	**EOT Week 20 Day 141**	**Week 24 Day 169**
Review use of rescue therapy (RBC transfusions and ESA therapy)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of therapeutic phlebotomy				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluations																	
Serum Pregnancy test [n]		X															
CBC [o] [p]	X	X	X [q]	X	X	X	X	X	X	X	X	X	X	X	X	X [q]	
Reticulocyte count			X	X		X		X		X	X	X		X		X	
Folate and vitamin B12	X																
CRP			X								X					X	
Serum chemistry [r]	X		X								X					X	
LFTs [s]	X		X			X		X			X			X		X	
Iron indices [t]	X		X			X		X			X			X		X	
Lipid panel [u]			X													X	
Biomarkers (VEGF and Hepcidin) [v]			X								X					X	
PK/PD for vadadustat arm [w]			X	X						X		X [x]					
PK for epoetin alfa arm [y]			X	X													
Medication Assessments and Procedures																	
Concomitant medication review [z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Epoetin alfa dosing during Screening and resume standard of care after EOT	X [aa]															X [bb]	

Study Period	Screening [a]		Study Treatment Period													Safety Follow-Up	
Visit	SV1	SV2	1	2	3	4	5	6	7	8	9	10	11	12	13	14 [c]	15
Weeks of study completed Study Day	Day -28 to 0		Baseline/ Day 1 [b]	Week 1 Day 8	Week 2 Day 15	Week 4 Day 29	Week 6 Day 43	Week 8 Day 57	Week 10 Day 71	Week 11 Day 78	Week 12 Day 85	Week 13 Day 92	Week 14 Day 99	Week 16 Day 113	Week 18 Day 127	EOT Week 20 Day 141	Week 24 Day 169
Study Drug (vadadustat or epoetin alfa) dosing [cc]			X	X	X	X	X	X	X	X	X [dd]	X	X	X	X		
Vadadustat dispensation [ee]			X			X		X			X			X			
Review vadadustat dosing instructions and vadadustat dosing compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vadadustat reconciliation				X	X	X	X	X	X	X	X	X	X	X	X	X	
Review use of iron supplementation [ff]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visit Registration in IWRS	X	X	X			X [gg]		X [gg]			X [gg]			X [gg]		X	
eDiary instruction		X															

Abbreviations: AE = adverse event; ALT/SGPT = alanine transaminase/serum glutamic-pyruvic transaminase; AST/SGOT = aspartate aminotransaminase/serum glutamic oxaloacetic transaminase; BUN = blood urea nitrogen; CBC = complete blood count; CPK = creatine phosphokinase; CRP = C-reactive protein; ECG = electrocardiogram; EOT = end of treatment; EPO = erythropoietin; ESA = erythropoiesis-stimulating agent; HDL = high density lipoprotein; IWRS = Interactive Web Response System; LDL = low density lipoprotein; LFT = liver function test; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PD = pharmacodynamics; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; RBC = red blood cell; RDW = red cell distribution width; SF-36 = 36-Item Short-Form General Health Survey; SV1 = Screening visit 1; SV2 = Screening visit 2; TIBC = total iron binding capacity; TSAT = transferrin saturation; VEGF = vascular endothelial growth factor; WBC = white blood cell; wks = weeks.

[a] The Screening Period is a maximum of 28 days in duration and starts at the time the informed consent is signed.
[b] The Investigator will arrange for sufficient time (a minimum of 4 days) between SV2 or last retest (if applicable) and Baseline/Day 1 to allow for all laboratory results to be available that are required to assess eligibility for the next study visit.
[c] The EOT evaluations will be performed when the Treatment Period (Baseline/Day 1 to Week 20 [Visits 1 to 13]) is completed. Subjects who permanently discontinue study drug for any reason or discontinue prematurely from the study will complete the EOT visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14
[d] Eligibility criteria will be reviewed at the SV1, SV2, and Baseline/Day 1.
[e] Contraception methods will be reviewed at Screening and Baseline/Day 1, as well as throughout the study as needed.
[f] Vital signs will include temperature, HR, BP, RR, SO_2, and dry weight. Temperature, HR, BP, RR and SO_2 will be assessed in the seated position after 5 minutes of rest. For BP, a total of two measurements at intervals of at least 2 minutes should be performed. Temperature, HR, BP, RR and SO_2 will be collected at SV1, SV2, Baseline/Day 1, during all study visits, and Visit 14 (EOT). Measurements will be and will be taken prior to blood draws when possible.
[g] Dry weight will be collected as part of the vital signs for all subjects at SV2, Baseline/Day 1, Visit 9 and 14 (EOT). For subjects on epoetin alfa, subjects will be weighed for dosing as per the local standard of care.
[h] Relevant medical history (with particular emphasis on previous medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases will be documented.

[i] Review of medical history for new conditions since SV2.
[j] A physical examination (including height) is required at SV2. Thereafter, an abbreviated symptom-directed physical examination will be performed at the discretion of the Investigator, as clinically indicated.
[k] A standard 12-lead ECG will be performed at Baseline/Day 1, which may be obtained up to 3 days prior to Baseline/Day 1. The ECG will be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and will be taken prior to vital sign assessments and blood draws when possible. 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.
[l] In weeks where there is no scheduled study visit (Weeks 3, 5, 7, 9, 15, and 17), a subject will have a status check performed during one of their dialysis treatment appointments in the week. It will include a review of the subject's vital signs and a review of current health status for identification of any issues that may require follow-up by the Investigator or delegated staff personnel. Documentation of the review must be done in the subject's source documentation. No data will be captured on the status checks in the EDC system. If an AE is identified at the status check or other actions result from the status check, these will be captured per the protocol.
[m] Beginning with the first dose of study drug (vadadustat or epoetin alfa) at Baseline/Day 1 and through 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. Subjects must be followed for AEs until the final required protocol visit (study end date) or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
[n] A serum pregnancy test will be performed at SV2 for females of childbearing potential. Additional serum 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 drug. A FSH test will be performed at SV2 for post-menopausal females.
[o] A CBC without differential will be performed at all noted visits, except Baseline/Day 1 and Visit 14 (EOT). The CBC without differential will include: Hb, hematocrit, RBCs, MCV, MCH, MCHC, RDW, WBC count, and platelets.
[p] Hb will be monitored throughout the study via central laboratory to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive. Hb levels can be measured more frequently based on Investigator's clinical judgment. For eligibility purposes, one retest for Hb may be performed during the Screening Period. Two Hb values measured at least 4 days apart by the central laboratory during Screening (SV1, SV2 or retest) must be between 8.5 and 11.0 g/dL, inclusive, for the Main study and 8.0 and 10.0 g/dL, inclusive, for the ESA hyporesponder parallel study.
[q] A CBC with differential will be performed at Baseline/Day 1 and Visit 14 (EOT). The CBC with differential will include the same parameters as CBC without differential with the addition of WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
[r] The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, BUN, CPK, uric acid, albumin, and total protein.
[s] LFTs: total bilirubin, ALP, ALT/SGPT, AST/SGOT, and lactate dehydrogenase.
[t] Iron Indices: ferritin, iron, transferrin, TIBC, and TSAT.
[u] Lipid Profile: total cholesterol, LDL, HDL, and triglycerides.
[v] The biomarkers will include, but are not limited to, VEGF and hepcidin. Samples for VEGF and hepcidin biomarker analyses will be drawn at Baseline/Day 1, Visit 9 and 14 (EOT).
[w] Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study will be collected at Baseline/Day 1, Week 1, and Week 11 as outlined in Section 9.2.2.1. For all PK and PD sampling, the time of the previous dose of vadadustat will be collected for the pre-dose sample and the timing of administration of vadadustat, and the start and stop time of the dialysis session will be recorded.
[x] Visit 10/Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Visit 10/Week 13 PK/PD sampling.
[y] Blood for measurement of EPO level in the epoetin alfa arm, in both the Main study and ESA hyporesponder parallel study, will be collected at Baseline/Day 1 and Week 1 as outlined in Section 9.2.2.2. For all PK sampling the time of the previous dose of epoetin alfa is to be collected for the pre-dose sample and the timing of administration of epoetin alfa and the start and stop time of the dialysis session will be recorded.
[z] Concomitant medications should be collected and recorded at each visit as noted. All medications taken within 30 days prior to Baseline/Day 1 will be recorded.
[aa] Epoetin alfa dosing will stop for a minimum of 5 days before Baseline/Day 1 in the Main study or 2 days before Baseline/Day 1 in the ESA hyporesponder parallel study.
[bb] After the end of vadadustat treatment at Visit 14/Week 20 (or following early discontinuation of vadadustat), subjects will resume dosing with epoetin alfa (or another ESA), based on standard of care.
[cc] Subjects in the low epoetin alfa dose group randomized to vadadustat treatment will start at an initial dose of vadadustat 300 mg or 450 mg daily. Subjects in the high epoetin alfa dose group randomized to vadadustat treatment will receive an initial dose of 300 mg, 450 mg, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat treatment will receive a starting dose of vadadustat 600 mg daily. For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.
[dd] After completing the 12-week once daily dosing regimen, subjects randomized to vadadustat who meet criteria for switching from daily to TIW dosing will initiate TIW dosing at a starting dose 1 tablet greater (+150 mg) than the final dose in the daily dosing period. Central laboratory Hb values from Visit 8/Week 11 (11 weeks of treatment completed) will be used to determine if subjects meet Week 12 Transition criteria.
[ee] Subjects will be provided with a supply of vadadustat at Baseline/Day 1 and will be resupplied at Visit 4, 6, 9 and 12 or an unscheduled dispensing visit as needed. Subjects will be instructed to complete 1 bottle before opening a new bottle. The dose should be taken at approximately the same time each day.

[ff] IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol in Section 8.4.8. Oral iron supplementation including iron-containing phosphate binders are prohibited during the study.
[gg] IWRS visit registration for vadadustat arm only for bottle dispensing

APPENDIX B: PK/PD SAMPLING

PK/PD Sampling in Vadadustat Arm Subjects Who Transition to TIW Dosing at Week 12

	Baseline/Day 1 QD	Week 1 QD	Week 1 + 1 day	Week 11 QD		Week 13 TIW	
	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	●						
15 minutes (pre-dose)		●	●	●		●	
2 hours ± 15 minutes (post-dose)		●	●	●		●	
3.5 hours ± 15 minutes (post-dose)		●	●	●		●	
5 hours ± 30 minutes (post-dose)		●	●	●		●	
7 hours ± 30 minutes (post-dose)		●	●	●		●	
10.5 hours ± 1.5 hours (post-dose)		●		●		●	

Note: Gray shading indicates sample collection at a subset of study sites only.

PK/PD Sampling in Vadadustat Arm Subjects Who Do Not Transition to TIW Dosing at Week 12

	Baseline/Day 1 QD	Week 1 QD	Week 1 + 1 day	Week 11 QD	Week 13 TIW		
	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	•						
15 minutes (pre-dose)		•	•	•			
2 hours ± 15 minutes (post-dose)		•	•	•			
3.5 hours ± 15 minutes (post-dose)		•	•	•			
5 hours ± 30 minutes (post-dose)		•	•	•			
7 hours ± 30 minutes (post-dose)		•	•	•			
10.5 hours ± 1.5 hours (post-dose)		•		•			

Note: Gray shading indicates sample collection at a subset of study sites only.

PK Sampling in Epoetin Alfa Arm

	Baseline/Day 1 TIW	Week 1 TIW	Week 1 + 2 days	Week 11 TIW		Week 13 TIW	
	Dialysis Day	Dialysis Day	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	•						
15 minutes (pre-dose)		•	•				
2 hours ± 15 minutes (post-dose)		•					
3.5 hours ± 15 minutes (post-dose)		•					
5 hours ± 30 minutes (post-dose)		•					
7 hours ± 30 minutes (post-dose)		•					
10.5 hours ± 1.5 hours (post-dose)		•					

Note: Gray shading indicates sample collection at a subset of study sites only.

CLINICAL PROTOCOL

PHASE 2, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS STUDY OF ORAL VADADUSTAT FOR THE TREATMENT OF ANEMIA IN HEMODIALYSIS SUBJECTS CONVERTING FROM EPOETIN ALFA

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0025
US IND Number:	102,465
Phase:	Phase 2
Protocol Version / Date:	Amendment 1 (Version 2.0 / 11 SEPTEMBER 2018) Original Version 1.0 / 27 JUNE 2018
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Cambridge, MA 02142 United States of America

1 SIGNATURE PAGES

1.1 Protocol Approval

[redacted]

Signature

Date

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Date

[redacted]

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Phone Number

_____

Full Address

_____

_____

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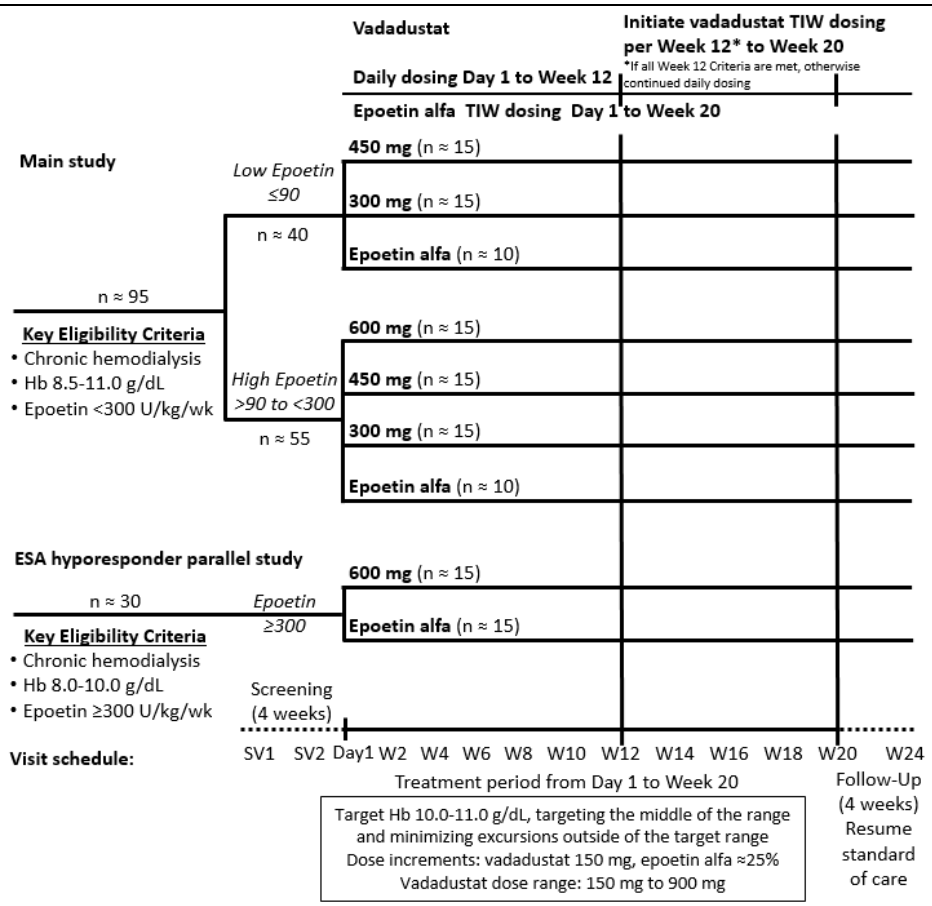
2 PROTOCOL SYNOPSIS

Study Title	Phase 2, Randomized, Open-Label, Active-Controlled, Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics Study of Oral Vadadustat for the Treatment of Anemia in Hemodialysis Subjects Converting from Epoetin Alfa
Protocol Number	AKB-6548-CI-0025
Study Phase	Phase 2
Investigational Product	Vadadustat; 150 mg tablets
Reference Medicinal Product	Epoetin alfa solution for intravenous (IV) injection in multi-dose vials or in single-dose vials
Study Population	The Main study population will consist of adult subjects receiving chronic, outpatient in-center hemodialysis three times weekly (TIW), with 2 screening hemoglobin (Hb) values between 8.5 and 11.0 g/dL (inclusive) and on maintenance treatment with epoetin alfa <300 U/kg/week. The erythropoiesis stimulating agent (ESA) hyporesponder parallel study will consist of adult subjects receiving chronic, outpatient in-center hemodialysis TIW, with 2 screening Hb values between 8.0 and 10.0 g/dL (inclusive) and on maintenance treatment with epoetin alfa ≥300 U/kg/week.
Study Sites	Approximately 40 study sites in the United States
Planned Number of Subjects	Approximately 125 subjects • Main study: ~95 subjects • ESA hyporesponder parallel study: ~30 subjects
Primary Objective	To assess the efficacy and safety of daily dosing of vadadustat compared to epoetin alfa for 12 weeks in hemodialysis subjects
Secondary Objectives	• To assess the efficacy and safety of TIW dosing of vadadustat in selected hemodialysis subjects who have been successfully managed with daily dosing of vadadustat through Week 12 • To evaluate the pharmacokinetics (PK)/pharmacodynamics (PD) of daily and TIW dosing of vadadustat in hemodialysis subjects compared to epoetin alfa • To assess the efficacy and safety of several dosing strategies of vadadustat compared to epoetin alfa during a 20-week Treatment Period in hemodialysis subjects
Overview of Study Design	This is a Phase 2, randomized, open-label study to evaluate vadadustat for the treatment of anemia in hemodialysis subjects converting from epoetin alfa therapy. For all subjects (Main and ESA hyporesponder parallel study), the study will include a Screening Period, a Treatment Period, and a Safety Follow-Up Period as described below. PK and PD sampling will be done throughout the study (see PK and PD Sampling sections for details). The aim is to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Screening Period (up to 28 days; Day -28 to Baseline/Day 1) For all subjects (Main and ESA hyporesponder parallel study) the Screening Period starts at the time the informed consent is signed and will be a maximum of 28 days in duration. Baseline/Day 1 will be performed within 28 days of the start of Screening. Subjects who meet all eligibility criteria will be randomized to a vadadustat treatment arm or an epoetin alfa treatment arm. Subjects will be required to stop epoetin alfa treatment for a minimum duration of 5 days before Baseline/Day 1 in the Main study and for a minimum of 2 days before Baseline/Day 1 in the ESA hyporesponder parallel

	study. In the Main study, randomization will be stratified by the mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to Screening Visit 2 (SV2). • Low epoetin alfa dose group (≤90 units [U]/kg/week) or • High epoetin alfa dose group (>90 to <300 U/kg/week) **Study Treatment Period (Baseline/Day 1 to Week 20)** For all subjects (Main and ESA hyporesponder parallel study), the Treatment Period will run from Baseline/Day 1 to Week 20. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/L, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range. Subjects in the Main study randomized to vadadustat: • Subjects in the low epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300 mg or 450 mg daily. • Subjects in the high epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300 mg, 450 mg, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat: • Subjects will receive a starting dose of vadadustat 600 mg daily. Transition to TIW for all subjects randomized to vadadustat: All subjects randomized to vadadustat (Main and ESA hyporesponder parallel study) who complete the 12-week once daily dosing regimen and who meet all the Week 12 transition criteria for switching from daily to TIW dosing, will initiate TIW dosing at a starting dose one tablet greater (+150 mg) than the final dose in the daily dosing period. Subjects who do not meet criteria for switching from daily to TIW dosing will remain on daily dosing. Subjects in both the Main and ESA hyporesponder parallel study randomized to epoetin alfa: All subjects randomized to epoetin alfa will receive TIW dosing for the entire Treatment Period based on the subject's central laboratory Hb value and the approved epoetin alfa United States (US) Package Insert (PI) for adult patients with chronic kidney disease (CKD) on dialysis. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range. **Safety Follow-Up Period (Weeks 20 to 24)** For all subjects (Main and ESA hyporesponder parallel study), the 4-week Safety Follow-Up Period starting at Week 20 will be followed by a post-treatment safety assessment conducted at the beginning of Week 24.

Study Schematic	
Study Duration	Individual subjects will participate in the study for up to 28 weeks, including a Screening Period of up to 4 weeks, a 20-week Treatment Period and a 4-week Safety Follow-Up Period.
Inclusion Criteria	Subjects must meet the following inclusion criteria: 1. ≥18 years of age 2. Receiving chronic, outpatient in-center hemodialysis (TIW) for end-stage renal disease for at least 12 weeks prior to Screening 3. Maintained on IV epoetin alfa therapy for 8 weeks prior to and including Screening through SV2 4. Eligibility in the Main study and ESA hyporesponder parallel study is based on the following mean weekly epoetin alfa doses: • Main study: Mean weekly epoetin alfa dose <300 U/kg/week for 8 weeks prior to SV2 • ESA hyporesponder parallel study: Mean weekly epoetin alfa dose ≥300 U/kg/week for 8 weeks prior to SV2 5. Two Hb values measured at least 4 days apart by the central laboratory during Screening as indicated below • Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive • ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive 6. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening

	7. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening 8. Hemodialysis adequacy as indicated by single-pool Kt/V_{urea} ≥1.2 using the most recent historical measurement within 8 weeks prior to or during Screening 9. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.
Exclusion Criteria	Subjects must not meet any of the following exclusion criteria: 1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia) 2. Active bleeding or recent blood loss within 8 weeks prior to randomization 3. Red blood cell (RBC) transfusion within 8 weeks prior to randomization 4. Anticipated to discontinue hemodialysis during the study 5. Judged by the Investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study 6. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver) 7. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >1.5 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded. 8. Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of epoetin alfa 9. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening 10. History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Subjects with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded. 11. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening 12. History of hemosiderosis or hemochromatosis 13. History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded) 14. Scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months 15. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded) 16. Known hypersensitivity to vadadustat, epoetin alfa, or any of their excipients 17. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to Screening (subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation) 18. Previous participation in this study, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor other than vadadustat

	19. For female subjects: a. Of non-childbearing potential i. Inability to confirm surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or ii. Not considered post-menopausal (no menses for >1 year with follicle stimulating hormone >40 U/L at Screening) b. Or, if of childbearing potential i. Lack of confirmation of the use of acceptable forms of contraception* for a minimum of one complete menstrual cycle prior to Screening ii. Positive serum pregnancy test at SV2 iii. Unwilling to use two acceptable forms of contraception* (at least one of which must be a barrier method) starting Baseline/Day 1, throughout the Treatment Period and for 30 days after the final study drug administration 20. Breastfeeding during Screening or throughout the Treatment Period and for 30 days after the final study drug administration. 21. Donation of ova starting at Screening, throughout the Treatment Period, and for 30 days after the final study drug administration. 22. Male subjects who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception* during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat. 23. Subjects with bilateral native nephrectomy. 24. Any other reason, which in the opinion of the Investigator, would make the subject not suitable for participation in the study. * *Acceptable forms of contraception include:* • *Established use of oral, injected or implanted hormonal methods of contraception.* • *Placement of an intrauterine device or intrauterine system.* • *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.*
Retesting/Rescreening	**Retesting** Retesting is defined as repeating laboratory tests within the same Screening Period. Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 4-week Screening Period, per Investigator discretion. **Rescreening** Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the Investigator if it is considered that the subject status has changed, and the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on inclusion criteria values for 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). A new informed consent is required to be signed prior to every rescreening.

Efficacy Endpoints	**Primary Endpoint** Mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 10 to 12) **Key Secondary Endpoints** • Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) • For subjects who transitioned to TIW vadadustat dosing, mean change in Hb from primary evaluation period (average Hb from Weeks 10 to 12) to the secondary evaluation period (average Hb from Weeks 18 to 20) **Other Secondary Endpoints** • Mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 18 to 20) • Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • For subjects who transitioned to TIW vadadustat dosing, proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • Proportion of subjects with a mean increase in Hb from Baseline to the primary evaluation period ≥0.5 g/dL (average Hb from Weeks 10 to 12) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) • Proportion of subjects with a mean increase in Hb from Baseline to the secondary evaluation period ≥0.5 g/dL (average Hb from Weeks 18 to 20) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • IV iron supplementation • ESA rescue • RBC transfusion **Exploratory Endpoints** [redacted]
PK/PD Endpoints	An exposure-response analysis of vadadustat and PD measures will be conducted as deemed appropriate. The PK parameters will include (but are not limited to) the following: • AUC_{last} • AUC_{inf} • Time to reach C_{max} (T_{max}) • Apparent total body clearance (CL/F) • Apparent volume of distribution (V_d/F) • Terminal half-life ($t_{1/2}$)

	The PD parameters will include (but are not limited to) the following: • Erythropoietin (EPO) • Reticulocytes • Iron • Ferritin • Total iron binding capacity (TIBC) • Hepcidin
Safety Endpoints	• Adverse events (AEs) • Vital sign measurements and clinical laboratory values • Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL • Hb <8.0 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (Main Study); Hb <7.5 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (ESA hyporesponder parallel study) • Hb increase >1.0 g/dL within any 2-week interval
Dosage and Regimens	The aim is to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Dosing will be initiated at Baseline/Day 1 and the first dose of vadadustat will be administered at the study site after other Baseline/Day 1 procedures have been completed. Thereafter, vadadustat will be taken once daily on an outpatient basis. Subjects may take vadadustat with or without food and will be instructed to swallow the tablet(s) whole. Subjects will be instructed to take vadadustat at roughly the same time each day. Epoetin alfa dose will be administered intravenously at the hemodialysis clinic, based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis. **Note:** For all subjects, no epoetin alfa will be administered after SV2 after the subject has met all eligibility criteria and before Baseline/Day 1, for a minimum duration of 5 days in the Main study and 2 days in the ESA hyporesponder parallel study. <u>Main Study:</u> Subjects will be randomized to either a vadadustat treatment arm or epoetin alfa treatment arm. Randomization will be stratified by mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to SV2: • Low epoetin alfa dose group (≤90 U/kg/week) or • High epoetin alfa dose group (>90 to <300 U/kg/week) In the low epoetin alfa dose group, subjects will be randomized in a 3:3:2 ratio to receive either an initial vadadustat daily dose of 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa. In the high epoetin alfa dose group, subjects will be randomized in a 3:3:3:2 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets), 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa. <u>ESA Hyporesponder Parallel Study</u> Subjects will be randomized in a 1:1 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets) or epoetin alfa.

Epoetin alfa arm in both the Main study and ESA hyporesponder parallel study:

For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.

Study Drug Guidelines for Dose Adjustment

Dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment (see below). Hb will be monitored via central laboratory throughout the study to determine if the dose of study drug (vadadustat or epoetin alfa) will be adjusted, interrupted, or maintained as follows:

- Dose adjustments are based on the Investigator's clinical discretion, incorporating the protocol guidance below as well as the subject's current Hb level, trajectory, and variability; symptoms; cardiovascular risk; and other features of his/her clinical condition(s).
- If a dose increase or decrease is required to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for epoetin alfa approximately 25%).
- In general, do not increase the dose more frequently than once every 4 weeks. A one-time dose increase after 2 weeks is allowed on only two occasions.
    - A subject's dose may be increased by 1 dose level if the subject has a decline in Hb ≥0.5 g/dL from Baseline/Day 1 in the first 2-week period (the initial period from Baseline/Day 1 to Week 2 following conversion from prior epoetin alfa therapy).
    - A subject's dose may also be increased by 1 dose level in the first 2-week period after initiation of TIW dosing (from Week 12 to Week 14) for subjects that meet criteria for transitioning from daily to TIW dosing.
- Reduce or interrupt the dose in the setting of a rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Reduce or interrupt the dose in the setting of Hb >11.0 g/dL
- Interrupt the dose in the setting of a Hb >12.0 g/dL until Hb value falls below 11.0 g/dL. After Hb falls below 11.0 g/dL, restart study drug and consider restarting at a lower dose.

The minimum dose of vadadustat will be 150 mg daily or TIW (1 tablet daily/TIW) and the maximum dose will be 900 mg daily or TIW (6 tablets daily/TIW).

Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen

All subjects randomized to vadadustat who complete 12 weeks of once daily dosing regimen **and** who meet all the Week 12 criteria below will be transitioned to a TIW vadadustat dosing regimen. Subjects who meet all of the Week 12 criteria will transition to TIW dosing.

Week 12 Transition criteria:

- Vadadustat daily dose of 600 mg or lower at Week 12
- Hb within target range of 10.0 to 11.0 g/dL, inclusive, at Week 12 confirmed by central laboratory Hb value from Week 11 (11 weeks of treatment completed)
- No receipt of rescue therapy (ESA or RBC transfusion) for worsening of anemia due to CKD from Baseline to Week 12.
    - ESA or RBC transfusion prior to Week 12 for reasons unrelated to worsening of anemia due to CKD (e.g., surgery, gastrointestinal bleed, or inadvertent administration) is not considered rescue therapy

	• No other reason, based on the Investigator's clinical discretion, that would make the subject not suitable for TIW dosing. Selected subjects who meet Week 12 transition criteria will transition to the TIW vadadustat dosing regimen at the Week 12 visit. Subjects on 150 mg, 300 mg, 450 mg, or 600 mg of vadadustat daily at the Week 12 visit will transition to an initial vadadustat TIW dose one tablet greater (+150 mg), i.e., 300 mg, 450 mg, 600 mg, or 750 mg vadadustat TIW, respectively. Subjects will be instructed to take vadadustat on dialysis days. After 2 weeks of treatment in the TIW vadadustat dosing regimen (at Week 14), subjects in any vadadustat TIW dosing arms who have a decline in Hb ≥0.5 g/dL will be eligible for a dose increase by 1 tablet, based on the Investigator's clinical discretion. Subjects who are not eligible to switch from daily vadadustat to TIW dosing at Week 12 will remain on daily dosing for the remainder of the study. Subjects on TIW dosing may be converted back to vadadustat once daily dosing at the discretion of the Investigator in the setting of inadequate Hb response. The starting daily dose after the switch from TIW to daily dosing will be based on the Investigator's discretion after review of the subject's clinical status and dosing history, in particular, the daily dose previously administered to the subject prior to the transition to TIW dosing (Week 12). Subjects who switch from vadadustat TIW to daily dosing will continue once daily vadadustat until the end of the Treatment Period. Subjects in the vadadustat arm will be guided for dosing compliance using an electronic diary (eDiary).
PK/PD Sampling - vadadustat arm	Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below (see Appendix B). Preferably, PK/PD samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week). At Baseline/Day 1, PK/PD samples will be collected prior to dialysis and administration of vadadustat. At Week 1 (after at least a full week of vadadustat treatment), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose On the following non-dialysis day, blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes post-dose At Week 11, vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

<table>
<tr><td></td><td>At Week 13 (after at least one week on TIW vadadustat dosing regimen), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:
15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes hours post-dose
From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose
Note: Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Week 13 PK/PD sampling.</td></tr>
<tr><td>PK Sampling - epoetin alfa arm</td><td>Blood for measurement of EPO level in the epoetin alfa arm in both the Main study and ESA hyporesponder parallel study will be collected as outlined below (see Appendix B). Preferably, PK samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).
At Baseline/Day 1, a sample will be collected prior to dialysis and administration of epoetin alfa.
At Week 1 (after at least a full week of study epoetin alfa treatment), epoetin alfa will be administered within 1 hour after start of dialysis. Blood samples will be collected as follows:
15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose
On the following dialysis day, one blood sample will be collected 15 minutes prior to administration of epoetin alfa.</td></tr>
<tr><td>Iron Supplementation</td><td>IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol below:
<table>
<tr><th></th><th>Ferritin
<200 ng/mL</th><th>Ferritin
200-500 ng/mL</th><th>Ferritin
>500 ng/mL</th></tr>
<tr><td>TSAT
<20%</td><td>IV Iron 100 mg every treatment (max 400 mg/month)</td><td>IV Iron 50 mg weekly</td><td>Hold</td></tr>
<tr><td>TSAT
20-50%</td><td>IV Iron 100 mg every week</td><td>IV Iron 50 mg weekly</td><td>Hold</td></tr>
<tr><td>TSAT
>50%</td><td>Hold</td><td>Hold</td><td>Hold</td></tr>
</table>
Intra-dialytic iron preparations (e.g., Triferic) and oral iron supplementation including iron-containing phosphate binders are prohibited during the study.
Important: As the study will be assessing PK/PD parameters, and as there are no empirical data on concurrent administration of vadadustat and phosphate binders, vadadustat will not be administered concurrently with a phosphate binder. Subjects will be instructed to take phosphate binders at least 3 hours before or at least 2 hours after the dose of vadadustat based on the guidance in the phosphate binder package inserts.</td></tr>
</table>

Rescue Therapy Guidelines	To ensure the safety of subjects and to standardize the use of rescue in the study, rescue therapy guidelines are provided. 1. 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 will 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 medical necessity. Study drug (vadadustat or epoetin alfa) may be continued during the transfusion period. Reasons for RBC transfusion will be captured in the appropriate CRF. 2. ESA Use: ESA administration will be allowed when medically necessary at the discretion of the Investigator. In general, ESA will not be administered in subjects with Hb ≥8.5 g/dL, and ESA rescue will be stopped when Hb ≥9.0 g/dL. ESA therapy will be administered using an approved ESA and dosing as per the local institution's guidelines and per the approved product label. While receiving ESA therapy, subjects randomized to vadadustat must temporarily interrupt vadadustat. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA, and treatment will be resumed after the following intervals: • 2 days after last dose of epoetin alfa • 7 days after last dose of darbepoetin alfa • 14 days after last dose of methoxy polyethylene glycol-epoetin beta Following ESA administration, vadadustat will be resumed at the same dose as previously used or with one additional tablet (+150 mg) at the discretion of the Investigator. Reasons for ESA use will be captured in the appropriate CRF.
Phlebotomy	If a subject's Hb exceeds 14.0 g/dL or the rate of rise of Hb raises concern to the Investigator, the subject may be phlebotomized based on the Investigator's clinical judgment. The method of phlebotomy will be in accordance with the study site's standard clinical practice.
Concomitant Medications	1. ESA Co-administration of any ESA with vadadustat is 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 ESA Rescue) if deemed medically necessary at the discretion of the Investigator. Guidelines for ESA administration as rescue therapy are provided above. All efforts will be made to avoid inadvertent administration of ESAs resulting from adherence to ESA hemodialysis center protocols (e.g., DaVita ESA protocols for patients 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. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA. Vadadustat treatment may be resumed after the following intervals: • 2 days after last dose of epoetin alfa • 7 days after last dose of darbepoetin alfa • 14 days after last dose of methoxy polyethylene glycol-epoetin beta 2. Iron See guidance above (Iron Supplementation).

Study Completion, Subject Completion, Temporary Interruption of Study Drug, Early Discontinuation from Study (Early Termination)	**Study Completion** The study will be considered completed after all randomized subjects have completed their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination). **Subject Completion** A subject will be considered as having completed the study after completion of their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination). **Temporary Interruption of Study Drug** During the study, a subject may interrupt study drug (vadadustat or epoetin alfa) for any of the following reasons: • AE • Missed dialysis visit (epoetin alfa arm) • Investigator's discretion • Rapid rise in Hb (defined as >1.0 g/dL in any 2-week period) • Hb above 11.0 g/dL • ESA use (vadadustat arm) Unless contraindicated, treatment will be resumed whenever possible and assessed at every visit following study drug interruption. **Early Discontinuation from Study (Early Termination)** Subjects who discontinue prematurely from the study will complete the End-of-Treatment visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14. Subjects may discontinue for any of the following reasons: • AE • Investigator's discretion • Subject withdrawal of consent • Lack of efficacy • Lost to follow up despite reasonable efforts by the Investigator to locate the subject • Death • Other reasons (pregnancy, kidney transplantation, specific reasons to be documented by the Investigator) Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or epoetin alfa) permanently discontinued and will complete the End-of-Treatment (Visit 14) and Safety Follow-Up (Visit 15) visit assessments.
Study Termination/ Individual Study Site Termination	The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advanced notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator and subsequently provide written instructions for study termination. If the study has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.
Statistical Considerations	Efficacy and safety endpoint analysis will be descriptive in nature. Continuous variables will be summarized using number of subjects with mean, standard deviation (SD), median, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated.

	PK and PD parameters will be summarized using descriptive statistics: number of subjects, mean, median, SD, minimum, maximum, and coefficient of variation, geometric mean and geometric mean SD. Mean and individual plasma concentration-time profiles will be presented graphically in both linear scale and log-linear scale. The ESA hyporesponder parallel study will be analyzed separately from the main study.
PK Analysis	A population PK analysis will be conducted to describe vadadustat PK and determine the covariates that impact the PK profile (i.e., demographics, laboratory values, concomitant iron, dosing relative to dialysis, etc). PK analysis will be reported separately.
PD Analysis	An exposure-response analysis of vadadustat, EPO and other PD measures will be conducted as deemed appropriate. PD analysis will be reported separately.
Sample Size Estimation	Approximately 95 subjects are planned for enrollment in the Main study with 40 and 55 subjects randomized to the low epoetin alfa dose group and the high epoetin alfa dose group respectively. Approximately 30 subjects are planned for enrollment in the ESA hyporesponder parallel study. Sample size reflects the exploratory nature of this study. Enrollment may be increased by up to 20 additional subjects in the Main study, and by up to 30 additional subjects in the ESA hyporesponder parallel study to ensure adequate data is captured for the primary, PK/PD, and safety endpoints.
Safety Monitoring	This is an open label study allowing the study team full access to safety data which will be reviewed on a regular basis, throughout the course of the study. Safety monitoring will be performed as described in the Medical Monitor Plan.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC_{inf}	area under concentration-time curve from dosing to infinity
AUC_{last}	area under concentration-time curve from dosing to last measurable concentration
BP	blood pressure
CBC	complete blood count
CKD	chronic kidney disease
CL/F	apparent total body clearance
C_{max}	maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
DD-CKD	dialysis dependent chronic kidney disease
ECG	electrocardiogram
EDC	electronic data capture
eDiary	electronic diary
EOT	end-of-treatment
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FAS	Full Analysis Population
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Hb	hemoglobin
HF	heart failure
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl-hydroxylase
HIF-PHI	hypoxia-inducible factor prolyl-hydroxylase inhibitor
HR	heart rate
HRQOL	health-related quality of life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web Response System
LFT	liver function test
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid

NDD-CKD	non-dialysis dependent chronic kidney disease
PGI-C	patient global impression of change
PGI-S	patient global impression of severity
PHD	prolyl 4-hydroxylase domains
PI	Package Insert
PK	pharmacokinetic(s)
PD	pharmacodynamics(s)
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SF-36	36-Item Short-Form General Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TIW	three times a week
T_{max}	time to reach C_{max}
TSAT	transferrin saturation
U	unit
ULN	upper limit of normal
US	United States
V_d/F	apparent volume of distribution
VEGF	vascular endothelial growth factor

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% to 16% of the population (Jha 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, infection, cancer, and mortality (Iseki 2007).

The prevalence and severity of renal anemia in CKD increases as renal function deteriorates (Di Iorio 2007; Stauffer 2014). As CKD progresses, the combined effect of decreased red blood cell (RBC) production from lower erythropoietin (EPO) signaling, increased rate of RBC destruction, and reduced iron availability to the bone marrow results in the increased prevalence and severity of anemia (Pergola 2016). Anemia generally exists when hemoglobin (Hb) is less than 13.0 g/dL in men or less than 12.0 g/dL in women (KDIGO 2012). Three principal factors contribute to the development of anemia as CKD progresses:

- Peritubular fibroblasts, a type of cell in the kidney, are designed to sense the amount of oxygen carried by the blood. These cells secrete EPO to adjust the production of RBCs by the bone marrow and maintain circulating oxygen levels at normal physiologic levels. As kidney disease progresses, the number of peritubular fibroblasts is reduced and EPO secretion is significantly decreased, leading to a reduction in RBC production (Iseki 2007; Nurko 2006).
- On average, the RBCs in CKD patients have a shorter lifespan (approximate lifespan of 70 days) compared with the RBCs in healthy people (approximate lifespan of 90 to 120 days) (Ly 2004; Nurko 2006). Such a condition leads to increased RBC production in CKD patients to maintain normal physiologic levels.
- The availability of iron to the bone marrow is impaired. Iron is a required component in the formation of Hb, and is essential for the transport of oxygen to the tissues of the body.

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

The risks associated with erythropoiesis-stimulating agents (ESAs), including an increased risk of death and cardiovascular events (Besarab 1998; Drueke 2006; Pfeffer 2009a; Pfeffer 2009b; Singh 2006), 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 dialysis dependent CKD (DD-CKD) patients remains high. To fulfill this unmet need, the vadadustat clinical program is focused on developing an orally active therapeutic agent 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 (HIF-PHs) for the treatment of anemia associated with CKD. HIF-PH enzymes are also referred to as prolyl 4-hydroxylase domains (PHDs), of which the 2 most commonly expressed isoforms 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.

The efficacy, safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of vadadustat have been characterized in 10 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 non-dialysis dependent CKD (NDD-CKD) subjects, 1 completed Phase 2b study in NDD-CKD subjects, and 1 completed Phase 2 study in DD-CKD subjects. The United States (US) 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, double-blind, placebo-controlled study with 5 different dose groups dosed for 42 days. The US Phase 2b, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 20 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 16 weeks. The US Phase 2 open-label study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. In the studies completed to date, a total of 630 subjects have received vadadustat, including 200 healthy volunteers and 430 subjects with CKD.

Vadadustat has shown 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 and Hb 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 consistent bioavailability with area under concentration-time curve (AUC) and C_{max} 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 for 10 days. The plasma half-life of vadadustat was about 4 to 6 hours, 7 to 8 hours, and 9 to 10 hours in healthy subjects, NDD-CKD patients, and DD-CKD patients, respectively.

Vadadustat is extensively metabolized and its metabolites are eliminated from the body by dual routes of excretion (both 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.

Multiple doses of 700 mg and 900 mg daily for up to 10 days (Study AKB-6548-CI-0002 [CI-0002]) and single doses of 1200 mg (Study AKB-6548-CI-0001 [CI-0001], Study AKB-6548-CI-0010 [CI-0010]) have been examined in healthy volunteers. Vadadustat demonstrated dose-proportional PK and achieved serum EPO concentrations up to 34.4 mIU/mL, levels considered physiologic and below exposures achieved with injectable ESAs (Besarb 1992). A higher incidence of adverse events (AEs) in the gastrointestinal System Organ Class (SOC) – nausea, diarrhea, abdominal pain, dyspepsia – was observed in groups treated with 700 mg, 900 mg, or 1200 mg compared with lower vadadustat doses or placebo. Most AEs were mild to moderate, short-lived (1 or 2 days), and assessed as unrelated by investigators. No AEs led to study withdrawal, and no serious adverse events (SAEs) were reported. No clinically meaningful changes or abnormalities in vital signs, safety laboratory studies, or ECG parameters were reported.

A 16-week, open-label, multicenter, Phase 2 trial evaluated vadadustat in 94 subjects receiving chronic hemodialysis previously maintained on epoetin alfa and IV iron form the 3 months prior to Screening (Study AKB-6548-CI-0011 [CI-0011]). Subjects were assigned to one of three vadadustat dose cohorts: 300 mg daily, 450 mg daily, or 450 mg three times a week (TIW). Dosing was fixed for the first 8 weeks; for the subsequent 8 weeks dose was adjusted according to Hb response based upon a dose adjustment algorithm. Sixty-nine of the 94 subjects completed the study. The primary endpoint was the mean Hb concentration change from pre-treatment average (Screening Visit 1, Screening Visit 2, and Baseline Visit) to mid-study (Weeks 7 to 8) and end-of-study (Weeks 15 to 16) and was analyzed using observed Hb values (no imputation for missing data). No statistically significant mean change in Hb from pre-treatment average was observed for either of the two time points for any of the three treatment groups.

Among subjects randomized to an initial dose of 300 mg daily, 450 mg daily, or 450 mg TIW, 0% (0 of 30), 3% (1 of 33), and 19% (6 of 31) of subjects withdrew from the study due to worsening anemia, respectively. In a sensitivity analysis using last observation carried forward (LOCF) for the primary efficacy endpoint, no significant mean change in Hb from pre-treatment levels was observed in the 300 mg daily dosing group. At Weeks 15 to 16, modest, statistically significant mean decreases were observed in the 450 mg daily and 450 mg TIW dosing groups.

In a post-hoc univariate analysis of baseline characteristics, higher pre-baseline epoetin alfa dose was associated with a decrease in mean Hb at Weeks 7 to 8 and Weeks 15 to 16 in the dosing cohorts. Subjects who discontinued the study due to worsening anemia had a higher mean pre-baseline epoetin alfa dose compared with subjects who discontinued due to other reasons or subjects who completed the study.

Based on 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.

In the ongoing global Phase 3 and Japanese Phase 3 clinical studies, over 7000 subjects are planned to be treated with vadadustat or comparator.

This study will evaluate efficacy, safety and PK/PD with different vadadustat dosing strategies in hemodialysis subjects converting from epoetin alfa to further characterize the optimal vadadustat regimen.

4.3 Potential Benefits and Risks

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

Trials of injectable 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 2009a). Post-hoc analyses performed by the Food and Drug Administration (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 2007). Potential clinical benefits include enhanced erythropoiesis and decreased exogenous iron requirements.

In nonclinical safety studies, the main findings originated from an exaggerated pharmacological response that results in increased erythropoiesis, polycythemia, blood hyperviscosity, and the formation of fibrin thrombi in multiple organs. Early mortality noted in the mouse and rat and moribundity in the dog were due to the sequelae associated with polycythemia. These findings were reproducible across species and studies, dose-dependent and showed reversibility. Dose-limiting toxicity in the exploratory toxicology studies was due to hemoglobinuric nephropathy (rat) and emesis associated with body weight loss (dog).

In completed Phase 1 clinical studies of vadadustat in healthy volunteers, there were low numbers of treatment-emergent AEs. The most frequently reported AEs were in the gastrointestinal disorders (i.e., nausea, diarrhea, abdominal pain, flatulence, dyspepsia) and nervous system disorders (i.e., headache, dizziness) SOC. The majority of AEs were mild to moderate in severity.

The most frequently reported AEs in completed Phase 2 studies of NDD- and DD-CKD subjects were in the following SOCs: gastrointestinal disorders (nausea, diarrhea, vomiting), cardiovascular disorders (hypertension, hypotension, coronary artery disease), renal (renal failure chronic, renal failure acute), infections and infestations (gastroenteritis, urinary tract infection,

pneumonia), and metabolism and nutrition disorders (hyperkalemia, fluid overload). Four deaths occurred in the completed Phase 2 clinical studies.

Identified risks include nausea, diarrhea, vomiting, headache, abdominal pain, and uric acid elevations. Hypersensitivity, hyperkalemia and hypertension have been identified as potential risks associated with vadadustat therapy.

Review of safety data from completed Phase 1 and 2 clinical studies, as well as review of accumulating data from ongoing studies, continue to support further development of the vadadustat program.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

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

5.2 Secondary Objectives

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

5.3 Efficacy Endpoints

5.3.1 Primary Endpoints

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

5.3.2 Key Secondary Endpoints

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

5.3.2.1 Other Secondary Endpoints

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

- Intravenous (IV) iron supplementation
- ESA rescue
- RBC transfusion

5.3.2.2 Exploratory Endpoints

[redacted]

5.4 PK/PD Endpoints

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

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

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

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

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

5.5 Safety Endpoints

Safety endpoints in this study include the following:

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

6 STUDY DESIGN

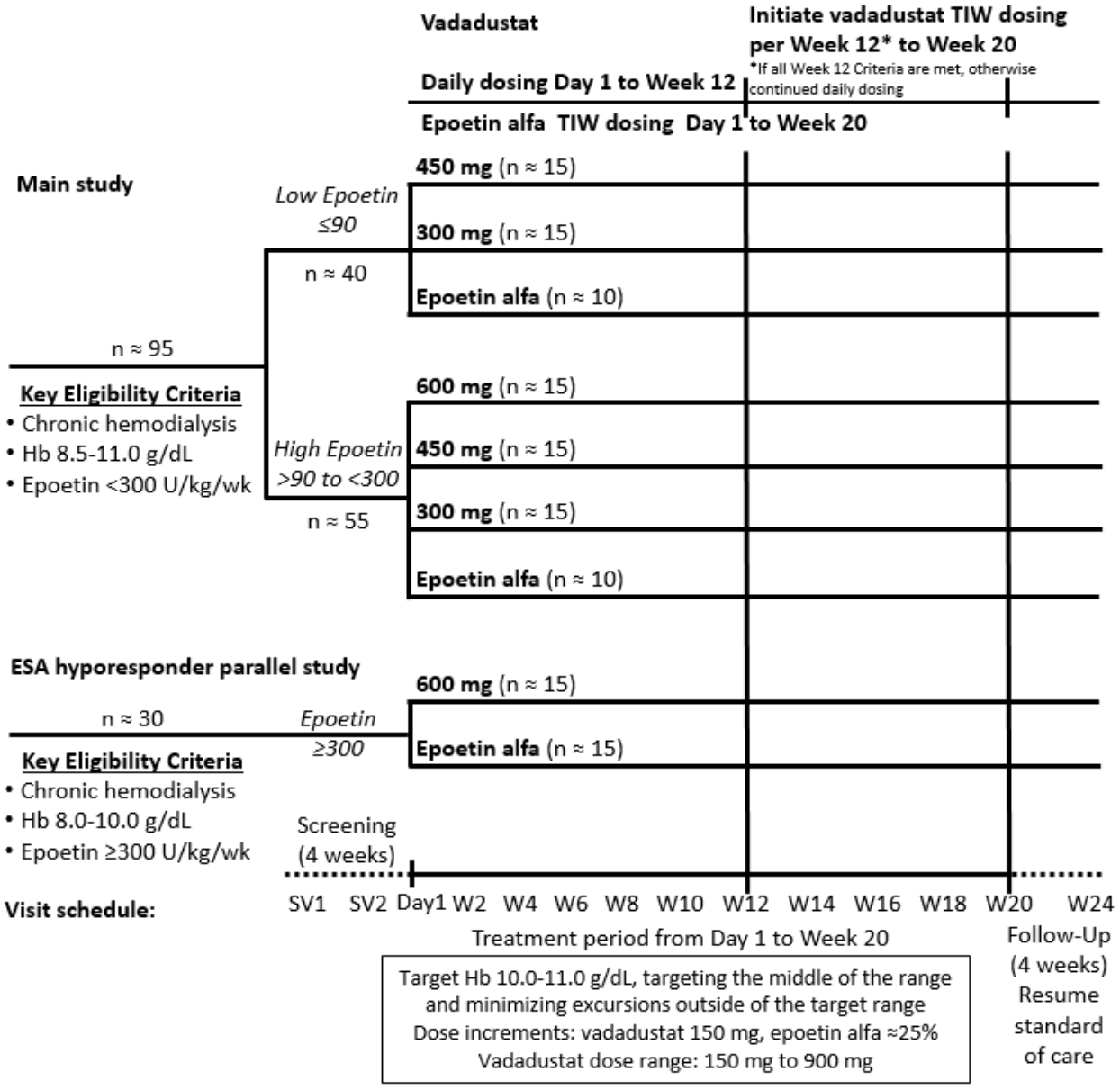
6.1 Study Design

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

For all subjects (Main and ESA hyporesponder parallel study), the study (as shown in Figure 1) will include a Screening Period, a study Treatment Period, and a Safety Follow-Up Period as described below. PK and PD sampling will be done throughout the study (see PK and PD Sampling Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa, respectively, for details).

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

Figure 1: Overview of Study Design



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

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

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

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

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

6.1.2.1 Vadadustat Treatment

Subjects in the Main study randomized to vadadustat:

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

Subjects in the ESA hyporesponder parallel study randomized to vadadustat:

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

Transition to TIW for all subjects randomized to vadadustat:

All subjects randomized to vadadustat (Main and ESA hyporesponder parallel study), who complete the 12-week once daily dosing regimen and who meet all the Week 12 transition criteria for switching from daily to TIW dosing, will initiate TIW dosing at a starting dose one tablet greater (+150 mg) than the final dose in the daily dosing period (see Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen).

Note: Subjects who are not eligible to switch from daily vadadustat to TIW dosing at Week 12 will remain on daily dosing from the remainder of the study (see Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment).

6.1.2.2 Epoetin Alfa Treatment

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

All subjects randomized to epoetin alfa will receive TIW dosing for the entire Treatment Period based on the subject's central laboratory Hb value and the approved epoetin alfa United States (US) Package Insert (PI) for adult patients with CKD on dialysis. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range (see Section 8.4.4, Epoetin Alfa Dosing Regimen).

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

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

6.2 Rationale for Study Design

The Main Study and the ESA hyporesponder parallel study will evaluate different starting doses of vadadustat based on pre-baseline ESA doses. Numerous studies have demonstrated that hemodialysis patients requiring higher ESA doses to treat their anemia have a higher burden of comorbidities, a more inflammatory state, and a greater risk of adverse outcomes (Besarb 1998; Parfrey 2005; Unger 2010). As described above (Section 4.2, Summary of Clinical Experience) in a Phase 2 hemodialysis study (CI-0011), a post-hoc analysis suggested higher pre-baseline ESA doses were associated with lower observed mean Hb levels. Subjects on higher pre-baseline ESA doses may benefit from a higher starting dose of vadadustat after initial conversion from ESAs.

Three levels of pre-baseline ESA dose will be evaluated. In the Main Study subjects will be randomized to one of two cohorts based on pre-baseline ESA dose (≤90 U/kg/week and >90 to <300 U/kg/week). The ESA threshold of 90 U/kg/week was based on the median ESA doses reported in the US Renal Data System and US Dialysis Outcomes and Practice Patterns Study, which ranged from approximately 90 to 110 U/kg/week.

The ESA hyporesponder parallel study will evaluate subjects with Hb levels below the target range despite receiving ≥300 U/kg/week of epoetin alfa. This ESA threshold was based on the definition of resistance to ESAs proposed in the ERA-EDTA 2004 guidelines (Locatelli 2004).

The Main study and the ESA hyporesponder parallel study incorporate an approach to vadadustat dose adjustment designed to maximize the probability that Hb can be maintained within the target range of 10.0 to 11.0 g/dL, inclusive (see Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment). The approach to vadadustat dose adjustment in this Phase 2 study includes several modifications as compared to the vadadustat dosing algorithms used in previously completed Phase 2 studies and the dosing algorithm used in the ongoing Phase 3 studies.

During this study, dose increases for vadadustat will be allowed at 4-week intervals, with the exception of the initial 2 weeks of treatment, in the daily and TIW dosing periods of the study. Dose increases will be permitted in the initial 2 weeks of treatment, in the daily and TIW dosing periods, in subjects with a Hb decline ≥0.5 g/dL from baseline and Week 12, respectively. This approach is commonly used in clinical practice to treat patients with declining or low Hb values (Pfeffer 2009a; Singh 2006). Risk of abrupt or excessive increases in Hb is minimized due to the underlying Hb trajectory and is further mitigated by close Hb monitoring.

In the present study, the safety and efficacy of a vadadustat TIW dosing regimen is being evaluated as a potential alternative treatment regimen to a once daily dosing regimen in hemodialysis subjects. Specifically, this study will evaluate conversion from once daily dosing to TIW dosing. As described above (Section 4.2, Summary of Clinical Experience), the 16-week Phase 2 hemodialysis study evaluated hemodialysis subjects switching from ESA to vadadustat 450 mg TIW for an 8-week fixed-dose period followed by 8 weeks of dose adjustment according to Hb response. The primary efficacy analysis in CI-0011 using observed data showed stable mean Hb levels in this group. Six of 31 (19%) subjects withdrew due to worsening anemia, and a sensitivity analysis imputing missing Hb values using LOCF demonstrated a decline in mean Hb levels. To maximize the probability that subjects treated with vadadustat TIW will maintain Hb levels within the target range, this study will: examine subjects successfully treated with

daily dosing converting to TIW dosing; allow for earlier dose increase after 2 weeks of initial treatment; and permit dose increases up to 900 mg TIW.

6.3 Dose Justification

In this study, vadadustat starting daily doses will be determined by pre-baseline ESA dose (Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment). In the Main study starting doses of vadadustat will be 300 mg and 450 mg daily in subjects converting from epoetin alfa doses ≤90 U/kg/week and 300 mg, 450 mg, and 600 mg daily in subjects converting from epoetin alfa doses >90 to <300 U/kg/week. For the ESA hyporesponder parallel study, the starting doses will be 600 mg daily. As described above (Section 4.2, Summary of Clinical Experience), the maximum vadadustat starting dose evaluated in completed Phase 2 NDD-CKD studies was 630 mg or 600 mg daily, in Study AKB-6548-CI-0005 (CI-0005) and Study AKB-6548-CI-0021 (CI-0021) respectively, and in completed Phase 2 DD-CKD studies was 450 mg or 600 mg in Study AKB-6548-CI-0011 (CI-0011) and Study AKB-6548-CI-0022 (CI-0022), respectively.

Based on the dosing algorithm, vadadustat will be titrated to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive. The dose range for titration is 150 mg to 900 mg daily or TIW. Doses of 150 mg to 630 mg daily have been evaluated in studies evaluating subjects with NDD-CKD and DD-CKD. The maximum vadadustat dose evaluated in healthy volunteers was 1200 mg in a single dose study (CI-0001 and CI-0010) and 900 mg daily in a 10-day multiple dose study (CI-0002), as described in Section 4.2, Summary of Clinical Experience.

The rationale to evaluate higher maximum doses for titration is that to date, dose-ranging clinical studies have not identified a vadadustat dose at which a plateau in exposure or effect has been observed. In Phase 1 studies in healthy volunteers, dose-proportional increases in AUC and C_{max} and dose-related increases in serum EPO were observed up to the maximum doses studied, single doses of 1200 mg and multiple doses of 900 mg daily for 10 days (CI-0001, CI-0002). In Phase 2 studies in anemic NDD-CKD and DD-CKD subjects, dose-dependent increases in Hb were observed up to the maximum dose studied of 600 mg or 630 mg daily (CI-0005, CI-0021, CI-0022). It is anticipated that daily doses of vadadustat at 750 mg or 900 mg would yield an incremental erythropoietic effect greater than 600 mg for the treatment of renal anemia.

This study design mitigates the risk of vadadustat doses of 750 mg or 900 mg. Intensive Hb monitoring, a strict dose adjustment algorithm, and phlebotomy will be implemented to mitigate the potential risk of a rapid Hb rise, as follows:

- Hb measurements are scheduled at least every 2 weeks to Week 20
- The dose adjustment algorithm will target a narrow Hb range, 10.0 to 11.0 g/dL, inclusive
- The protocol specifies that phlebotomy may be considered in the setting of high Hb levels (>14.0 g/dL) or a high Hb rate of rise, based on the Investigator's judgment

Importantly, the Phase 2 studies demonstrated that cessation of treatment resulted in prompt reduction in mean Hb to baseline values.

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 the subject must meet all eligibility criteria. No study procedures (including Screening tests) may be performed until after the informed consent has been legally signed.

7.2 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. ≥18 years of age
2. Receiving chronic, outpatient in-center hemodialysis (TIW) for ESRD for at least 12 weeks prior to Screening
3. Maintained on IV epoetin alfa therapy for 8 weeks prior to and including Screening through SV2
4. Eligibility in the Main study and ESA hyporesponder parallel study is based on the following mean weekly epoetin alfa doses:
    - Main study: Mean weekly epoetin alfa dose <300 U/kg/week for 8 weeks prior to SV2
    - ESA hyporesponder parallel study: Mean weekly epoetin alfa dose ≥300 U/kg/week for 8 weeks prior to SV2
5. Two Hb values measured at least 4 days apart by the central laboratory during Screening as indicated below
    - Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive
    - ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive
6. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening
7. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening
8. Hemodialysis adequacy as indicated by single-pool Kt/V_{urea} ≥1.2 using the most recent historical measurement within 8 weeks prior to or during Screening
9. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.

7.3 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia)
2. Active bleeding or recent blood loss within 8 weeks prior to randomization
3. RBC transfusion within 8 weeks prior to randomization
4. Anticipated to discontinue hemodialysis during the study
5. Judged by the Investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study
6. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver)

7. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >1.5 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded.
8. Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of epoetin alfa
9. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening
10. History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Subjects with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded.
11. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening
12. History of hemosiderosis or hemochromatosis
13. History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded)
14. Scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months
15. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded)
16. Known hypersensitivity to vadadustat, epoetin alfa, or any of their excipients
17. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to Screening (subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation)
18. Previous participation in this study, or previous participation in a study with another hypoxia-inducible factor prolyl-hydroxylase inhibitor (HIF-PHI) other than vadadustat
19. For female subjects:
    - Of non-childbearing potential
      - Inability to confirm surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or
      - Not considered post-menopausal (no menses for >1 year with follicle stimulating hormone [FSH] >40 U/L at Screening)
    - Or, if of childbearing potential,
      - Lack of confirmation of the use of acceptable forms of contraception* for a minimum of one complete menstrual cycle prior to Screening
      - Positive serum pregnancy test at SV2
      - Unwilling to use two acceptable forms of contraception* (at least one of which must be a barrier method) starting Baseline/Day 1, throughout the Treatment Period and for 30 days after the final study drug administration (refer to Section 9.1.5, Contraception and Pregnancy Avoidance Measures)

20. Breastfeeding during Screening or throughout the Treatment Period and for 30 days after the final study drug administration.
21. Donation of ova starting at Screening, throughout the Treatment Period, and for 30 days after the final study drug administration.
22. Male subjects who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception* (refer to Section 9.1.5, Contraception and Pregnancy Avoidance Measures) during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat.
23. Subjects with bilateral native nephrectomy.
24. Any other reason, which in the opinion of the Investigator, would make the subject not suitable for participation in the study.

7.4 Retesting and Rescreening

7.4.1 Retesting

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

Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 4-week Screening Period, per Investigator discretion.

7.4.2 Rescreening

Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the Investigator if it is considered that the subject status has changed, and the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on inclusion criteria values for 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). A new informed consent is required to be signed prior to every rescreening.

7.5 Study Completion, Study Termination, and Individual Site Termination

7.5.1 Study Completion

The study will be considered completed after all randomized subjects have completed their final study visit (Visit 15/Week 24), Safety Follow-Up or Early Termination).

7.5.2 Study Termination

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advanced notice is not required if the study is stopped due to safety concerns. If a study site has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements. Criteria and procedures 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 study site for various reasons. Criteria and procedures for premature termination or suspension of an study site are detailed in Section 14.2, Criteria for Premature Termination or Suspension of Study Sites and Section 14.3, Procedures for Premature Termination or Suspension of the Study or Study Sites. If a study site has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

7.6 Subject Completion and Subject Discontinuation

7.6.1 Subject Completion

A subject will be considered as having completed the study after completion of their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination).

7.6.2 Temporary Interruption of Study Drug

Subjects who temporarily interrupt their study drug (vadadustat or epoetin alfa) after receiving the first dose and prior to completion of the study, will continue with the study visits, safety assessments, and other activities as deemed applicable through Week 20, and will complete the 4-week Safety Follow-Up Period and the Visit 15/Week 24 assessments (see Appendix A: Schedule of Activities.

During the study, a subject may interrupt study drug (vadadustat or epoetin alfa) for any of the following reasons:

- AE
- Missed dialysis visit (epoetin alfa arm)
- Investigator's discretion
- Rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Hb above 11.0 g/dL
- ESA use (vadadustat arm)

Unless contraindicated, treatment will be resumed whenever possible and assessed at every visit following study drug interruption.

7.6.3 Early Discontinuation from Study (Early Termination)

Subjects who discontinue prematurely from the study will complete the End-of-Treatment (EOT) visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14.

Subjects may discontinue for any of the following reasons:

- AE
- Investigator's discretion
- Subject withdrawal of consent

- Lack of efficacy, defined as inadequate response to vadadustat or epoetin alfa in the Investigator's opinion
- Lost to follow-up despite reasonable efforts by the Investigator to locate the subject. Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.
- Death
- Other reasons (pregnancy, kidney transplantation, specific reasons to be documented by the Investigator)

Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or epoetin alfa) permanently discontinued and will complete the End-of-Treatment (Visit 14) and Safety Follow-Up (Visit 15) visit assessments.

8 STUDY DRUG AND TREATMENT OF SUBJECTS

Subjects will receive either vadadustat or epoetin alfa according to the randomization assignments provided via the Interactive Web Response System (IWRS) (see Section 8.4.1, Randomization).

Both vadadustat and epoetin alfa will be used as open-label supplies. All study drug supplies will 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 drug for dispensing to the subject (Section 8.1, Epoetin Alfa and Section 8.2.2, Dispensing of Vadadustat) and for study drug supply accountability (Section 8.3, Vadadustat Accountability and Destruction).

8.1 Epoetin Alfa

Epoetin alfa solution for IV injection in multi-dose vials (e.g., 20,000 Units/2 mL and 20,000 Units/1 mL) or in single-dose vials (e.g., 2,000 Units/mL, 3,000 Units/mL, 4,000 Units/mL, and 10,000 Units/mL) will be provided by the sites in commercially-approved primary packaging and stored per the approved label.

8.2 Vadadustat

8.2.1 Supplies and Storage

Vadadustat will be provided as 150 mg, white to off-white, round, bi-convex film-coated, debossed or non-debossed 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 and local regulatory requirements.

Dose levels utilized in this study will include: 150 mg (1 tablet), 300 mg (2 tablets), 450 mg (3 tablets), 600 mg (4 tablets), 750 mg (5 tablets), and 900 mg (6 tablets) per day or TIW.

Vadadustat will be stored per the product label.

8.2.2 Dispensing of Vadadustat

At Baseline/Day 1, subjects who are randomized to vadadustat treatment will be administered the first dose of vadadustat at the study site.

Thereafter, vadadustat will be taken once daily from Baseline/Day 1 to Week 12 and TIW from Weeks 12 to 20 **if** Week 12 criteria are met (Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen). If the Investigator determined criteria for Week 12 is not met, daily dosing will continue on an outpatient basis. Subjects who are randomized to the vadadustat treatment arm will be provided with up to 2 bottles of vadadustat. Each bottle of vadadustat will contain 100 tablets of vadadustat (150 mg/tablet). Subjects may take vadadustat with or without food and will be instructed to swallow the tablet(s) whole. Subjects will be instructed to take vadadustat at approximately the same time each day.

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

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

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

8.3 Vadadustat Accountability and Destruction

Drug accountability will be an ongoing process throughout the study. All vadadustat will 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 study site, and study drug dispensed to or returned from each subject. Records will be maintained that accurately reflect the drug accountability of vadadustat at all times. An electronic Diary (eDiary) will be utilized throughout the study to guide dosing for subjects in the vadadustat arm (see Section 9.1.2, eDiary).

Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for all vadadustat received and that all required fields are complete, accurate, and legible.

If any dispensing errors or discrepancies are discovered, the Sponsor will 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 study site will complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the Sponsor or its designee for destruction as specified by the Sponsor.

Prior to study 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 other study materials will be returned to the Sponsor or destroyed at the study site, as specified by the Sponsor. Appropriate records of the disposal will be documented and maintained. No unused vadadustat 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

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

8.4.1 Randomization

Main Study:

Subjects will be randomized to either a vadadustat treatment arm or epoetin alfa treatment arm. Randomization will be stratified by mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to SV2:

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

In the low epoetin alfa dose group, subjects will be randomized in a 3:3:2 ratio to receive either an initial vadadustat daily dose of 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa.

In the high epoetin alfa dose group, subjects will be randomized in a 3:3:3:2 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets), 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa.

ESA Hyporesponder Parallel Study:

Subjects will be randomized in a 1:1 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets) or epoetin alfa.

Note: No epoetin alfa will be administered after SV2 after the subject has met all eligibility criteria and before Baseline/Day 1, for a minimum duration of 5 days in the Main study and 2 days in the ESA hyporesponder parallel study.

8.4.2 Blinding

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

8.4.3 Measurement of Hb Levels for Dose Adjustment Consideration

Hb values will be measured by a central laboratory. Study drug treatment will aim to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Hb will be monitored throughout the study to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive (see Section 8.4.6, Guidelines for Dose Adjustments). Hb levels can be measured more frequently based on Investigator's clinical judgment.

In both the vadadustat and epoetin alfa arm, if dose adjustment is recommended based on Hb value and protocol-specified guidelines, dosing instructions can be provided to the subject over the telephone or at the next dialysis session at the study site (or dialysis center) or during an unscheduled site visit within 3 business days after receiving the Hb result from the central laboratory.

8.4.4 Epoetin Alfa Dosing Regimen

Epoetin alfa arm in both the Main study and ESA hyporesponder parallel study:

For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.

Epoetin alfa dose will be administered based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis.

From Baseline/Day 1 to Week 20, dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 and 11.0 g/dL, inclusive.

8.4.5 Vadadustat Dosing Regimen and Guidelines for Dose Adjustment

8.4.5.1 Dosing Regimen for the Vadadustat Treatment Arm

Subjects in the low epoetin alfa dose group randomized to vadadustat treatment will start at an initial dose of vadadustat 300 mg or 450 mg daily. Subjects in the high epoetin alfa dose group randomized to vadadustat treatment will receive an initial dose of 300 mg, 450 mg, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat treatment will receive a starting dose of vadadustat 600 mg daily.

After completing the 12-week once daily dosing regimen, subjects randomized to vadadustat who meet criteria for switching from daily to TIW dosing will initiate TIW dosing at a starting dose 1 tablet greater (+150 mg) than the final dose in the daily dosing period (see Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen). Subjects who do not meet criteria for switching from daily to TIW dosing will remain on daily dosing. From Baseline/Day 1 to Week 20, dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive.

8.4.5.2 Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen

All subjects randomized to vadadustat who complete 12 weeks of once daily dosing regimen **and** who meet all the Week 12 criteria below will be transitioned to a TIW vadadustat dosing regimen.

Week 12 Transition criteria:

- Vadadustat daily dose of 600 mg or lower at Week 12
- Hb within target range of 10.0 to 11.0 g/dL, inclusive, at Week 12 confirmed by central laboratory Hb value from Week 11 (11 weeks of treatment completed)
- No receipt of rescue therapy (ESA or RBC transfusion) for worsening of anemia due to CKD from Baseline/Day 1 to Week 12.
    - ESA or RBC transfusion prior to Week 12 for reasons unrelated to worsening of anemia due to CKD (e.g., surgery, gastrointestinal bleed, or inadvertent administration) is not considered rescue therapy
- No other reason, based on the Investigator's clinical discretion, that would make the subject not suitable for TIW dosing.

Selected subjects who meet Week 12 transition criteria will transition to the TIW vadadustat dosing regimen at the Week 12 visit. Subjects on 150 mg, 300 mg, 450 mg, or 600 mg of vadadustat daily at the Week 12 visit will transition to an initial vadadustat TIW dose one tablet greater (+150 mg), i.e., 300 mg, 450 mg, 600 mg, or 750 mg vadadustat TIW, respectively. Subjects will be instructed to take vadadustat on dialysis days.

After 2 weeks of treatment in the TIW vadadustat dosing regimen (at Week 14), subjects in any vadadustat TIW dosing arms who have a decline in Hb ≥0.5 g/dL will be eligible for a dose increase by 1 tablet, based on the Investigator's clinical discretion.

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

Subjects on TIW dosing may be converted back to vadadustat once daily dosing at the discretion of the Investigator in the setting of inadequate Hb response. The starting daily dose after the switch from TIW to daily dosing will be based on the Investigator's discretion after review of the subject's clinical status and dosing history, in particular, the daily dose previously administered to the subject prior to the transition to TIW dosing (Week 12). Subjects who switch from vadadustat TIW to daily dosing will continue once daily vadadustat until the end of the Treatment Period.

Subjects in the vadadustat arm will be guided for dosing compliance using an eDiary (see Section 9.1.2, eDiary).

8.4.6 Guidelines for Dose Adjustments

Dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment (see below). Hb will be monitored via central laboratory throughout the study to determine if the dose of study drug (vadadustat or epoetin alfa) will be adjusted, interrupted, or maintained as follows:

- Dose adjustments are based on the Investigator's clinical discretion, incorporating the protocol guidance below as well as the subject's current Hb level, trajectory, and variability; symptoms; cardiovascular risk; and other features of his/her clinical condition(s).
- If a dose increase or decrease is required to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for epoetin alfa approximately 25%).
- In general, do not increase the dose more frequently than once every 4 weeks. A one-time dose increase after 2 weeks is allowed on only two occasions.
    - A subject's dose may be increased by 1 dose level if the subject has a decline in Hb ≥0.5 g/dL from Baseline/Day 1 in the first 2-week period (the initial period from Baseline/Day 1 to Week 2 following conversion from prior epoetin alfa therapy).
    - A subject's dose may also be increased by 1 dose level in the first 2-week period after initiation of TIW dosing (from Week 12 to Week 14) for subjects that meet criteria for transitioning from daily to TIW dosing.
- Reduce or interrupt the dose in the setting of a rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Reduce or interrupt the dose in the setting of Hb >11.0 g/dL
- Interrupt the dose in the setting of a Hb >12.0 g/dL until Hb value falls below 11.0 g/dL. After Hb falls below 11.0 g/dL, restart study drug and consider restarting at a lower dose.

Note: The minimum dose of vadadustat will be 150 mg daily or TIW (1 tablet daily/TIW) and the maximum dose will be 900 mg daily or TIW (6 tablets daily/TIW).

8.4.7 Late or Missed Doses

Subjects on vadadustat will be instructed to take the study drug at approximately the same time each day. If a dose is forgotten, subjects will be instructed to take the dose as soon as they remember during the same day.

- Daily dosing regimen: If a forgotten dose is not remembered on the same day, the subject will skip the dose and resume the normal dosing schedule the following day.
- TIW dosing regimen: If a forgotten dose is not remembered on the same day, the subject will take the dose on the following day (a non-dialysis day). If a forgotten dose is not remembered on the same day or the following day of a long interdialytic gap, the subject will take the dose on the subsequent day (the second non-dialysis day). Thereafter, the subject should resume the normal dosing schedule.
- Subjects will not double-up on missed doses.

Epoetin alfa dose (including handling of late or missed dose) will be administered at the site and titrated based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis.

8.4.8 Iron Supplementation

IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol in Table 1.

Table 1: Iron Supplementation Protocol

	Ferritin <200 ng/mL	**Ferritin 200-500 ng/mL**	**Ferritin >500 ng/mL**
TSAT <20%	IV Iron 100 mg every treatment (max 400 mg/month)	IV Iron 50 mg weekly	Hold
TSAT 20-50%	IV Iron 100 mg every week	IV Iron 50 mg weekly	Hold
TSAT >50%	Hold	Hold	Hold

Intra-dialytic iron preparations (e.g., Triferic) and oral iron supplementation including iron-containing phosphate binders are prohibited during the study.

Important: As the study will be assessing PK/PD parameters, and as there are no empirical data on concurrent administration of vadadustat and phosphate binders, vadadustat will not be administered concurrently with a phosphate binder. Subjects will be instructed to take phosphate binders at least 3 hours before or at least 2 hours after the dose of vadadustat based on the guidance in the phosphate binder package inserts.

8.4.9 Rescue Therapy

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

8.4.9.1 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 will 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 medical necessity. Study drug (vadadustat or epoetin alfa) may be continued during the transfusion period.

Reasons for RBC transfusion will be captured in the appropriate CRF.

8.4.9.2 ESA Use

ESA administration will be allowed when medically necessary at the discretion of the Investigator. In general, ESA will not be administered in subjects with Hb ≥8.5 g/dL, and ESA will be stopped when Hb ≥9.0 g/dL. ESA therapy will be administered using an approved ESA and dosing as per the local institution's guidelines and per the approved product label.

While receiving ESA therapy, subjects randomized to vadadustat must temporarily interrupt vadadustat. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA, and treatment will be resumed after the following intervals:

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

Following ESA administration, vadadustat will be resumed at the same dose as previously used or with one additional tablet (+150 mg) at the discretion of the Investigator.

Reasons for ESA use will be captured in the appropriate CRF.

8.4.10 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 clinical judgment. The method of phlebotomy will be in accordance with the study site's standard clinical practice.

8.4.11 Treatment Compliance

Throughout the study, subjects in the vadadustat arm will be guided regarding dosing compliance using an eDiary. The focus of the vadadustat eDiary is to guide subjects to remind them of the dose, instruct them to hold their dose for the PK/PD sample dates and guide them if they have transitioned from daily dosing to TIW dosing. Subjects will also be questioned at study visits on whether they have questions or have experienced any problems related to the dosing of vadadustat. Subject compliance with eDiary data entry will be routinely monitored to identify potential issues that may impact or prevent data entry. The Investigator will also maintain drug accountability logs itemizing all study drugs dispensed to and returned from each subject during

the study. Treatment compliance will be determined from these logs, subject questioning, and the study drug Case Report Form (CRF)

For epoetin alfa, the dose that is administered is required to be entered in the electronic data capture (EDC) system, and the EDC system will be used to determine dosing compliance.

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

8.4.12 Continuation of Treatment

Subjects in the vadadustat dosing groups will not receive vadadustat beyond the Treatment Period of approximately 20 weeks. However, enrollment may be increased by up to 20 additional subjects on the Main study and up to 30 additional subjects on the ESA hyporesponder parallel study to ensure adequate data is captured for the primary, PK/PD, and safety endpoints. Subjects in the vadadustat dosing groups who complete Visit 14 (Week 20), or discontinue early, will resume dosing with epoetin alfa (or another ESA) as per standard of care after all EOT procedures are completed.

8.5 Prior and Concomitant Therapy

8.5.1 General

Any medicinal product, prescribed or non-prescribed (including vitamins, minerals, natural and herbal remedies, topicals, inhaled, intranasal and dietary supplements) taken before entering the study is considered prior medication. All medicinal products other than the study drug, including prescribed or non-prescribed treatments used during the Treatment Period will be considered concomitant medication.

8.5.2 ESAs

Co-administration of any ESA with vadadustat is 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 8.4.9.2, ESA Use) if deemed medically necessary at the discretion of the Investigator. Guidelines for ESA administration as rescue therapy are provided in Section 8.4.9.2, ESA Use. All efforts will be made to avoid inadvertent administration of ESAs resulting from adherence to ESA hemodialysis center protocols (e.g., DaVita ESA protocols for patients 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. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA. Vadadustat treatment may be resumed after the following intervals:

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

8.5.3 Rosuvastatin, Pravastatin, and Other HMG-CoA Reductase Inhibitors (Statins)

Rosuvastatin exposure (AUC, C_{max}) was increased 2- to 3-fold with co-administration of vadadustat based on preliminary data of a drug-drug interaction study in healthy volunteers. For subjects randomized to vadadustat who are concomitantly taking rosuvastatin, the recommended

maximum daily dose of rosuvastatin is 10 mg. Investigators should review rosuvastatin dosing to consider clinical guidelines and local prescribing information including specific guidance and product labels with reference to renal impairment as well as hepatic function, concomitant medications and other medical factors relevant to the management of the subject.

Pravastatin exposure was studied in the setting of vadadustat co-administration in healthy volunteers. Preliminary results indicate no clinically significant interaction. No dose adjustment of pravastatin is necessary.

Exposure to atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin may be increased with co-administration of vadadustat. When used with vadadustat, these statins should be used with caution.

Co-administration of vadadustat may increase exposures to other drugs that are substrates of BCRP, OATP1B1, and/or OATP1B3.

8.5.4 Dialysis Treatment and Renal Replacement Therapy

Information on dialysis treatment including dialysis vascular access type, dialysis adequacy, and history of and changes in renal replacement therapies will be collected as described in Section 9, Study Procedures and Schedule of Activities and Appendix A: Schedule of Activities.

8.5.5 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 had previous participation in a study with another HIF-PHI other than vadadustat.

Additionally, subjects should not take another investigational medication while participating in this study. Subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation.

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:

- Eligibility Screening Period (from Day -28 to Baseline/Day 1)

  The Screening Period starts at the time the informed consent is signed and will be a maximum of 28-days in duration. Two Screening visits (SV1 and SV2) must be performed within the Screening Period and prior to dosing (Baseline/Day 1).

  - Screening Visit 1 (SV1)
  - Screening Visit 2 (SV2)
- Study Treatment Period will consist of study visits from Baseline/Day 1 through Week 20 visit. In weeks where there is no schedule study visit a subject will have a status check performed during one of their dialysis treatment appointments.
  - Baseline/Day 1, Visit 1
  - Visit 2, Week 1 +5 days
  - Visit 3, Week 2 ± 3 days
  - Visit 4, Week 4 ± 3 days
  - Visit 5, Week 6 ± 3 days
  - Visit 6, Week 8 ± 3 days
  - Visit 7, Week 10 ± 3 days
  - Visit 8, Week 11 ± 3 days
  - Visit 9, Week 12 ± 3 days (Transition to TIW dosing if all Week 12 criteria are met)
  - Visit 10, Week 13 +5 days
  - Visit 11, Week 14 ± 3 days
  - Visit 12, Week 16 ± 3 days
  - Visit 13, Week 18 ± 3 days
  - Visit 14, Week 20 ± 3 days (EOT visit)
- Safety Follow-Up Period (from Week 20 to 24)
  - Visit 15, Week 24 visit ± 5 days

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

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent will be obtained and legally signed prior to the subject entering into the study and before any protocol-directed procedures (including Screening activities) are performed (see Section 15.3, Subject Information and Consent). After providing informed consent and receiving a unique subject identification number, subjects will undergo various Screening activities.

9.1.2 eDiary

An eDiary will be utilized throughout the study for completion of SF-36 and PGI assessments. In addition, the eDiary will guide dosing for subjects in the vadadustat arm. The focus of the vadadustat eDiary is to guide subjects to remind them of the dose, instruct them to hold their dose for the PK/PD sample dates and guide them if they have transitioned from daily dosing to TIW dosing. At SV2, subjects will be instructed on data entry procedures for the eDiary. Subject compliance with eDiary data entry will be routinely monitored to identify potential issues that may impact or prevent data entry.

9.1.3 Documentation of Screen Failures

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

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

9.1.4 Status Check

In weeks where there is no scheduled study visit, a subject will have a status check performed during one of their dialysis treatment appointments in the week. It will include a review of the subject's vital signs and a review of current health status for identification of any issues that may require follow-up by the Investigator or delegated staff personnel. Documentation of the review must be done in the subject's source documentation. No data will be captured on the status checks in the EDC system. If an AE is identified at the status check or other actions result from the status check, these will be captured per the protocol.

9.1.5 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 of vadadustat in the rat are ongoing, and there are no data on the transmission of vadadustat in breast milk or the effect of vadadustat on infants.

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 drug.

Adequate contraception for subjects is defined as follows:

- For females of non-childbearing potential
    - Confirmation of surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or
    - Post-menopausal (no menses for >1 year with FSH >40 U/L at Screening)
- For females of childbearing potential
    - Subjects must confirm the use of acceptable forms of contraception*, for a minimum of one complete menstrual cycle prior to Screening.

- Must have a negative serum pregnancy test at SV2.
- Starting Baseline/Day 1, subjects must use two acceptable forms of contraception* (at least one of which must be a barrier method) throughout the Treatment Period and for 30 days after the final study drug administration

- For males subjects who have not had a vasectomy must agree to the following: use of an acceptable form of contraception* during the study and for 30 days after the last dose of the study drug; to not donate sperm during the study and for at least 30 days after the last dose of vadadustat.

* *Acceptable forms of contraception include:*

- *Established use of oral, injected or implanted hormonal methods of contraception.*
- *Placement of an intrauterine device or intrauterine system.*
- *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.*

9.1.6 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. If the evaluations occur on a hemodialysis day, the evaluations will be completed before dialysis, if applicable.

- 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 will be documented. After SV2, an abbreviated, symptom-directed physical examination will be performed at the discretion of the Investigator, as clinically indicated.
- Dialysis Adequacy: Dialysis adequacy, as available from local collection, will be recorded in the CRF at SV1 and Visits 9 and 14 (EOT).
- SF-36 HRQOL and PGI-S: The SF-36, a patient-reported survey of patient health, and PGI-S will be completed at SV2, Visits 9, 14 (EOT) and 15. Assessments will be completed by subjects using the eDiary. The PGI assessment will be completed after the other assessments.
- PGI-C: The PGI-C will be completed at the Safety Follow-Up (Visit 15). The assessment will be completed by subjects using the eDiary. The PGI assessment will be completed after the other assessments.
- Vital Sign Measurements: Vital signs will include temperature, heart rate (HR), BP, respiratory rate (RR), and dry weight. Temperature, HR, BP, and RR will be assessed in

the seated position after 5 minutes of rest. For BP, a total of two measurements at intervals of at least 2 minutes should be performed. Temperature, HR, BP, and RR will be collected at SV1, SV2, Baseline/Day 1, during all study visits, and Visit 14 (EOT). Measurements will be taken prior to blood draws when possible.

Dry weight will be collected for all subjects at SV2, Baseline/Day 1, Visit 9 and 14 (EOT). For subjects on epoetin 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/Day 1, which may be obtained up to 3 days prior to Baseline/Day 1. The ECG will be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and will be taken prior to vital sign assessments and blood draws when possible. 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.
- AE Assessments: AE collection will begin from time of randomization through 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 (study end date) or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
- Prior and Concomitant Medication Recording: All prior and concomitant medications (except those routinely administered as part of the hemodialysis procedures, such as heparin or saline flushes used for routine catheter maintenance, unless relevant for an AE or SAE) taken within 30 days prior to Baseline/Day 1 and through the final study visit will be recorded on the appropriate CRF.

  Iron treatment regimen 30 days prior to Baseline/Day 1 and through the final study visit will be recorded on the appropriate CRF. In addition, to ensure adequate collection of prior ESA dosing history, a minimum of 8 weeks of ESA therapy prior to start of study drug will be recorded on the appropriate CRF page.

  At each study visit, subjects will be asked whether they have started, changed or discontinued any medication since their previous study visit. This includes single use or as needed medication use. All medications and changes in dosage and frequency will be recorded on the appropriate CRF Page. Documentation for all medicinal products will include the medication name, indication, dose, dosing frequency and dates of administration.

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. If blood is collected on a dialysis day, blood draws will be done prior to dialysis, if applicable. The Investigator is responsible for reviewing laboratory results for clinical significance.

For eligibility purposes, one retest for each parameter may be performed during the Screening window. Refer to Section 7.4.1, Retesting and Section 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening Period.

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 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 drug. A FSH test will be performed at SV2 for post-menopausal females.
- Complete Blood Count (CBC): A CBC with differential will be performed at Baseline/Day 1 and at Visit 14 (EOT). At all other noted visits in Appendix A: Schedule of Activities, including SV1 and SV2, a CBC without differential will be performed. The CBC without differential will include: Hb, hematocrit, RBCs, mean corpuscular Hb, mean corpuscular Hb concentration, red cell width distribution, white blood cell count and platelets. The CBC with differential will include the same parameters as CBC without differential with the addition of white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

  Hb will be monitored throughout the study via central laboratory to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive. Refer to Section 8.4.3, Measurement of Hb Levels for Dose Adjustment Consideration. Hb levels can be measured more frequently based on Investigator's clinical judgment.
- Reticulocyte Count: An automated reticulocyte count (both absolute and percent) will be performed at Baseline/Day 1 and at Visits 2, 4, 6, 8, 9, 10, 12, and 14 (EOT).
- Folate and Vitamin B_{12}: A blood sample will be drawn at SV1 to assess the folate and Vitamin B_{12} levels.
- CRP: A blood sample for CRP will be collected at the Baseline/Day 1, Visit 9 and 14 (EOT).
- Serum Chemistry: Blood samples to assess serum chemistry will be collected at SV1, Baseline/Day 1, Visit 9 and 14 (EOT). The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen, creatine phosphokinase, uric acid, albumin, and total protein.
- Liver Function Tests (LFTs): Blood samples to assess liver function will be collected at SV1, Baseline/Day 1, Visit 4, 6, 9, 12 and 14 (EOT). LFTs will include: total bilirubin, alkaline phosphatase (ALP), ALT/SGPT, AST/SGOT, and lactate dehydrogenase.
- Iron Indices: Blood samples to assess the iron indices will be collected at SV1, Baseline/Day 1, Visit 4, 6, 9, 12 and 14 (EOT). Assessments will include the following indices: ferritin, iron, transferrin, TIBC, and TSAT.

- Lipid Profile: Blood samples will be collected at the Baseline/Day 1 and Visit 14 (EOT) to assess the cholesterol levels and will be tested for the following types of lipids: total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides.
- Biomarkers (including, but not limited to, vascular endothelial growth factor [VEGF], and hepcidin): Samples for VEGF and hepcidin biomarker analyses will be drawn at the Baseline/Day 1, Visit 9 and 14 (EOT).

9.2.2.1 PK/PD Sampling for Subjects Randomized to Vadadustat

Refer to Appendix B for a schematic overview of the PK/PD samples for the vadadustat arm.

Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below. Preferably, PK/PD samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).

At Baseline/Day 1, PK/PD samples will be collected prior to dialysis and administration of vadadustat.

At Week 1 (after at least a full week of vadadustat treatment), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

On the following non-dialysis day, blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes post-dose

At Week 11, vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

At Week 13 (after at least one week on TIW vadadustat dosing regimen), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

Note: Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Week 13 PK/PD sampling.

9.2.2.2 PK Sampling for Subjects Randomized to Epoetin Alfa

Refer to Appendix B for a schematic overview of the PK samples for the epoetin alfa arm.

Blood for measurement of EPO level in the epoetin alfa arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below. Preferably, PK samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).

At Baseline/Day 1, a sample will be collected prior to dialysis and administration of epoetin alfa.

At Week 1 (after at least a full week of study epoetin alfa treatment), epoetin alfa will be administered within 1 hour after start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

On the following **dialysis day**, one blood sample will be collected 15 minutes prior to administration of epoetin alfa.

9.2.2.3 PK/PD Sampling

For all PK and PD sampling the time of the previous dose of study drug (vadadustat or epoetin alfa) is to be collected for the pre-dose sample and the timing of administration of study drug (epoetin alfa and vadadustat) and the start and stop time of the dialysis session will be recorded.

9.3 Schedule of Activities

The Schedule of Activities (see Appendix A: Schedule of Activities) shows the timing of planned study procedures. Every effort will be made to adhere to this procedure schedule and all assessments will be completed at each study visit. Where possible, study visits will be performed and scheduled as part of a patients regularly scheduled dialysis session.

9.3.1 Screening Visits

Subjects will need to sign a full consent form prior to SV1 procedures. The consent form may be signed in advance of the SV1 procedures. The Screening Period starts at the time the informed consent is signed and will be a maximum of 28-days in duration. Two Screening visits (SV1 and SV2) must be performed within the Screening Period and prior to dosing (Baseline/Day 1).

The Investigator will arrange for sufficient time (a minimum 4 days) between SV1 and SV2 and between SV2 or last retest (if applicable) and Baseline/Day 1 to allow for all laboratory results to be available that are required to assess eligibility for the next study visit.

In addition, subjects will be required to stop epoetin alfa treatment for a minimum duration of 5 days before Baseline/Day 1 in the Main study and for a minimum of 2 days before Baseline/Day 1 in the ESA hyporesponder parallel study.

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

9.3.1.1 SV1

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

- Informed consent
- Review of eligibility criteria
- Review of acceptable methods of contraception
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Dialysis adequacy
- Laboratory procedures:
  - CBC (without differential)
  - Folate and vitamin B_{12} levels
  - Serum Chemistry
  - LFTs
  - Iron indices

  Refer to Section 7.4.1, Retesting and Section 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening Period.
- Visit registration in IWRS
- Review of prior medication
- Epoetin alfa dosing will continue

9.3.1.2 SV2

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

- Review of eligibility criteria
- Review of acceptable methods of contraception
- SF-36 and PGI-S assessments
- Physical examination (including height)
- Demographics and medical history
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws), and dry weight
- Laboratory procedures:
  - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method see Section 9.2.2, Laboratory Evaluations for additional information). A FSH test will be performed at SV2 for post-menopausal females.
  - CBC (without differential)

  Subjects must have 2 Hb values measured by the central laboratory during Screening as indicated below:
  - Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive
  - ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive

  If the subject's Hb does not qualify after SV1, SV2, or retest Hb, the subject will be considered a screen failure

- Visit registration in IWRS
- Introduction to and instruction on the use of the eDiary
- Prior and current medication use
- Epoetin alfa dosing will stop for a minimum of 5 days in the Main study or 2 days in the ESA hyporesponder parallel study until Baseline/Day 1

9.3.2 Baseline/Day 1 (Visit 1)

Epoetin alfa dosing will have been stopped for a minimum of 5 days in the Main study or 2 days in the ESA hyporesponder parallel study until Baseline/Day 1.

On Baseline/Day 1, blood sample collection and other Baseline/Day 1 procedures will be completed prior to dosing with study drug (vadadustat or epoetin alfa). On Baseline/Day 1, study drug will be administered at the study site, and will be administered after the PK sample is collected and prior to the dialysis session.

At Baseline/Day 1, the following activities/procedures will be performed:

- Review of study eligibility criteria
- Review acceptable methods of contraception
- Abbreviated, symptom-directed physical examination, at the discretion of the Investigator, as clinically indicated
- 12-lead ECG. ECGs will be completed prior to blood draws when possible and will be obtained after the subject has been resting supine comfortably for approximately 5 minutes; ECG may be completed and reviewed by the Investigator on Baseline/Day 1 or if needed for scheduling reasons (e.g., dialysis treatment is scheduled for early morning of Baseline/Day 1), the ECG can be completed and reviewed up to 1-3 days prior to Baseline/Day 1.
- Randomization
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws), and dry weight
- Laboratory Procedures:
  - CBC (including differential)
  - Reticulocyte count
  - CRP
  - Serum chemistry
  - LFTs
  - Iron indices
  - Lipid profile
  - Biomarkers (VEGF, and Hepcidin)
  - PK prior to vadadustat or epoetin alfa dosing (see Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa) and prior to the dialysis session
- Review of medical history for new conditions since SV2
- Review of medication use since SV2
- Study drug assessments and procedures:
  - Subject will take/receive their first dose of study drug at the study site during Baseline/Day 1

  - For subjects in the vadadustat treatment arm only:
    - Initiate vadadustat dosing
    - Vadadustat drug dispensation
    - Review vadadustat dosing instructions
  - Epoetin alfa dosing will continue for the subjects in the epoetin alfa arm
  - Iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation
  - Visit registration in IWRS
- Safety assessments:
  - AE review as needed
  - Review use of rescue therapy

9.3.3 Visit 2 to Visit 13 (Weeks 1 to 20)

At the Baseline/Day 1, Visit 7 and Visit 9, subjects in the vadadustat treatment arm will be reminded and instructed to hold their vadadustat dose on the day of Visit 2, Visit 8, and if applicable Visit 10, respectively, as blood sample for PK analysis will be collected on the day of Visit 2, Visit 8, and Visit 10 prior to vadadustat administration at the study site.

The following activities/procedures will be performed at Visit 2 to Visit 13, unless noted otherwise:

- Abbreviated, symptom-directed physical examination, at the discretion of the Investigator, as clinically indicated
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws). Dry weight will be collected at Visit 9 only.
  - A status check (BP, vital signs, and review of current health status) will be performed during weeks with no scheduled study visit.
- Dialysis adequacy, as available from local information (Visit 9 only)
- SF-36 and PGI-S assessments (Visit 9 only)
- Safety assessments:
  - AE review
  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws will be done prior to dialysis, if applicable):
  - CBC
  - Reticulocyte count (Visit 2, 4, 6, 8, 9, 10 and 12 only)
  - CRP (Visit 9 only)
  - Serum chemistry (Visit 9 only)
  - LFTs (Visit 4, 6, 9 and 12 only)
  - Iron indices (Visit 4, 6, 9 and 12 only)
  - Biomarkers (VEGF and Hepcidin, Visit 9 only)
  - Vadadustat PK/PD sampling (Visit 2, 8 and 10 only) for details, see Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.3, PK/PD Sampling)

    - Epoetin alfa PK sampling (Visit 2 only) for details, see Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa and Section 9.2.2.3, PK/PD Sampling)
- Medication assessments and procedures:
    - Review of concomitant medications
    - Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa
    - For subjects in the vadadustat treatment arm only:
        - Visit registration in IWRS (for bottle dispensing only)
        - Vadadustat drug dispensation (scheduled Visits 4, 6, 9 and 12)
        - Review vadadustat dosing instructions
        - Review of vadadustat dosing compliance
        - Vadadustat reconciliation
    - Review of iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation)

9.3.4 EOT Visit 14 (Week 20)

EOT evaluations will be performed when the Treatment Period (Baseline/Day 1 to Visit 13) is completed. Subjects who prematurely discontinue study drug for any reason will also attend this visit.

At Visit 14 (EOT), the following activities/procedures will be performed:

- Vital signs including, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws), as well as temperature and dry weight
- Dialysis adequacy, as available from local information
- SF-36 and PGI-S assessments
- Safety assessments:
    - AE review
    - RBC transfusions and ESA rescue
    - Therapeutic phlebotomy
- Laboratory Procedures:
    - CBC (with differential)
    - Reticulocyte count
    - CRP
    - Serum chemistry
    - LFTs
    - Iron indices
    - Lipid panel
    - Biomarkers (VEGF and Hepcidin)
- Medication assessments and procedures:
    - Review of concomitant medications
    - Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa.
    - For subjects in the vadadustat treatment arm only:
        - Review of vadadustat dosing compliance
        - Vadadustat reconciliation
        - Resume dosing with epoetin alfa (or another ESA): After the end of vadadustat treatment at Visit 14 (or following early discontinuation of

vadadustat), subjects may resume dosing with epoetin alfa (or another ESA), based on standard of care.
- Visit registration in IWRS
- Review of iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation)

9.3.5 Safety Follow-Up Visit 15 (Week 24)

At the Visit 15, the following activities/procedures will be performed:
- SF-36 HRQOL, PGI-S, and PGI-C assessments
- AE review
- Review use of rescue therapy (RBC transfusions and ESA rescue therapy)
- Review use of therapeutic phlebotomy
- Concomitant medication review

9.3.6 Unscheduled Visits

Unscheduled assessments may be conducted at any time as medically warranted. The following activities/procedures will be performed at minimum:
- Safety assessments:
  - AE review
  - RBC transfusions and ESA rescue
  - Therapeutic phlebotomy
- Medication assessments and procedures:
  - Review of concomitant medications
- Any other procedures that are medically warranted at the discretion of the Investigator.

10 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

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.

AEs therefore include the following:

- All AEs, whether suspected to be causally related to study drug or otherwise.
- All AEs secondary to any medication overdose, medication error, abuse, withdrawal, sensitivity, or toxicity.
- Illnesses apparently unrelated to study drug, including the worsening of a pre-existing illness (see paragraph below on Pre-existing Conditions).
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) will 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 (e.g., elevated liver enzymes in a subject with jaundice) will 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 will 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 will be the reported AE term, instead of fever and dyspnea, when the diagnosis has been established. Signs and symptoms will 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, will not be reported as AEs. However, the medical condition for which the procedure was performed will be reported if it meets the definition of an AE. For example, an acute

appendicitis that begins during the AE reporting period will 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 will not be reported as AEs.

Pre-existing Conditions – In this study, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) will 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 will 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 will also be reported as AEs. Any abnormal laboratory value which requires treatment or further diagnostic testing and/or results in discontinuation from study will 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 will be reported to the Sponsor's Medical Monitor or Contract Research Organization (CRO) designee within 24 hours of awareness as an SAE with 'other medically important event' 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 (e.g., viral hepatitis, acute liver disease).

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

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

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 will <u>not</u> be considered an AE unless the worsening of anemia is associated with a cause *other than* the subject's CKD.

Transplantation – During this study, it is anticipated that subjects may receive a kidney transplant. These events will not be recorded as AEs. Subjects will discontinue study drug for

receipt of a kidney, other solid organ, hematopoietic stem cell or bone marrow transplant, will complete the EOT visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14 as described in Section 7.6.3, Early Discontinuation from Study.

10.1.2 SAEs

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 situation will also be classified as serious for purposes of this study:

- Malignancies – Newly diagnosed malignancies or a recurrence of a malignancy will 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 of skin, 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.

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

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

Hospitalization – Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the study for a pre-existing condition that has not worsened during the AE reporting period does not constitute an SAE unless an untoward event occurs related to the procedure (e.g., 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 AE 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 randomization.

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 this protocol will be reported, whether or not the event is considered related to study drug (vadadustat or epoetin alfa).

10.3.1 Reporting Period

The AE reporting period for this study begins from time of randomization and ends at the final protocol-required Safety Follow-Up (Visit 15).

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

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, will 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 will contain, at a minimum items number 1 to 6:

1. Subject number/ID, sex, and age/date of birth
2. The date of report
3. Name of the reporter
4. Name of the suspected medicinal product
5. A description of the event, including event term(s), seriousness criteria, and a clinical summary of the event
6. Causality assessment

If the causality assessment is not provided in the initial report an updated report with the causality must be provided within 24 hours, once assessed.

Information about all SAEs (either initial or follow-up information) will be collected and recorded in English on the electronic SAE Report Form within the EDC system. The Investigator will assess the relationship to each specific component of the study treatment. If the event meets serious criteria and it is not possible to access the EDC system, a paper SAE Report Form will 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 again, the SAE information will be entered within 24 hours of the system becoming available.

The Investigator will report follow-up information relating to an SAE to the Sponsor's Medical Monitor or CRO designee within 24 hours of awareness 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 will be entered within 24 hours. The subject will 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 IRB 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 study site.

10.3.4 Relationship to Study Drug

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

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

Examples of evidence that would suggest a causal relationship between the study drug and the AE include the occurrence of an AE that is uncommon and known to be strongly associated with drug exposure (e.g., 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 drug are generally uninformative and do not contribute meaningfully to the development of the safety profile of the drug or to subject protection.

Investigators are encouraged to choose the most plausible cause for the event(s) from the following list: medical history, lack of efficacy/worsening of treated condition, study treatment,

other treatment (concomitant, or previous), withdrawal of study treatment, administration error, protocol-related procedure, others (specify).

10.3.5 Severity

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

MILD: Does not interfere with subject's usual function

MODERATE: Interferes to some extent with subject's usual function

SEVERE: Interferes significantly with subject's usual function

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

10.3.6 Follow-up of Unresolved Events

All AEs will be followed until they are resolved or the Investigator assesses them as chronic or stable or the subject's participation in the trial ends (i.e., until a final report is completed for that subject).

In addition, all SAEs and those nonserious events assessed by the Investigator as related to the study drug will continue to be followed even after the subject's participation in the trial is over. Such events will 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 will be confirmed by a positive serum β human chorionic gonadotropin test.

The study drug will 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 drug (vadadustat or epoetin alfa) or within 30 days of discontinuing the study drug, the pregnancy will be recorded on the Pregnancy Reporting Form/Exposure in Utero Form in 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 will also be reported.

The Pregnancy Reporting Form/Exposure in Utero Form will be completed with all known information regarding the pregnancy at the time of reporting. Study 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 an SAE (i.e., 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 an SAE within 24 hours of awareness. A pregnancy in and of itself is not considered an AE; however, unexpected complications are considered AEs.

Additional information about pregnancy outcomes follows:

- Note that "spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth will be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as related or unrelated to the in utero exposure to the study drug will also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

10.5 Special Situations

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

- Overdose of the medicinal product
    - Epoetin alfa overdose – The PI or SmPC will be referenced for information on epoetin alfa overdosing.
    - Vadadustat overdose – There is no known antidote for vadadustat. In cases of suspected overdose, subjects will 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 will be discontinued and standard treatment for polycythemic hyperviscosity syndrome will be initiated (i.e., phlebotomy).

      Dose-limiting toxicity in exploratory toxicology studies was due to hemoglobinuric nephropathy in the rat and emesis associated with body weight loss in the dog. In the rat, doses ≥500 mg/kg were not tolerated in two 7-day exploratory toxicology studies. The probable cause of the findings is considered to be intravascular hemolysis leading to hemoglobinuric nephropathy.

      The clinical data from human volunteer subjects and renal study subjects demonstrate that currently there is no evidence of any drug-related hemolysis associated with vadadustat at the doses studied. The highest dose in the majority of subjects exposed to vadadustat was up to 600 mg daily with minimal exposures at doses higher than this (up to 1200 mg single dose and up to 900 mg daily for 10 days). No conclusion concerning the safety profile of vadadustat at doses higher than 600 mg daily can be drawn.

- 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 exposure to the Sponsor's medicinal product [e.g., name confusion])
- Drug-drug interaction.

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

10.6 Safety Monitoring

This is an open label study allowing the study team full access to safety data which will be reviewed on a regular basis, throughout the course of the study. Safety monitoring will be performed as described in the Medical Monitor Plan.

11 DATA ANALYSIS

Data collected throughout the study will be summarized using descriptive statistics and listed in the by-subject listings. Continuous variables will be summarized using number of subjects with mean, standard deviation (SD), 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.

11.1 Sample Size Estimation

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

Sample size reflects the exploratory nature of this study.

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

11.2 Study Analysis Populations

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects. Analyses of this population will be based on the randomized treatment.
- Full Analysis Population (FAS): all subjects in the randomized population who received at least one dose of study drug and had at least one Hb assessment during the primary efficacy evaluation period. Analyses of this population will be based on the randomized treatment.
- Safety Population: all subjects in the randomized population who received at least one dose of study treatment. Analysis of this population will be based on the actual treatment received. Subjects who received in error some vadadustat and some epoetin alfa will be classified by the more frequently received drug.
- Per protocol (PP) population: all randomized subjects who received study drug during the primary evaluation period, had at least one Hb assessment during the primary efficacy evaluation period, received no rescue therapy (with ESA or transfusion) prior to the evaluation period, and had no major protocol deviation affecting the primary endpoint analyses. Major protocol deviations leading to exclusion from the PP population will be specified prior to database lock and recorded in a separate document. Analyses of this population will be based on actual treatment received.

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 Randomized Population and other analysis populations which will be defined in detail in the Statistical Analysis Plan.

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

11.4 Disposition of Subjects

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

The number of randomized subjects who completed the study, discontinued early from study drug, completed or discontinued from the study, and reasons for discontinuation will be summarized by treatment group and overall.

11.5 Missing Data

It is expected that few subjects will discontinue Follow-Up. The reasons for any missing data will be summarized by treatment arm. Missing Hb values will be imputed using last observation carried forward (LOCF).

11.6 Efficacy Analyses

The primary efficacy endpoint as well as all other secondary endpoints will be summarized using descriptive statistics (means or proportions) by treatment groups and in total, 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.

11.7 Safety Analyses

Safety analyses will be descriptive in nature.

All AEs will be coded using MedDRA. Treatment-emergent and post-treatment AEs will be summarized by SOC and PT for each treatment group. AEs will also be summarized by their maximum severity.

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

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

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

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

PK and PD parameters will be summarized using descriptive statistics: number of subjects, mean, median, SD, minimum, maximum, and coefficient of variation, geometric mean and geometric mean SD. Mean and individual plasma concentration-time profiles will be presented graphically in both linear scale and log-linear scale.

11.8.1 PK Assessments

A population PK analysis will be conducted to describe vadadustat PK and determine the covariates that impact the PK profile (i.e., demographics, laboratory values, concomitant iron, dosing relative to dialysis, etc.). PK analysis will be reported separately.

11.8.2 PD Assessments

An exposure-response analysis of vadadustat, EPO and other PD measures will be conducted as deemed appropriate. PD analysis will be reported separately.

11.8.3 Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug dictionary. Refer to Section 8.5, Prior and Concomitant Therapy.

11.8.4 Biomarkers

Biomarkers (including, but not limited to, hepcidin and VEGF) will be summarized descriptively at Baseline/Day 1 and by visit post-Baseline/Day 1.

12 DATA HANDLING AND RECORD KEEPING

12.1 CRFs/EDC

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

Any form of data from the electronic system are the sole property of the Sponsor and will 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 will 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 will 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, e.g., 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 (e.g., letters, meeting minutes, and telephone calls reports). The records will be retained by the Investigator according to the International Council for Harmonisation of Technical Requires for Pharmaceuticals for Human Use (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 (e.g., retirement and relocation), the Sponsor will be prospectively notified. The study records will be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator will obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study 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 study site may also be subject to Quality Assurance audits performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or review by the IRB, 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

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an Investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the Investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File.

Note: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

14 STUDY DISCONTINUATION/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 will contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the study.

14.1 Criteria for Premature Termination or Suspension of the Study

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

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

The Sponsor reserves the right to discontinue the study for other valid administrative reasons.

If the study has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

14.2 Criteria for Premature Termination or Suspension of 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.

The Investigator will notify the Sponsor if the trial is terminated by the Investigator or the IRB at the site. If the Investigator, IRB, or Sponsor decides to terminate or suspend the trial conduct at a particular study site for safety, non-enrollment, non-compliance with the protocol, or other unanticipated reasons, the above parties will be promptly notified.

14.3 Procedures for Premature Termination or Suspension of the Study or Study 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 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 E6 guideline on GCP, and applicable local regulatory requirements and laws.

15.2 IRB

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

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

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

15.3 Subject Information and Consent

The Investigator or designee will explain the nature of the study to the subject or their legally acceptable representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or their legally acceptable representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

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, will be prospectively approved by both the IRB 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 (i.e., clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor will 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 (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

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

16 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor will 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 will 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	**Screening [a]**		**Study Treatment Period**													**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [c]**	**15**
Weeks of study completed Study Day	**Day -28 to 0**		**Baseline/ Day 1 [b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57**	**Week 10 Day 71**	**Week 11 Day 78**	**Week 12 Day 85**	**Week 13 Day 92**	**Week 14 Day 99**	**Week 16 Day 113**	**Week 18 Day 127**	**EOT Week 20 Day 141**	**Week 24 Day 169**
Visit Window (Days)	—		—	+5	±3	±3	±3	±3	±3	±3	±3	+5	±3	±3	±3	±3	±5
Administrative Procedures																	
Informed consent	X																
Eligibility criteria [d]	X	X	X														
Review Contraception methods [e]	X	X	X														
Vital Signs [f]	X	X [g]	X [g]	X	X	X	X	X	X	X	X [g]	X	X	X	X	X [g]	
Demographics, Medical History [h]		X	X [i]														
Physical Exam [j]		X															
12-Lead ECG [k]			X														
Dialysis Adequacy (Kt/V)	X										X					X	
SF-36		X									X					X	X
PGI-S		X									X					X	X
PGI-C																	X
Randomization			X														
Assessment for meeting criteria to switch from daily to TIW dosing (vadadustat arm)											X						
Status check [l]																	
Safety Assessments																	
AE review [m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening [a]		Study Treatment Period													Safety Follow-Up	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [c]**	**15**
Weeks of study completed Study Day	**Day -28 to 0**		**Baseline/ Day 1 [b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57**	**Week 10 Day 71**	**Week 11 Day 78**	**Week 12 Day 85**	**Week 13 Day 92**	**Week 14 Day 99**	**Week 16 Day 113**	**Week 18 Day 127**	**EOT Week 20 Day 141**	**Week 24 Day 169**
Review use of rescue therapy (RBC transfusions and ESA therapy)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of therapeutic phlebotomy				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluations																	
Serum Pregnancy test [n]		X															
CBC [o] [p]	X	X	X [q]	X	X	X	X	X	X	X	X	X	X	X	X	X [q]	
Reticulocyte count			X	X		X		X		X	X	X		X		X	
Folate and vitamin B12	X																
CRP			X								X					X	
Serum chemistry [r]	X		X								X					X	
LFTs [s]	X		X			X		X			X			X		X	
Iron indices [t]	X		X			X		X			X			X		X	
Lipid panel [u]			X													X	
Biomarkers (VEGF and Hepcidin) [v]			X								X					X	
PK/PD for vadadustat arm [w]			X	X						X		X [x]					
PK for epoetin alfa arm [y]			X	X													
Medication Assessments and Procedures																	
Concomitant medication review [z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Epoetin alfa dosing during Screening and resume standard of care after EOT	X [aa]															X [bb]	

Study Period	Screening [a]		Study Treatment Period													Safety Follow-Up	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [c]**	**15**
Weeks of study completed Study Day	**Day -28 to 0**		**Baseline/ Day 1 [b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57**	**Week 10 Day 71**	**Week 11 Day 78**	**Week 12 Day 85**	**Week 13 Day 92**	**Week 14 Day 99**	**Week 16 Day 113**	**Week 18 Day 127**	**EOT Week 20 Day 141**	**Week 24 Day 169**
Study Drug (vadadustat or epoetin alfa) dosing [cc]			X	X	X	X	X	X	X	X	X [dd]	X	X	X	X		
Vadadustat dispensation [ee]			X			X		X			X			X			
Review vadadustat dosing instructions and vadadustat dosing compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vadadustat reconciliation				X	X	X	X	X	X	X	X	X	X	X	X	X	
Review use of iron supplementation [ff]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visit Registration in IWRS	X	X	X			X [gg]		X [gg]			X [gg]			X [gg]		X	
eDiary instruction		X															

Abbreviations: AE = adverse event; ALT/SGPT = alanine transaminase/serum glutamic-pyruvic transaminase; AST/SGOT = aspartate aminotransaminase/serum glutamic oxaloacetic transaminase; BUN = blood urea nitrogen; CBC = complete blood count; CPK = creatine phosphokinase; CRP = C-reactive protein; ECG = electrocardiogram; EOT = end of treatment; EPO = erythropoietin; ESA = erythropoiesis-stimulating agent; HDL = high density lipoprotein; IWRS = Interactive Web Response System; LDL = low density lipoprotein; LFT = liver function test; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PD = pharmacodynamics; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; RBC = red blood cell; RDW = red cell distribution width; SF-36 = 36-Item Short-Form General Health Survey; SV1 = Screening visit 1; SV2 = Screening visit 2; TIBC = total iron binding capacity; TSAT = transferrin saturation; VEGF = vascular endothelial growth factor; WBC = white blood cell; wks = weeks.

[a] The Screening Period is a maximum of 28 days in duration and starts at the time the informed consent is signed.
[b] The Investigator will arrange for sufficient time (a minimum of 4 days) between SV2 or last retest (if applicable) and Baseline/Day 1 to allow for all laboratory results to be available that are required to assess eligibility for the next study visit.
[c] The EOT evaluations will be performed when the Treatment Period (Baseline/Day 1 to Week 20 [Visits 1 to 13]) is completed. Subjects who permanently discontinue study drug for any reason or discontinue prematurely from the study will complete the EOT visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14
[d] Eligibility criteria will be reviewed at the SV1, SV2, and Baseline/Day 1.
[e] Contraception methods will be reviewed at Screening and Baseline/Day 1, as well as throughout the study as needed.
[f] Vital signs will include temperature, HR, BP, RR, and dry weight. Temperature, HR, BP, and RR will be assessed in the seated position after 5 minutes of rest. For BP, a total of two measurements at intervals of at least 2 minutes should be performed. Temperature, HR, BP, and RR will be collected at SV1, SV2, Baseline/Day 1, during all study visits, and Visit 14 (EOT). Measurements will be and will be taken prior to blood draws when possible.
[g] Dry weight will be collected as part of the vital signs for all subjects at SV2, Baseline/Day 1, Visit 9 and 14 (EOT). For subjects on epoetin alfa, subjects will be weighed for dosing as per the local standard of care.
[h] Relevant medical history (with particular emphasis on previous medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases will be documented.

[i] Review of medical history for new conditions since SV2.
[j] A physical examination (including height) is required at SV2. Thereafter, an abbreviated symptom-directed physical examination will be performed at the discretion of the Investigator, as clinically indicated.
[k] A standard 12-lead ECG will be performed at Baseline/Day 1, which may be obtained up to 3 days prior to Baseline/Day 1. The ECG will be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and will be taken prior to vital sign assessments and blood draws when possible. 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.
[l] In weeks where there is no scheduled study visit (Weeks 3, 5, 7, 9, 15, and 17, and 19), a subject will have a status check performed during one of their dialysis treatment appointments in the week. It will include a review of the subject's vital signs and a review of current health status for identification of any issues that may require follow-up by the Investigator or delegated staff personnel. Documentation of the review must be done in the subject's source documentation. No data will be captured on the status checks in the EDC system. If an AE is identified at the status check or other actions result from the status check, these will be captured per the protocol.
[m] AE collection will begin from time of randomization through 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. Subjects must be followed for AEs until the final required protocol visit (study end date) or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
[n] A serum pregnancy test will be performed at SV2 for females of childbearing potential. Additional serum 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 drug. A FSH test will be performed at SV2 for post-menopausal females.
[o] A CBC without differential will be performed at all noted visits, except Baseline/Day 1 and Visit 14 (EOT). The CBC without differential will include: Hb, hematocrit, RBCs, MCV, MCH, MCHC, RDW, WBC count, and platelets.
[p] Hb will be monitored throughout the study via central laboratory to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive. Hb levels can be measured more frequently based on Investigator's clinical judgment. For eligibility purposes, one retest for Hb may be performed during the Screening Period. Two Hb values measured at least 4 days apart by the central laboratory during Screening (SV1, SV2 or retest) must be between 8.5 and 11.0 g/dL, inclusive, for the Main study and 8.0 and 10.0 g/dL, inclusive, for the ESA hyporesponder parallel study.
[q] A CBC with differential will be performed at Baseline/Day 1 and Visit 14 (EOT). The CBC with differential will include the same parameters as CBC without differential with the addition of WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
[r] The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, BUN, CPK, uric acid, albumin, and total protein.
[s] LFTs: total bilirubin, ALP, ALT/SGPT, AST/SGOT, and lactate dehydrogenase.
[t] Iron Indices: ferritin, iron, transferrin, TIBC, and TSAT.
[u] Lipid Profile: total cholesterol, LDL, HDL, and triglycerides.
[v] The biomarkers will include, but are not limited to, VEGF and hepcidin. Samples for VEGF and hepcidin biomarker analyses will be drawn at Baseline/Day 1, Visit 9 and 14 (EOT).
[w] Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study will be collected at Baseline/Day 1, Week 1, and Week 11 as outlined in Section 9.2.2.1. For all PK and PD sampling, the time of the previous dose of vadadustat will be collected for the pre-dose sample and the timing of administration of vadadustat, and the start and stop time of the dialysis session will be recorded.
[x] Visit 10/Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Visit 10/Week 13 PK/PD sampling.
[y] Blood for measurement of EPO level in the epoetin alfa arm, in both the Main study and ESA hyporesponder parallel study, will be collected at Baseline/Day 1 and Week 1 as outlined in Section 9.2.2.2. For all PK sampling the time of the previous dose of epoetin alfa is to be collected for the pre-dose sample and the timing of administration of epoetin alfa and the start and stop time of the dialysis session will be recorded.
[z] Concomitant medications should be collected and recorded at each visit as noted. All medications taken within 30 days prior to Baseline/Day 1 will be recorded.
[aa] Epoetin alfa dosing will stop for a minimum of 5 days before Baseline/Day 1 in the Main study or 2 days before Baseline/Day 1 in the ESA hyporesponder parallel study.
[bb] After the end of vadadustat treatment at Visit 14/Week 20 (or following early discontinuation of vadadustat), subjects will resume dosing with epoetin alfa (or another ESA), based on standard of care.
[cc] Subjects in the low epoetin alfa dose group randomized to vadadustat treatment will start at an initial dose of vadadustat 300 mg or 450 mg daily. Subjects in the high epoetin alfa dose group randomized to vadadustat treatment will receive an initial dose of 300 mg, 450 mg, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat treatment will receive a starting dose of vadadustat 600 mg daily. For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.
[dd] After completing the 12-week once daily dosing regimen, subjects randomized to vadadustat who meet criteria for switching from daily to TIW dosing will initiate TIW dosing at a starting dose 1 tablet greater (+150 mg) than the final dose in the daily dosing period. Central laboratory Hb values from Visit 8/Week 11 (11 weeks of treatment completed) will be used to determine if subjects meet Week 12 Transition criteria.
[ee] Subjects will be provided with a supply of vadadustat at Baseline/Day 1 and will be resupplied at Visit 4, 6, 9 and 12 or an unscheduled dispensing visit as needed. Subjects will be instructed to complete 1 bottle before opening a new bottle. The dose should be taken at approximately the same time each day.

[ff] IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol in Section 8.4.8. Oral iron supplementation including iron-containing phosphate binders are prohibited during the study.
[gg] IWRS visit registration for vadadustat arm only for bottle dispensing

APPENDIX B: PK/PD SAMPLING

PK/PD Sampling in Vadadustat Arm Subjects Who Transition to TIW Dosing at Week 12

	Baseline/Day 1 QD	Week 1 QD	Week 1 + 1 day	Week 11 QD	Week 13 TIW		
	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	●						
15 minutes (pre-dose)		●	●	●		●	
2 hours ± 15 minutes (post-dose)		●	●	●		●	
3.5 hours ± 15 minutes (post-dose)		●	●	●		●	
5 hours ± 30 minutes (post-dose)		●	●	●		●	
7 hours ± 30 minutes (post-dose)		●	●	●		●	
10.5 hours ± 1.5 hours (post-dose)		●		●		●	

Note: Gray shading indicates sample collection at a subset of study sites only.

PK/PD Sampling in Vadadustat Arm Subjects Who Do Not Transition to TIW Dosing at Week 12

	Baseline/Day 1 QD	Week 1 QD	Week 1 + 1 day	Week 11 QD	Week 13 TIW		
	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	•						
15 minutes (pre-dose)		•	•	•			
2 hours ± 15 minutes (post-dose)		•	•	•			
3.5 hours ± 15 minutes (post-dose)		•	•	•			
5 hours ± 30 minutes (post-dose)		•	•	•			
7 hours ± 30 minutes (post-dose)		•	•	•			
10.5 hours ± 1.5 hours (post-dose)		•		•			

Note: Gray shading indicates sample collection at a subset of study sites only.

PK Sampling in Epoetin Alfa Arm

	Baseline/Day 1 TIW	Week 1 TIW	Week 1 + 2 days	Week 11 TIW	Week 13 TIW		
	Dialysis Day	Dialysis Day	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	•						
15 minutes (pre-dose)		•	•				
2 hours ± 15 minutes (post-dose)		•					
3.5 hours ± 15 minutes (post-dose)		•					
5 hours ± 30 minutes (post-dose)		•					
7 hours ± 30 minutes (post-dose)		•					
10.5 hours ± 1.5 hours (post-dose)		•					

Note: Gray shading indicates sample collection at a subset of study sites only.

APPENDIX C: HISTORY OF AMENDMENTS TO THE PROTOCOL

Amendment 1 (Version 1.3 10 September 2018)

Amendment 1 was issued based on sponsor assessment and external input.

The major changes introduced in the amendment are summarized below:

- Addition of an Exclusion Criterion of Subjects with bilateral native nephrectomy, to minimize potential variability in hemoglobin response observed in this Phase 2 PK/PD study that may arise from a decreased capacity to augment endogenous erythropoietin (EPO) production in the setting of bilateral nephrectomy.
- Addition of language to provide explicit guidance on early termination from the study for subjects who undergo a solid organ, hematopoietic stem cell, or bone marrow transplantation while participating in the study.
- Update to the description of the vadadustat tablet since new lots of vadadustat may include imprinting on the tablet. This is also referred to as a debossed tablet.
- Preliminary results of clinical drug-drug interaction studies showed a moderate interaction between vadadustat and rosuvastatin and no clinically significant interaction between vadadustat and pravastatin. Based on the data from these studies, guidance has been added to the protocol on how to manage the use of statins in combination with vadadustat.
- Removal of the requirement to assess and document oxygen saturation (SO_2) levels in study subjects for consistency with past and current Akebia DD-CKD protocols, and given that measurement of SO_2 levels is not required in the setting of vadadustat or epoetin alfa use or in the routine management of subjects with DD-CKD.
- AE reporting period clarified as starting at randomization in case there is a delay between date of randomization and date of first study drug dose.

CLINICAL PROTOCOL

PHASE 2, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS STUDY OF ORAL VADADUSTAT FOR THE TREATMENT OF ANEMIA IN HEMODIALYSIS SUBJECTS CONVERTING FROM EPOETIN ALFA (FO_2RWARD-2)

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0025
US IND Number:	102,465
Phase:	Phase 2
Protocol Version / Date:	Amendment 2 (Version 3.0 / 05 APRIL 2019) Amendment 1 (Version 2.0 / 11 SEPTEMBER 2018) Original Version 1.0 / 27 JUNE 2018
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Cambridge, MA 02142 United States of America

1 SIGNATURE PAGES

1.1 Protocol Approval

[redacted]

Signature

[redacted]

Signature Date

[redacted]

Signature Date

[redacted]

Signature Date

[redacted]

Signature Date

[redacted]

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Phone Number

Full Address

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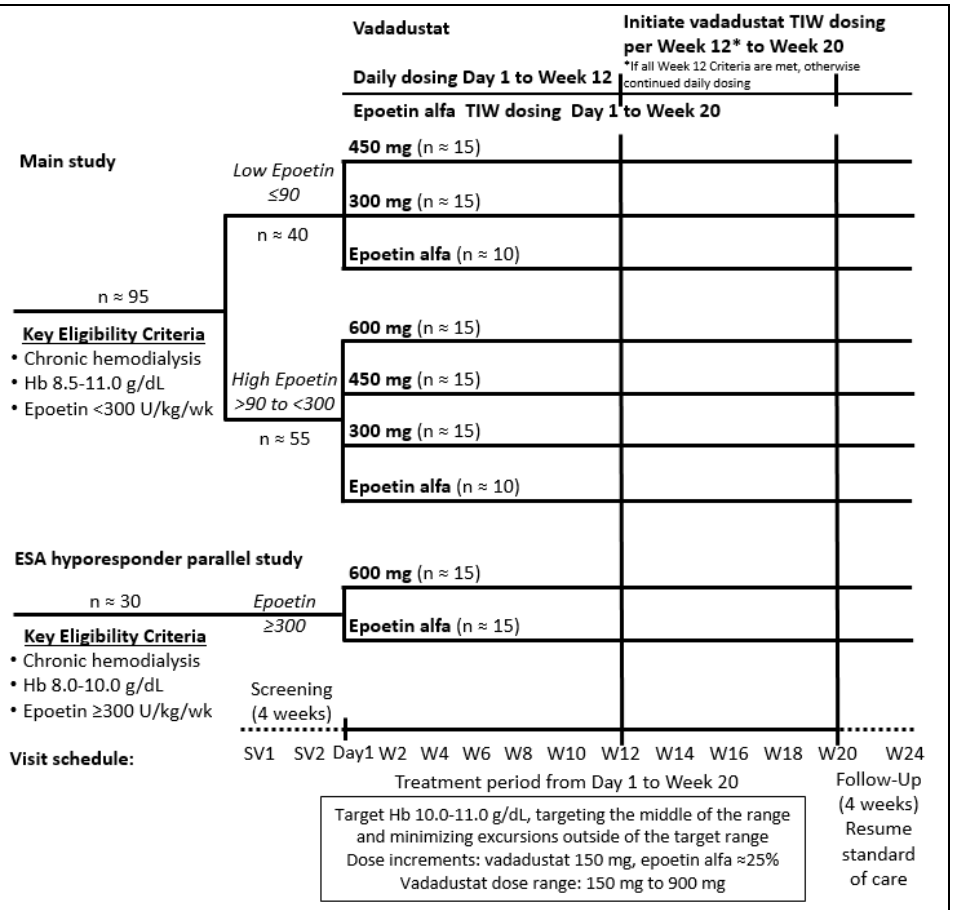
2 PROTOCOL SYNOPSIS

Study Title	Phase 2, Randomized, Open-Label, Active-Controlled, Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics Study of Oral Vadadustat for the Treatment of Anemia in Hemodialysis Subjects Converting from Epoetin Alfa (FO_2RWARD-2)
Protocol Number	AKB-6548-CI-0025
Study Phase	Phase 2
Investigational Product	Vadadustat; 150 mg tablets
Reference Medicinal Product	Epoetin alfa solution for intravenous (IV) injection in multi-dose vials or in single-dose vials
Study Population	The Main study population will consist of adult subjects receiving chronic, outpatient in-center hemodialysis three times weekly (TIW), with 2 screening hemoglobin (Hb) values between 8.5 and 11.0 g/dL (inclusive) and on maintenance treatment with epoetin alfa <300 U/kg/week. The erythropoiesis-stimulating agent (ESA) hyporesponder parallel study will consist of adult subjects receiving chronic, outpatient in-center hemodialysis TIW, with 2 screening Hb values between 8.0 and 10.0 g/dL (inclusive) and on maintenance treatment with epoetin alfa ≥300 U/kg/week.
Study Sites	Approximately 40 study sites in the United States (US)
Planned Number of Subjects	Approximately 125 subjects • Main study: ~95 subjects • ESA hyporesponder parallel study: ~30 subjects
Primary Objective	To assess the efficacy and safety of daily dosing of vadadustat compared to epoetin alfa for 12 weeks in hemodialysis subjects
Secondary Objectives	• To assess the efficacy and safety of TIW dosing of vadadustat in selected hemodialysis subjects who have been successfully managed with daily dosing of vadadustat through Week 12 • To evaluate the pharmacokinetics (PK)/pharmacodynamics (PD) of daily and TIW dosing of vadadustat in hemodialysis subjects compared to epoetin alfa • To assess the efficacy and safety of several dosing strategies of vadadustat compared to epoetin alfa during a 20-week Treatment Period in hemodialysis subjects
Overview of Study Design	This is a Phase 2, randomized, open-label study to evaluate vadadustat for the treatment of anemia in hemodialysis subjects converting from epoetin alfa therapy. For all subjects (Main study and ESA hyporesponder parallel study), the study will include a Screening Period, a Treatment Period, and a Safety Follow-Up Period as described below. PK and PD sampling will be done throughout the study (see PK and PD Sampling sections for details). The aim is to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Screening Period (up to 28 days; Day -28 to Baseline/Day 1) For all subjects (Main study and ESA hyporesponder parallel study) the Screening Period starts at the time the informed consent is signed and will be a maximum of 28 days in duration. Baseline/Day 1 will be performed within 28 days of the start of Screening. Subjects who meet all eligibility criteria will be randomized to a vadadustat treatment arm or an epoetin alfa treatment arm. Subjects will be required to stop epoetin alfa treatment for a minimum duration of 5 days before Baseline/Day 1 in the Main study and for a minimum of 2 days before Baseline/Day 1 in the ESA

	hyporesponder parallel study. In the Main study, randomization will be stratified by the mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to Screening Visit 2 (SV2). • Low epoetin alfa dose group (≤90 U/kg/week) or • High epoetin alfa dose group (>90 to <300 U/kg/week) **Study Treatment Period (Baseline/Day 1 to Week 20)** For all subjects (Main study and ESA hyporesponder parallel study), the Treatment Period will run from Baseline/Day 1 to Week 20. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/L, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range. Subjects in the Main study randomized to vadadustat: • Subjects in the low epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300 or 450 mg daily. • Subjects in the high epoetin alfa dose group will start vadadustat at an initial, randomly allocated dose of 300, 450, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat: • Subjects will receive a starting dose of vadadustat 600 mg daily. Transition to TIW for all subjects randomized to vadadustat: All subjects randomized to vadadustat (Main study and ESA hyporesponder parallel study) who complete the 12-week once daily dosing regimen and who meet all the Week 12 transition criteria for switching from daily to TIW dosing, will initiate TIW dosing at a starting dose one tablet greater (+150 mg) than the final dose in the daily dosing period. Subjects who do not meet criteria for switching from daily to TIW dosing will remain on daily dosing. Subjects in both the Main study and ESA hyporesponder parallel study randomized to epoetin alfa: All subjects randomized to epoetin alfa will receive TIW dosing for the entire Treatment Period based on the subject's central laboratory Hb value and the approved epoetin alfa US Package Insert (PI) for adult patients with chronic kidney disease (CKD) on dialysis. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range. **Safety Follow-Up Period (Weeks 20 to 24)** For all subjects (Main study and ESA hyporesponder parallel study), the 4-week Safety Follow-Up Period starting at Week 20 will be followed by a post-treatment safety assessment conducted at the beginning of Week 24.

Study Schematic	
Study Duration	Individual subjects will participate in the study for up to 28 weeks, including a Screening Period of up to 4 weeks, a 20-week Treatment Period and a 4-week Safety Follow-Up Period.
Inclusion Criteria	Subjects must meet the following inclusion criteria: 1. ≥18 years of age 2. Receiving chronic, outpatient in-center hemodialysis (TIW) for end-stage renal disease for at least 12 weeks prior to Screening 3. Maintained on IV epoetin alfa therapy for 8 weeks prior to and including Screening through SV2 4. Eligibility in the Main study and ESA hyporesponder parallel study is based on the following mean weekly epoetin alfa doses: • Main study: Mean weekly epoetin alfa dose <300 U/kg/week for 8 weeks prior to SV2 • ESA hyporesponder parallel study: Mean weekly epoetin alfa dose ≥300 U/kg/week for 8 weeks prior to SV2 5. Two Hb values measured by the central laboratory at least 4 days apart between SV1 and SV2 as indicated below: • Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive • ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive 6. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening

	7. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening 8. Hemodialysis adequacy as indicated by single-pool Kt/V_{urea} ≥1.2 using the most recent historical measurement within 8 weeks prior to or during Screening 9. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.
Exclusion Criteria	Subjects must not meet any of the following exclusion criteria: 1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia) 2. Active bleeding or recent blood loss within 8 weeks prior to randomization 3. Red blood cell (RBC) transfusion within 8 weeks prior to randomization 4. Anticipated to discontinue hemodialysis during the study 5. Judged by the investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study 6. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver) 7. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >1.5 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded. 8. Current uncontrolled hypertension as determined by the investigator that would contraindicate the use of epoetin alfa 9. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening 10. History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Subjects with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded. 11. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening 12. History of hemosiderosis or hemochromatosis 13. History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded) 14. Scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months 15. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded) 16. Known hypersensitivity to vadadustat, epoetin alfa, or any of their excipients 17. Any prior use of a HIF-PH inhibitor or any use of an investigational medication within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to randomization. 18. For female subjects: a. Of non-childbearing potential i. Inability to confirm surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or

	ii. Not considered post-menopausal (no menses for >1 year with follicle stimulating hormone >40 U/L at Screening) b. Or, if of childbearing potential i. Lack of confirmation of the use of acceptable forms of contraception* for a minimum of one complete menstrual cycle prior to Screening ii. Positive serum pregnancy test at SV2 iii. Unwilling to use two acceptable forms of contraception* (at least one of which must be a barrier method) starting Baseline/Day 1, throughout the Treatment Period and for 30 days after the final study drug administration 19. Breastfeeding during Screening or throughout the Treatment Period and for 30 days after the final study drug administration. 20. Donation of ova starting at Screening, throughout the Treatment Period, and for 30 days after the final study drug administration. 21. Male subjects who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception* during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat. 22. Subjects with bilateral native nephrectomy. 23. Any other reason, which in the opinion of the investigator, would make the subject not suitable for participation in the study. * *Acceptable forms of contraception include:* • *Established use of oral, injected or implanted hormonal methods of contraception.* • *Placement of an intrauterine device or intrauterine system.* • *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.*
Retesting/Rescreening	**Retesting** Retesting is defined as repeating laboratory tests within the same Screening Period. Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 4-week Screening Period, per investigator discretion. **Rescreening** Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the investigator if it is considered that the subject status has changed, and the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on inclusion criteria values for 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). A new informed consent is required to be signed prior to every rescreening.

Efficacy Endpoints	**Primary Endpoint** Mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 10 to 12) **Key Secondary Endpoints** • Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) • For subjects who transitioned to TIW vadadustat dosing, mean change in Hb from primary evaluation period (average Hb from Weeks 10 to 12) to the secondary evaluation period (average Hb from Weeks 18 to 20) **Other Secondary Endpoints** • Mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 18 to 20) • Proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • For subjects who transitioned to TIW vadadustat dosing, proportion of subjects with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • Proportion of subjects with a mean increase in Hb from Baseline to the primary evaluation period ≥0.5 g/dL (average Hb from Weeks 10 to 12) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the primary evaluation period (Weeks 10 to 12) • Proportion of subjects with a mean increase in Hb from Baseline to the secondary evaluation period ≥0.5 g/dL (average Hb from Weeks 18 to 20) or with Hb values within the target range (10.0 to 11.0 g/dL, inclusive) at the secondary evaluation period (Weeks 18 to 20) • IV iron supplementation • ESA rescue • RBC transfusion **Exploratory Endpoints** [redacted]
PK/PD Endpoints	An exposure-response analysis of vadadustat and PD measures will be conducted as deemed appropriate. The PK parameters will include (but are not limited to) the following: • area under concentration-time curve from dosing to last measurable concentration (AUC_{last}) • area under concentration-time curve from dosing to infinity (AUC_{inf}) • maximum concentration (C_{max}) • Apparent total body clearance (CL/F) • Apparent volume of distribution (V_d/F)

	• Terminal half-life ($t_{1/2}$) The PD parameters will include (but are not limited to) the following: • Erythropoietin (EPO) • Reticulocytes • Iron • Ferritin • Total iron binding capacity (TIBC) • Hepcidin
Safety Endpoints	• Adverse events (AEs) • Vital sign measurements and clinical laboratory values • Hb >12.0 g/dL, >13.0 g/dL, or >14.0 g/dL • Hb <8.0 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (Main Study); Hb <7.5 g/dL and decline in Hb ≥0.5 g/dL from Baseline Hb (ESA hyporesponder parallel study) • Hb increase >1.0 g/dL within any 2-week interval
Dosage and Regimens	The aim is to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Dosing will be initiated at Baseline/Day 1 and the first dose of vadadustat will be administered at the study site after other Baseline/Day 1 procedures have been completed. Thereafter, vadadustat will be taken once daily on an outpatient basis. Subjects may take vadadustat with or without food and will be instructed to swallow the tablet(s) whole. Subjects will be instructed to take vadadustat at roughly the same time each day. Epoetin alfa dose will be administered intravenously at the hemodialysis clinic, based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis. **Note:** A subject may enter the washout period only after all eligibility criteria have been met. During the washout period, no epoetin alfa will be administered for 5 days in the Main study, and 2 days in the ESA hyporesponder parallel study. <u>Main Study:</u> Subjects will be randomized to either a vadadustat treatment arm or epoetin alfa treatment arm. Randomization will be stratified by mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to SV2: • Low epoetin alfa dose group (≤90 U/kg/week) or • High epoetin alfa dose group (>90 to <300 U/kg/week) In the low epoetin alfa dose group, subjects will be randomized in a 3:3:2 ratio to receive either an initial vadadustat daily dose of 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa. In the high epoetin alfa dose group, subjects will be randomized in a 3:3:3:2 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets), 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa. <u>ESA Hyporesponder Parallel Study</u> Subjects will be randomized in a 1:1 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets) or epoetin alfa.

	Epoetin alfa arm in both the Main study and ESA hyporesponder parallel study: For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization. Study Drug Guidelines for Dose Adjustment Dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment (see below). Hb will be monitored via central laboratory throughout the study to determine if the dose of study drug (vadadustat or epoetin alfa) will be adjusted, interrupted, or maintained as follows: • Dose adjustments are based on the investigator's clinical discretion, incorporating the protocol guidance below as well as the subject's current Hb level, trajectory, and variability; symptoms; cardiovascular risk; and other features of his/her clinical condition(s). • If a dose increase or decrease is required to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for epoetin alfa approximately 25%). • In general, do not increase the dose more frequently than once every 4 weeks. A one-time dose increase after 2 weeks is allowed on only two occasions. o A subject's dose may be increased by 1 dose level if the subject has a decline in Hb ≥0.5 g/dL from Baseline/Day 1 in the first 2-week period (the initial period from Baseline/Day 1 to Week 2 following conversion from prior epoetin alfa therapy). o A subject's dose may also be increased by 1 dose level in the first 2-week period after initiation of TIW dosing (from Week 12 to Week 14) for subjects that meet criteria for transitioning from daily to TIW dosing. • Reduce or interrupt the dose in the setting of a rapid rise in Hb (defined as >1.0 g/dL in any 2-week period) • Reduce or interrupt the dose in the setting of Hb >11.0 g/dL • Interrupt the dose in the setting of a Hb >12.0 g/dL until Hb value falls below 11.0 g/dL. After Hb falls below 11.0 g/dL, restart study drug and consider restarting at a lower dose. The minimum dose of vadadustat will be 150 mg daily or TIW (1 tablet daily/TIW) and the maximum dose will be 900 mg daily or TIW (6 tablets daily/TIW). Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen All subjects randomized to vadadustat who complete 12 weeks of once daily dosing regimen **and** who meet all the Week 12 criteria below will be transitioned to a TIW vadadustat dosing regimen. Subjects who meet all of the Week 12 criteria will transition to TIW dosing. Week 12 Transition criteria: • Vadadustat daily dose of 600 mg or lower at Week 12 • Hb within target range of 10.0 to 11.0 g/dL, inclusive, at Week 12 confirmed by central laboratory Hb value from Week 11 (11 weeks of treatment completed) • No receipt of rescue therapy (ESA or RBC transfusion) for worsening of anemia due to CKD from Baseline/Day 1 to Week 12. o ESA or RBC transfusion prior to Week 12 for reasons unrelated to worsening of anemia due to CKD (e.g., surgery, gastrointestinal bleed, or inadvertent administration) is not considered rescue therapy

	• No other reason, based on the investigator's clinical discretion, that would make the subject not suitable for TIW dosing. Selected subjects who meet Week 12 transition criteria will transition to the TIW vadadustat dosing regimen at the Week 12 visit. Subjects on 150, 300, 450, or 600 mg of vadadustat daily at the Week 12 visit will transition to an initial vadadustat TIW dose one tablet greater (+150 mg), i.e., 300, 450, 600, or 750 mg vadadustat TIW, respectively. Subjects will be instructed to take vadadustat on dialysis days. After 2 weeks of treatment in the TIW vadadustat dosing regimen (at Week 14), subjects in any vadadustat TIW dosing arms who have a decline in Hb ≥0.5 g/dL will be eligible for a dose increase by 1 tablet, based on the investigator's clinical discretion. Subjects who are not eligible to switch from daily vadadustat to TIW dosing at Week 12 will remain on daily dosing for the remainder of the study. Subjects on TIW dosing may be converted back to vadadustat once daily dosing at the discretion of the investigator in the setting of inadequate Hb response. The starting daily dose after the switch from TIW to daily dosing will be based on the investigator's discretion after review of the subject's clinical status and dosing history, in particular, the daily dose previously administered to the subject prior to the transition to TIW dosing (Week 12). Subjects who switch from vadadustat TIW to daily dosing will continue once daily vadadustat until the end of the Treatment Period. Subjects in the vadadustat arm will be guided for dosing compliance using an electronic diary (eDiary) or through paper dosing reminders.
PK/PD Sampling - vadadustat arm	Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below. Preferably, PK/PD samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week). At Baseline/Day 1, PK/PD samples will be collected prior to dialysis and administration of vadadustat. At Week 1 (after at least a full week of vadadustat treatment), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose On the following non-dialysis day, blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes post-dose At Week 11, vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows: • 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose • From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose At Week 13 (after at least one week on TIW vadadustat dosing regimen), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

<table>
<tr><td></td><td>

15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes hours post-dose
From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

Note: Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Week 13 PK/PD sampling.
</td></tr>
<tr><td>PK Sampling - epoetin alfa arm</td><td>
Blood for measurement of EPO level in the epoetin alfa arm in both the Main study and ESA hyporesponder parallel study will be collected as outlined below. Preferably, PK samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).
At Baseline/Day 1, a sample will be collected prior to dialysis and administration of epoetin alfa.
At Week 1 (after at least a full week of study epoetin alfa treatment), epoetin alfa will be administered within 1 hour after start of dialysis. Blood samples will be collected as follows:

15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

On the following dialysis day, one blood sample will be collected 15 minutes prior to administration of epoetin alfa.
</td></tr>
<tr><td>Iron Supplementation</td><td>
IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol below:
<table>
<tr><th></th><th>Ferritin
<200 ng/mL</th><th>Ferritin
200-500 ng/mL</th><th>Ferritin
>500 ng/mL</th></tr>
<tr><td>TSAT
<20%</td><td>IV Iron 100 mg every treatment
(max 400 mg/month)</td><td>IV Iron 50 mg weekly</td><td>Hold</td></tr>
<tr><td>TSAT
20-50%</td><td>IV Iron 100 mg every week</td><td>IV Iron 50 mg weekly</td><td>Hold</td></tr>
<tr><td>TSAT
>50%</td><td>Hold</td><td>Hold</td><td>Hold</td></tr>
</table>
IV: intravenous; TSAT: transferrin saturation
Subjects already receiving oral iron supplementation as part of their treatment plan may continue their current treatment regimen. 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 oral medications containing iron.
Subjects will be instructed to take any oral medications containing iron at least 2 hours after the dose of vadadustat.
</td></tr>
</table>

Rescue Therapy Guidelines	To ensure the safety of subjects and to standardize the use of rescue in the study, rescue therapy guidelines are provided. 1. 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 will 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 medical necessity. Study drug (vadadustat or epoetin alfa) may be continued during the transfusion period. Reasons for RBC transfusion will be captured in the appropriate CRF. 2. ESA Use: ESA administration will be allowed when medically necessary at the discretion of the investigator. In general, ESA will not be administered in subjects with Hb ≥8.5 g/dL, and ESA rescue will be stopped when Hb ≥9.0 g/dL. ESA therapy will be administered using an approved ESA and dosing as per the local institution's guidelines and per the approved product label. While receiving ESA therapy, subjects randomized to vadadustat must temporarily interrupt vadadustat. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA, and treatment will be resumed after the following intervals: • 2 days after last dose of epoetin alfa • 7 days after last dose of darbepoetin alfa • 14 days after last dose of methoxy polyethylene glycol-epoetin beta Following ESA administration, vadadustat will be resumed at the same dose as previously used or with one additional tablet (+150 mg) at the discretion of the investigator. Reasons for ESA use will be captured in the appropriate CRF.
Phlebotomy	If a subject's Hb exceeds 14.0 g/dL or the rate of rise of Hb raises concern to the investigator, the subject may be phlebotomized based on the investigator's clinical judgment. The method of phlebotomy will be in accordance with the study site's standard clinical practice.
Study Medication Stopping Rules	Study medication must be permanently discontinued if a subject meets one of the following criteria: • ALT **or** AST >3x Upper Limit of Normal (ULN) **and** total bilirubin >2x ULN • ALT **or** AST >3x ULN **and** international normalized ratio (INR) >1.5 • ALT **or** AST >8x ULN • ALT **or** AST remains >5x ULN over 2 weeks • ALT **or** AST >3x ULN with symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash) **or** eosinophilia
Concomitant Medications	1. ESA Co-administration of any ESA with vadadustat is 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 ESA Rescue) if deemed medically necessary at the discretion of the investigator. Guidelines for ESA administration as rescue therapy are provided above. All efforts will be made to avoid inadvertent administration of ESAs resulting from adherence to ESA hemodialysis center protocols (e.g., DaVita ESA protocols for patients 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. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA. Vadadustat treatment may be resumed after the following intervals: • 2 days after last dose of epoetin alfa • 7 days after last dose of darbepoetin alfa • 14 days after last dose of methoxy polyethylene glycol-epoetin beta 2. Iron See guidance above (Iron Supplementation). 3. Phosphate binders Subjects will be instructed to take phosphate binders (iron-containing and non-iron-containing phosphate binders) at least 2 hours after the dose of vadadustat.
Study Completion, Subject Completion, Temporary Interruption of Study Drug, Early Discontinuation from Study (Early Termination)	**Study Completion** The study will be considered completed after all randomized subjects have completed their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination). **Subject Completion** A subject will be considered as having completed the study after completion of their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination). **Temporary Interruption of Study Drug** During the study, a subject may interrupt study drug (vadadustat or epoetin alfa) for any of the following reasons: • AE • Missed dialysis visit (epoetin alfa arm) • Investigator's discretion • Rapid rise in Hb (defined as >1.0 g/dL in any 2-week period) • Hb above 11.0 g/dL • ESA use (vadadustat arm) Unless contraindicated, treatment will be resumed whenever possible and assessed at every visit following study drug interruption. **Early Discontinuation from Study (Early Termination)** Subjects who discontinue prematurely from the study will complete the End-of-Treatment visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14. Subjects may discontinue for any of the following reasons: • AE • Investigator's discretion • Subject withdrawal of consent • Lack of efficacy • Lost to follow up despite reasonable efforts by the investigator to locate the subject • Death • Other reasons (pregnancy, kidney transplantation, specific reasons to be documented by the investigator) Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or epoetin alfa) permanently discontinued and will complete the End-of-Treatment (Visit 14) and

	Safety Follow-Up (Visit 15) visit assessments.
Study Termination/ Individual Study Site Termination	The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advanced notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination. If the study has been suspended or terminated, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.
Statistical Considerations	Efficacy and safety endpoint analysis will be descriptive in nature. Continuous variables will be summarized using number of subjects with mean, standard deviation (SD), median, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated. PK and PD parameters will be summarized using descriptive statistics: number of subjects, mean, median, SD, minimum, maximum, and coefficient of variation, geometric mean and geometric mean SD. The ESA hyporesponder parallel study will be analyzed separately from the main study.
PK Analysis	A PK analysis will be conducted using non-compartmental analyses to describe vadadustat PK parameters. PK analysis will be reported separately.
PD Analysis	Samples for the PD endpoints (EPO, reticulocytes, iron, Ferritin, hepcidin, and TIBC) will be collected at multiple intervals during the study. An exposure-response analysis of vadadustat, EPO and other PD measures will be conducted as deemed appropriate. PD analysis may be reported separately.
Sample Size Estimation	Approximately 95 subjects are planned for enrollment in the Main study with 40 and 55 subjects randomized to the low epoetin alfa dose group and the high epoetin alfa dose group respectively. Approximately 30 subjects are planned for enrollment in the ESA hyporesponder parallel study. Sample size reflects the exploratory nature of this study. Enrollment may be increased by up to approximately 20 additional subjects in the Main study, and by up to approximately 30 additional subjects in the ESA hyporesponder parallel study to ensure adequate data are captured for the primary, PK/PD, and safety endpoints.
Safety Monitoring	This is an open label study allowing the study team full access to safety data which will be reviewed on a regular basis, throughout the course of the study. Safety monitoring will be performed as described in the Medical Monitor Plan.

3 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under concentration-time curve
AUC_{inf}	area under concentration-time curve from dosing to infinity
AUC_{last}	area under concentration-time curve from dosing to last measurable concentration
BCRP	breast cancer resistance protein
BP	blood pressure
CBC	complete blood count
CKD	chronic kidney disease
CL/F	apparent total body clearance
C_{max}	maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
DD-CKD	dialysis dependent chronic kidney disease
DME	Designated Medical Event(s)
ECG	electrocardiogram
EDC	electronic data capture
eDiary	electronic diary
EOT	end-of-treatment
EPO	erythropoietin
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FAS	Full Analysis Population
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
Hb	hemoglobin
HF	heart failure
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl-hydroxylase
HR	heart rate
HRQOL	health-related quality of life
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive Web Response System

LFT	liver function test
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NDD-CKD	non-dialysis dependent chronic kidney disease
PGI-C	patient global impression of change
PGI-S	patient global impression of severity
PHD	prolyl 4-hydroxylase domains
PI	Package Insert
PK	pharmacokinetic(s)
PD	pharmacodynamics(s)
PT	Prothrombin Time
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SD	standard deviation
SF-36v2	36-Item Short-Form General Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
$t_{1/2}$	terminal half life
TIBC	total iron binding capacity
TIW	three times a week
T_{max}	time to reach C_{max}
TSAT	transferrin saturation
ULN	upper limit of normal
US	United States
V_d/F	apparent volume of distribution
VEGF	vascular endothelial growth factor

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% to 16% of the population (Jha 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, infection, cancer, and mortality (Iseki 2007).

The prevalence and severity of renal anemia in CKD increases as renal function deteriorates (Di Iorio 2007; Stauffer 2014). As CKD progresses, the combined effect of decreased red blood cell (RBC) production from lower erythropoietin (EPO) signaling, increased rate of RBC destruction, and reduced iron availability to the bone marrow results in the increased prevalence and severity of anemia (Pergola 2016). Anemia generally exists when hemoglobin (Hb) is less than 13.0 g/dL in men or less than 12.0 g/dL in women (KDIGO 2012). Three principal factors contribute to the development of anemia as CKD progresses:

- Peritubular fibroblasts, a type of cell in the kidney, are designed to sense the amount of oxygen carried by the blood. These cells secrete EPO to adjust the production of RBCs by the bone marrow and maintain circulating oxygen levels at normal physiologic levels. As kidney disease progresses, the number of peritubular fibroblasts is reduced and EPO secretion is significantly decreased, leading to a reduction in RBC production (Iseki 2007; Nurko 2006).
- On average, the RBCs in CKD patients have a shorter lifespan (approximate lifespan of 70 days) compared with the RBCs in healthy people (approximate lifespan of 90 to 120 days) (Ly 2004; Nurko 2006). Such a condition leads to increased RBC production in CKD patients to maintain normal physiologic levels.
- The availability of iron to the bone marrow is impaired. Iron is a required component in the formation of Hb, and is essential for the transport of oxygen to the tissues of the body.

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

The risks associated with erythropoiesis-stimulating agents (ESAs), including an increased risk of death and cardiovascular events (Besarab 1998; Drüeke 2006; Pfeffer 2009a; Pfeffer 2009b; Singh 2006), 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 dialysis dependent CKD (DD-CKD) patients remains high. To fulfill this unmet need, the vadadustat clinical program is focused on developing an orally active therapeutic agent 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 (HIF-PHs) for the treatment of anemia associated with CKD. HIF-PH enzymes are also referred to as prolyl 4-hydroxylase domains (PHDs), of which the 2 most commonly expressed isoforms 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.

The efficacy, safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of vadadustat have been characterized in 10 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 non-dialysis dependent CKD (NDD-CKD) subjects, 1 completed Phase 2b study in NDD-CKD subjects, and 1 completed Phase 2 study in DD-CKD subjects. The United States (US) 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, double-blind, placebo-controlled study with 5 different dose groups dosed for 42 days. The US Phase 2b, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 20 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 16 weeks. The US Phase 2 open-label study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. In the studies completed to date, a total of 630 subjects have received vadadustat, including 200 healthy volunteers and 430 subjects with CKD.

Vadadustat has shown 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 and Hb 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 consistent bioavailability with area under

concentration-time curve (AUC) and maximum concentration (C_{max}) in Phase 1 and Phase 2 studies covering the dose range of 80 to 1200 mg after single administration and 500 to 900 mg after repeated daily administration for 10 days. The plasma half-life of vadadustat was about 4 to 6 hours, 7 to 8 hours, and 9 to 10 hours in healthy subjects, NDD-CKD patients, and DD-CKD patients, respectively.

Vadadustat is extensively metabolized and its metabolites are eliminated from the body by dual routes of excretion (both 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.

Multiple doses of 700 and 900 mg daily for up to 10 days (Study AKB-6548-CI-0002 [CI-0002]) and single doses of 1200 mg (Study AKB-6548-CI-0001 [CI-0001], Study AKB-6548-CI-0010 [CI-0010]) have been examined in healthy volunteers. Vadadustat demonstrated dose-proportional PK and achieved serum EPO concentrations up to 34.4 mIU/mL, levels considered physiologic and below exposures achieved with injectable ESAs (Besarb 1992). A higher incidence of adverse events (AEs) in the gastrointestinal System Organ Class (SOC) – nausea, diarrhea, abdominal pain, dyspepsia – was observed in groups treated with 700, 900, or 1200 mg compared with lower vadadustat doses or placebo. Most AEs were mild to moderate, short-lived (1 or 2 days), and assessed as unrelated by investigators. No AEs led to study withdrawal, and no serious adverse events (SAEs) were reported. No clinically meaningful changes or abnormalities in vital signs, safety laboratory studies, or electrocardiogram (ECG) parameters were reported.

A 16-week, open-label, multicenter, Phase 2 trial evaluated vadadustat in 94 subjects receiving chronic hemodialysis previously maintained on epoetin alfa and IV iron form the 3 months prior to Screening (Study AKB-6548-CI-0011 [CI-0011]). Subjects were assigned to one of three vadadustat dose cohorts: 300 mg daily, 450 mg daily, or 450 mg three times a week (TIW). Dosing was fixed for the first 8 weeks; for the subsequent 8 weeks dose was adjusted from 150 to 600 mg according to Hb response based upon a dose adjustment algorithm. Sixty-nine of the 94 subjects completed the study. The primary endpoint was the mean Hb concentration change from pre-treatment average (Screening Visit 1, Screening Visit 2, and Baseline Visit) to mid-study (Weeks 7 to 8) and end-of-study (Weeks 15 to 16) and was analyzed using observed Hb values (no imputation for missing data). No statistically significant mean change in Hb from pre-treatment average was observed for either of the two time points for any of the three treatment groups.

Among subjects randomized to an initial dose of 300 mg daily, 450 mg daily, or 450 mg TIW, 0% (0 of 30), 3% (1 of 33), and 19% (6 of 31) of subjects withdrew from the study due to worsening anemia, respectively. In a sensitivity analysis using last observation carried forward (LOCF) for the primary efficacy endpoint, no significant mean change in Hb from pre-treatment levels was observed in the 300 mg daily dosing group. At Weeks 15 to 16, modest, statistically significant mean decreases were observed in the 450 mg daily and 450 mg TIW dosing groups.

In a post-hoc univariate analysis of baseline characteristics, higher pre-baseline epoetin alfa dose was associated with a decrease in mean Hb at Weeks 7 to 8 and Weeks 15 to 16 in the dosing cohorts. Subjects who discontinued the study due to worsening anemia had a higher mean pre-

baseline epoetin alfa dose compared with subjects who discontinued due to other reasons or subjects who completed the study.

Based on 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.

In the ongoing global Phase 3 and Japanese Phase 3 clinical studies, over 7000 subjects are planned to be treated with vadadustat or comparator.

This study will evaluate efficacy, safety and PK/PD with different vadadustat dosing strategies in hemodialysis subjects converting from epoetin alfa to further characterize the optimal vadadustat regimen. This study is the first study to examine vadadustat doses of 750 and 900 mg in DD-CKD subjects.

4.3 Potential Benefits and Risks

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

Trials of injectable 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 2009a). Post-hoc analyses performed by the Food and Drug Administration (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 2007). Potential clinical benefits include enhanced erythropoiesis and decreased exogenous iron requirements.

In nonclinical safety studies, the main findings originated from an exaggerated pharmacological response that results in increased erythropoiesis, polycythemia, blood hyperviscosity, and the formation of fibrin thrombi in multiple organs. Early mortality noted in the mouse and rat and moribundity in the dog were due to the sequelae associated with polycythemia. These findings were reproducible across species and studies, dose-dependent and showed reversibility. Dose-limiting toxicity in the exploratory toxicology studies was due to hemoglobinuric nephropathy (rat) and emesis associated with body weight loss (dog).

In completed Phase 1 clinical studies of vadadustat in healthy volunteers, there were low numbers of treatment-emergent AEs. The most frequently reported AEs were in the gastrointestinal disorders (i.e., nausea, diarrhea, abdominal pain, flatulence, dyspepsia) and nervous system disorders (i.e., headache, dizziness) SOC. The majority of AEs were mild to moderate in severity.

The most frequently reported AEs in completed Phase 2 studies of NDD- and DD-CKD subjects were in the following SOCs: gastrointestinal disorders (nausea, diarrhea, vomiting),

cardiovascular disorders (hypertension, hypotension, coronary artery disease), renal (renal failure chronic, renal failure acute), infections and infestations (gastroenteritis, urinary tract infection, pneumonia), and metabolism and nutrition disorders (hyperkalemia, fluid overload). Four deaths occurred in the completed Phase 2 clinical studies.

Identified risks include nausea, diarrhea, vomiting, headache, abdominal pain, and uric acid elevations. Hypersensitivity, hyperkalemia and hypertension have been identified as potential risks and hepatotoxicity has been identified as an important potential risk associated with vadadustat therapy.

Review of safety data from completed Phase 1 and 2 clinical studies, as well as review of accumulating data from ongoing studies, continue to support further development of the vadadustat program.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

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

5.2 Secondary Objectives

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

5.3 Efficacy Endpoints

5.3.1 Primary Endpoints

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

5.3.2 Key Secondary Endpoints

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

5.3.2.1 Other Secondary Endpoints

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

- ESA rescue
- RBC transfusion

5.3.2.2 Exploratory Endpoints

[redacted]

5.4 PK/PD Endpoints

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

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

- Area under concentration-time curve from dosing to last measurable concentration (AUC_{last})
- Area under concentration-time curve from dosing to infinity (AUC_{inf})
- C_{max}
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (V_d/F)
- Terminal half-life ($t_{1/2}$)

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

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

5.5 Safety Endpoints

Safety endpoints in this study include the following:

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

6 STUDY DESIGN

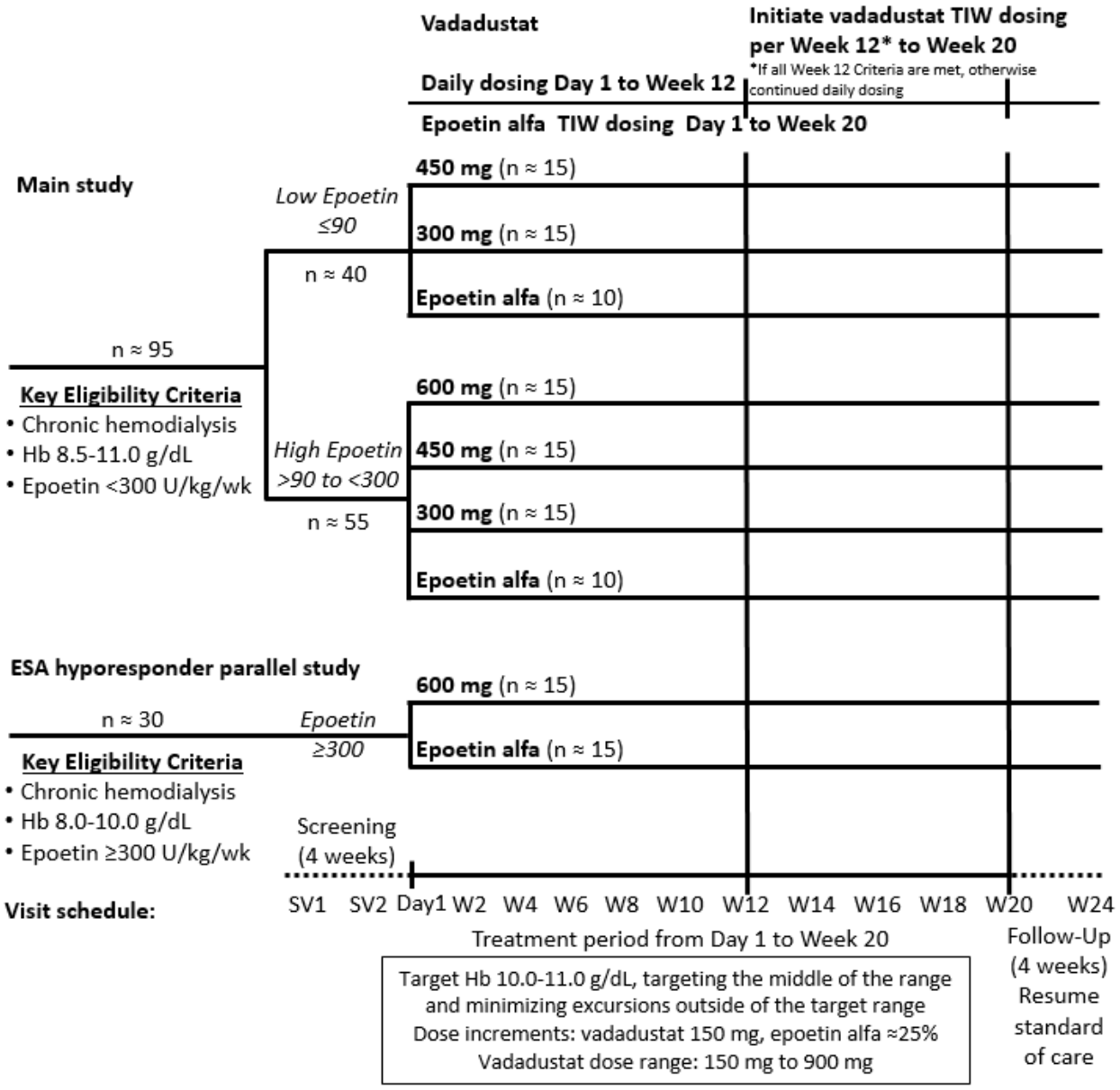
6.1 Study Design

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

For all subjects (Main study and ESA hyporesponder parallel study), the study (as shown in Figure 1) will include a Screening Period, a study Treatment Period, and a Safety Follow-Up Period as described below. PK and PD sampling will be done throughout the study (see PK and PD Sampling Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa, respectively, for details).

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

FIGURE 1:OVERVIEW OF STUDY DESIGN



ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; n: number of subjects; SV: screening visit; TIW: three times per week; W: week

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

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

be stratified by the mean weekly epoetin dose calculated over a period of 8 weeks prior to Screening Visit 2 (SV2):

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

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

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

6.1.2.1 Vadadustat Treatment

Subjects in the Main study randomized to vadadustat:

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

Subjects in the ESA hyporesponder parallel study randomized to vadadustat:

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

Transition to TIW for all subjects randomized to vadadustat:

All subjects randomized to vadadustat (Main study and ESA hyporesponder parallel study), who complete the 12-week once daily dosing regimen and who meet all the Week 12 transition criteria for switching from daily to TIW dosing, will initiate TIW dosing at a starting dose one tablet greater (+150 mg) than the final dose in the daily dosing period (see Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen).

Note: Subjects who are not eligible to switch from daily vadadustat to TIW dosing at Week 12 will remain on daily dosing from the remainder of the study (see Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment).

6.1.2.2 Epoetin Alfa Treatment

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

All subjects randomized to epoetin alfa will receive TIW dosing for the entire Treatment Period based on the subject's central laboratory Hb value and the approved epoetin alfa US Package Insert (PI) for adult patients with CKD on dialysis. Dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside of the target range (see Section 8.4.4, Epoetin Alfa Dosing Regimen).

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

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

6.2 Rationale for Study Design

The Main Study and the ESA hyporesponder parallel study will evaluate different starting doses of vadadustat based on pre-baseline ESA doses. Numerous studies have demonstrated that hemodialysis patients requiring higher ESA doses to treat their anemia have a higher burden of comorbidities, a more inflammatory state, and a greater risk of adverse outcomes (Besarb 1998; Parfrey 2005; Unger 2010). As described above (Section 4.2, Summary of Clinical Experience) in a Phase 2 hemodialysis study (CI-0011), a post-hoc analysis suggested higher pre-baseline ESA doses were associated with lower observed mean Hb levels. Subjects on higher pre-baseline ESA doses may benefit from a higher starting dose of vadadustat after initial conversion from ESAs.

Three levels of pre-baseline ESA dose will be evaluated. In the Main Study subjects will be randomized to one of two cohorts based on pre-baseline ESA dose (≤90 U/kg/week and >90 to <300 U/kg/week). The ESA threshold of 90 U/kg/week was based on the median ESA doses reported in the US Renal Data System and US Dialysis Outcomes and Practice Patterns Study, which ranged from approximately 90 to 110 U/kg/week.

The ESA hyporesponder parallel study will evaluate subjects with Hb levels below the target range despite receiving ≥300 U/kg/week of epoetin alfa. This ESA threshold was based on the definition of resistance to ESAs proposed in the ERA-EDTA 2004 guidelines (Locatelli 2004).

The Main study and the ESA hyporesponder parallel study incorporate an approach to vadadustat dose adjustment designed to maximize the probability that Hb can be maintained within the target range of 10.0 to 11.0 g/dL, inclusive (see Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment). The approach to vadadustat dose adjustment in this Phase 2 study includes several modifications as compared to the vadadustat dosing algorithms used in previously completed Phase 2 studies and the dosing algorithm used in the ongoing Phase 3 studies.

During this study, dose increases for vadadustat will be allowed at 4-week intervals, with the exception of the initial 2 weeks of treatment, in the daily and TIW dosing periods of the study. Dose increases will be permitted in the initial 2 weeks of treatment, in the daily and TIW dosing periods, in subjects with a Hb decline ≥0.5 g/dL from baseline and Week 12, respectively. This approach is commonly used in clinical practice to treat patients with declining or low Hb values (Pfeffer 2009a; Singh 2006). Risk of abrupt or excessive increases in Hb is minimized due to the underlying Hb trajectory and is further mitigated by close Hb monitoring.

In the present study, the safety and efficacy of a vadadustat TIW dosing regimen is being evaluated as a potential alternative treatment regimen to a once daily dosing regimen in hemodialysis subjects. Specifically, this study will evaluate conversion from once daily dosing to TIW dosing. As described above (Section 4.2, Summary of Clinical Experience), the 16-week Phase 2 hemodialysis study evaluated hemodialysis subjects switching from ESA to vadadustat 450 mg TIW for an 8-week fixed-dose period followed by 8 weeks of dose adjustment according to Hb response. The primary efficacy analysis in CI-0011 using observed data showed stable

mean Hb levels in this group. Six of 31 (19%) subjects withdrew due to worsening anemia, and a sensitivity analysis imputing missing Hb values using LOCF demonstrated a decline in mean Hb levels. To maximize the probability that subjects treated with vadadustat TIW will maintain Hb levels within the target range, this study will: examine subjects successfully treated with daily dosing converting to TIW dosing; allow for earlier dose increase after 2 weeks of initial treatment; and permit dose increases up to 900 mg TIW.

6.3 Dose Justification

In this study, vadadustat starting daily doses will be determined by pre-baseline ESA dose (Section 8.4.5, Vadadustat Dosing Regimen and Guidelines for Dose Adjustment). In the Main study starting doses of vadadustat will be 300 and 450 mg daily in subjects converting from epoetin alfa doses ≤90 U/kg/week and 300, 450, and 600 mg daily in subjects converting from epoetin alfa doses >90 to <300 U/kg/week. For the ESA hyporesponder parallel study, the starting doses will be 600 mg daily. As described above (Section 4.2, Summary of Clinical Experience), the maximum vadadustat starting dose evaluated in completed Phase 2 NDD-CKD studies was 630 or 600 mg daily, in Study AKB-6548-CI-0005 (CI-0005) and Study AKB-6548-CI-0021 (CI-0021) respectively, and in completed Phase 2 DD-CKD studies was 450 or 600 mg in Study CI-0011 and Study AKB-6548-CI-0022 (CI-0022), respectively.

Based on the dosing algorithm, vadadustat will be titrated to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive. The dose range for titration is 150 to 900 mg daily or TIW. Doses of 150 to 630 mg daily have been evaluated in studies evaluating subjects with NDD-CKD and DD-CKD. The maximum vadadustat dose evaluated in healthy volunteers was 1200 mg in a single dose study (CI-0001 and CI-0010) and 900 mg daily in a 10-day multiple dose study (CI-0002), as described in Section 4.2, Summary of Clinical Experience. This study is the first study to examine vadadustat doses of 750 and 900 mg in DD-CKD subjects.

The justification to evaluate higher doses is that to date, dose-ranging clinical studies have not identified a vadadustat dose at which a plateau in exposure or effect has been observed. In Phase 1 studies in healthy volunteers, dose-proportional increases in AUC and C_{max} and dose-related increases in serum EPO were observed up to the maximum doses studied, single doses of 1200 mg and multiple doses of 900 mg daily for 10 days (CI-0001, CI-0002). In Phase 2 studies in anemic NDD-CKD and DD-CKD subjects, dose-dependent increases in Hb were observed up to the maximum dose studied of 600 or 630 mg daily (CI-0005, CI-0021, CI-0022). It is anticipated that daily doses of vadadustat at 750 or 900 mg, which yield an increase in systemic exposure above 600 mg of approximately 25% and 50%, respectively, would yield an incremental erythropoietic effect greater than 600 mg for the treatment of anemia associated with CKD.

From a safety and tolerability standpoint, as described above (Section 4.2, Summary of Clinical Experience), multiple doses of 700 and 900 mg daily for up to 10 days (CI-0002) and single doses of 1200 mg (CI-0001, CI-0010) have been examined in healthy volunteers. Vadadustat demonstrated dose-proportional PK and achieved serum EPO concentrations up to 34.4 mIU/mL, levels considered physiologic and below exposures achieved with injectable ESAs (Besarb 1992). A higher incidence of AEs in the gastrointestinal SOC – nausea, diarrhea, abdominal pain, dyspepsia – was observed in groups treated with 700, 900, or 1200 mg compared with lower vadadustat doses or placebo. Most AEs were mild to moderate, short-lived

(1 or 2 days), and assessed as unrelated by investigators. No AEs led to study withdrawal, and no SAEs were reported. No clinically meaningful changes or abnormalities in vital signs, safety laboratory studies, or ECG parameters were reported.

Assessment of animal-to-human safety margins is presented in the Investigator Brochure.

This study design mitigates the risk of vadadustat doses of 750 or 900 mg. Intensive Hb monitoring, a strict dose adjustment algorithm, and phlebotomy will be implemented to mitigate the potential risk of a rapid Hb rise, as follows:

- Hb measurements are scheduled at least every 2 weeks to Week 20
- The dose adjustment algorithm will target a narrow Hb range, 10.0 to 11.0 g/dL, inclusive
- The protocol specifies that phlebotomy may be considered in the setting of high Hb levels (>14.0 g/dL) or a high Hb rate of rise, based on the investigator's judgment

Importantly, the Phase 2 studies demonstrated that cessation of treatment resulted in prompt reduction in mean Hb within 2 to 4 weeks.

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 the subject must meet all eligibility criteria. No study procedures (including Screening tests) may be performed until after the informed consent has been legally signed.

7.2 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. ≥18 years of age
2. Receiving chronic, outpatient in-center hemodialysis (TIW) for ESRD for at least 12 weeks prior to Screening
3. Maintained on IV epoetin alfa therapy for 8 weeks prior to and including Screening through SV2
4. Eligibility in the Main study and ESA hyporesponder parallel study is based on the following mean weekly epoetin alfa doses:
   - Main study: Mean weekly epoetin alfa dose <300 U/kg/week for 8 weeks prior to SV2
   - ESA hyporesponder parallel study: Mean weekly epoetin alfa dose ≥300 U/kg/week for 8 weeks prior to SV2
5. Two Hb values measured by the central laboratory at least 4 days apart between SV1 and SV2 as indicated below:
   - Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive
   - ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive
6. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening
7. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening
8. Hemodialysis adequacy as indicated by single-pool Kt/V_{urea} ≥1.2 using the most recent historical measurement within 8 weeks prior to or during Screening
9. Understands the procedures and requirements of the study and provides written informed consent and authorization for protected health information disclosure.

7.3 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia)
2. Active bleeding or recent blood loss within 8 weeks prior to randomization
3. RBC transfusion within 8 weeks prior to randomization
4. Anticipated to discontinue hemodialysis during the study
5. Judged by the investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study

6. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver)
7. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >1.5 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded.
8. Current uncontrolled hypertension as determined by the investigator that would contraindicate the use of epoetin alfa
9. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening
10. History of new or recurrent malignancy within 2 years prior to and during Screening or currently receiving treatment or suppressive therapy for cancer. Subjects with treated basal cell carcinoma of skin, curatively resected squamous cell carcinoma of skin, or cervical carcinoma in situ are not excluded.
11. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening
12. History of hemosiderosis or hemochromatosis
13. History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded)
14. Scheduled organ transplant from a living donor and subjects on the kidney transplant wait-list who are expected to receive a transplant within 6 months
15. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded)
16. Known hypersensitivity to vadadustat, epoetin alfa, or any of their excipients
17. Any prior use of a HIF-PH inhibitor or any use of an investigational medication within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to randomization
18. For female subjects:
    - Of non-childbearing potential
        - Inability to confirm surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or
        - Not considered post-menopausal (no menses for >1 year with follicle stimulating hormone [FSH] >40 U/L at Screening)
    - Or, if of childbearing potential,
        - Lack of confirmation of the use of acceptable forms of contraception* for a minimum of one complete menstrual cycle prior to Screening
        - Positive serum pregnancy test at SV2

- Unwilling to use two acceptable forms of contraception* (at least one of which must be a barrier method) starting Baseline/Day 1, throughout the Treatment Period and for 30 days after the final study drug administration

  (refer to Section 9.1.5, Contraception and Pregnancy Avoidance Measures)

19. Breastfeeding during Screening or throughout the Treatment Period and for 30 days after the final study drug administration.
20. Donation of ova starting at Screening, throughout the Treatment Period, and for 30 days after the final study drug administration.
21. Male subjects who have not had a vasectomy and do not agree to the following: use of an acceptable form of contraception* (refer to Section 9.1.5, Contraception and Pregnancy Avoidance Measures) during the study and for 30 days after the last dose of the study drug; to not donate semen during the study and for at least 30 days after the last dose of vadadustat.
22. Subjects with bilateral native nephrectomy.
23. Any other reason, which in the opinion of the investigator, would make the subject not suitable for participation in the study.

7.4 Retesting and Rescreening

7.4.1 Retesting

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

Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 4-week Screening Period, per investigator discretion.

7.4.2 Rescreening

Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the investigator if it is considered that the subject status has changed, and the subject may now qualify for the study. Additionally, subjects who fail to qualify for the study based on inclusion criteria values for 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). A new informed consent is required to be signed prior to every rescreening.

7.5 Study Completion, Study Termination, and Individual Site Termination

7.5.1 Study Completion

The study will be considered completed after all randomized subjects have completed their final study visit (Visit 15/Week 24), Safety Follow-Up or Early Termination).

7.5.2 Study Termination

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advanced notice is not required if the study is stopped due to safety concerns. If a study site has been suspended or terminated, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements. Criteria and

procedures 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 study site for various reasons. Criteria and procedures for premature termination or suspension of a study site are detailed in Section 14.2, Criteria for Premature Termination or Suspension of Study Sites and Section 14.3, Procedures for Premature Termination or Suspension of the Study or Study Sites. If a study site has been suspended or terminated, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

7.6 Subject Completion and Subject Discontinuation

7.6.1 Subject Completion

A subject will be considered as having completed the study after completion of their final study visit (Visit 15/Week 24, Safety Follow-Up or Early Termination).

7.6.2 Temporary Interruption of Study Drug

Subjects who temporarily interrupt their study drug (vadadustat or epoetin alfa) after receiving the first dose and prior to completion of the study, will continue with the study visits, safety assessments, and other activities as deemed applicable through Week 20, and will complete the 4-week Safety Follow-Up Period and the Visit 15/Week 24 assessments (see Appendix A: Schedule of Activities.

During the study, a subject may interrupt study drug (vadadustat or epoetin alfa) for any of the following reasons:

- AE
- Missed dialysis visit (epoetin alfa arm)
- Investigator's discretion
- Rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Hb above 11.0 g/dL
- ESA use (vadadustat arm)

Unless contraindicated, treatment will be resumed whenever possible and assessed at every visit following study drug interruption.

7.6.3 Early Discontinuation from Study (Early Termination)

Subjects who discontinue prematurely from the study will complete the End-of-Treatment (EOT) visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14.

Subjects may discontinue for any of the following reasons:

- AE
- Investigator's discretion
- Subject withdrawal of consent

- Lack of efficacy, defined as inadequate response to vadadustat or epoetin alfa in the investigator's opinion
- Lost to follow-up despite reasonable efforts by the investigator to locate the subject. Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.
- Death
- Other reasons (pregnancy, kidney transplantation, specific reasons to be documented by the investigator)

Subjects who undergo a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation will have their study medication (vadadustat or epoetin alfa) permanently discontinued and will complete the End-of-Treatment (Visit 14) and Safety Follow-up (Visit 15) visit assessments.

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

8 STUDY DRUG AND TREATMENT OF SUBJECTS

Subjects will receive either vadadustat or epoetin alfa according to the randomization assignments provided via the Interactive Web Response System (IWRS) (see Section 8.4.1, Randomization).

Both vadadustat and epoetin alfa will be used as open -label supplies. All study drug supplies will 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 drug for dispensing to the subject (Section 8.1, Epoetin Alfa and Section 8.2.2, Dispensing of Vadadustat) and for study drug supply accountability (Section 8.3, Vadadustat Accountability and Destruction).

8.1 Epoetin Alfa

Epoetin alfa solution for IV injection in multi-dose vials (e.g., 20000 U/2 mL and 20000 U/1 mL) or in single-dose vials (e.g., 2000, 3000, 4000, and 10000 U/mL) will be provided by the sites in commercially-approved primary packaging and stored per the approved label.

8.2 Vadadustat

8.2.1 Supplies and Storage

Vadadustat will be provided as 150 mg, white to off-white, round, bi-convex film-coated, debossed or non-debossed 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 and local regulatory requirements.

Dose levels utilized in this study will include: 150 mg (1 tablet), 300 mg (2 tablets), 450 mg (3 tablets), 600 mg (4 tablets), 750 mg (5 tablets), and 900 mg (6 tablets) per day or TIW.

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

8.2.2 Dispensing of Vadadustat

At Baseline/Day 1, subjects who are randomized to vadadustat treatment will be administered the first dose of vadadustat at the study site.

Thereafter, vadadustat will be taken once daily from Baseline/Day 1 to Week 12 and TIW from Weeks 12 to 20 if Week 12 criteria are met (Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen). If the investigator determined criteria for Week 12 is not met, daily dosing will continue on an outpatient basis. Subjects who are randomized to the vadadustat treatment arm will be provided with up to 2 bottles of vadadustat. Each bottle of vadadustat will contain 100 tablets of vadadustat (150 mg/tablet). Subjects may take vadadustat with or without food and will be instructed to swallow the tablet(s) whole. Subjects will be instructed to take vadadustat at approximately the same time each day.

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

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

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

8.3 Vadadustat Accountability and Destruction

Drug accountability will be an ongoing process throughout the study. All vadadustat will 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 study site, and study drug dispensed to or returned from each subject. Records will be maintained that accurately reflect the drug accountability of vadadustat at all times. An electronic Diary (eDiary) or paper dosing reminders will be utilized throughout the study to guide dosing for subjects in the vadadustat arm (see Section 9.1.2, eDiary).

Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for all vadadustat received and that all required fields are complete, accurate, and legible.

If any dispensing errors or discrepancies are discovered, the sponsor will 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 study site will complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction as specified by the sponsor.

Prior to study 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 other study materials will be returned to the sponsor or destroyed at the study site, as specified by the sponsor. Appropriate records of the disposal will be documented and maintained. No unused vadadustat 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

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

8.4.1 Randomization

Main Study:

Subjects will be randomized to either a vadadustat treatment arm or epoetin alfa treatment arm. Randomization will be stratified by mean weekly epoetin alfa dose calculated over a period of 8 weeks prior to SV2:

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

In the low epoetin alfa dose group, subjects will be randomized in a 3:3:2 ratio to receive either an initial vadadustat daily dose of 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa.

In the high epoetin alfa dose group, subjects will be randomized in a 3:3:3:2 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets), 450 mg (3 tablets) or 300 mg (2 tablets), or epoetin alfa.

ESA Hyporesponder Parallel Study:

Subjects will be randomized in a 1:1 ratio to receive either an initial vadadustat daily dose of 600 mg (4 tablets) or epoetin alfa.

Note: A subject may enter the washout period only after all eligibility criteria have been met. During the washout period, no epoetin alfa will be administered for 5 days in the Main study and 2 days in the ESA hyporesponder parallel study.

8.4.2 Blinding

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

8.4.3 Measurement of Hb Levels for Dose Adjustment Consideration

Hb values will be measured by a central laboratory. Study drug treatment will aim to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, while targeting the middle of the range and minimizing excursions outside the target range. Hb will be monitored throughout the study to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive (see Section 8.4.6, Guidelines for Dose Adjustments). Hb levels can be measured more frequently based on investigator's clinical judgment.

In both the vadadustat and epoetin alfa arm, if dose adjustment is recommended based on Hb value and protocol-specified guidelines, dosing instructions can be provided to the subject over the telephone or at the next dialysis session at the study site (or dialysis center) or during an unscheduled site visit within 3 business days after receiving the Hb result from the central laboratory.

8.4.4 Epoetin Alfa Dosing Regimen

Epoetin alfa arm in both the Main study and ESA hyporesponder parallel study:

For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.

Epoetin alfa dose will be administered based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis.

From Baseline/Day 1 to Week 20, dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 and 11.0 g/dL, inclusive.

8.4.5 Vadadustat Dosing Regimen and Guidelines for Dose Adjustment

8.4.5.1 Dosing Regimen for the Vadadustat Treatment Arm

Subjects in the low epoetin alfa dose group randomized to vadadustat treatment will start at an initial dose of vadadustat 300 mg or 450 mg daily. Subjects in the high epoetin alfa dose group randomized to vadadustat treatment will receive an initial dose of 300, 450, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat treatment will receive a starting dose of vadadustat 600 mg daily.

After completing the 12-week once daily dosing regimen, subjects randomized to vadadustat who meet criteria for switching from daily to TIW dosing will initiate TIW dosing at a starting dose 1 tablet greater (+150 mg) than the final dose in the daily dosing period (see Section 8.4.5.2, Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen). Subjects who do not meet criteria for switching from daily to TIW dosing will remain on daily dosing. From Baseline/Day 1 to Week 20, dose will be adjusted to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive.

8.4.5.2 Transition of Vadadustat Once Daily Dosing to TIW Dosing Regimen

All subjects randomized to vadadustat who complete 12 weeks of once daily dosing regimen **and** who meet all the Week 12 criteria below will be transitioned to a TIW vadadustat dosing regimen.

Week 12 Transition criteria:

- Vadadustat daily dose of 600 mg or lower at Week 12
- Hb within target range of 10.0 to 11.0 g/dL, inclusive, at Week 12 confirmed by central laboratory Hb value from Week 11 (11 weeks of treatment completed)
- No receipt of rescue therapy (ESA or RBC transfusion) for worsening of anemia due to CKD from Baseline/Day 1 to Week 12.
    - ESA or RBC transfusion prior to Week 12 for reasons unrelated to worsening of anemia due to CKD (e.g., surgery, gastrointestinal bleed, or inadvertent administration) is not considered rescue therapy

- No other reason, based on the investigator's clinical discretion that would make the subject not suitable for TIW dosing.

Selected subjects who meet Week 12 transition criteria will transition to the TIW vadadustat dosing regimen at the Week 12 visit. Subjects on 150, 300, 450, or 600 mg of vadadustat daily at the Week 12 visit will transition to an initial vadadustat TIW dose one tablet greater (+150 mg), i.e., 300, 450, 600, or 750 mg vadadustat TIW, respectively. Subjects will be instructed to take vadadustat on dialysis days.

After 2 weeks of treatment in the TIW vadadustat dosing regimen (at Week 14), subjects in any vadadustat TIW dosing arms who have a decline in Hb ≥0.5 g/dL will be eligible for a dose increase by 1 tablet, based on the investigator's clinical discretion.

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

Subjects on TIW dosing may be converted back to vadadustat once daily dosing at the discretion of the investigator in the setting of inadequate Hb response. The starting daily dose after the switch from TIW to daily dosing will be based on the investigator's discretion after review of the subject's clinical status and dosing history, in particular, the daily dose previously administered to the subject prior to the transition to TIW dosing (Week 12). Subjects who switch from vadadustat TIW to daily dosing will continue once daily vadadustat until the end of the Treatment Period.

Subjects in the vadadustat arm will be guided for dosing compliance using an eDiary or through paper dosing reminders (see Section 9.1.2, eDiary).

8.4.6 Guidelines for Dose Adjustments

Dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment (see below). Hb will be monitored via central laboratory throughout the study to determine if the dose of study drug (vadadustat or epoetin alfa) will be adjusted, interrupted, or maintained as follows:

- Dose adjustments are based on the investigator's clinical discretion, incorporating the protocol guidance below as well as the subject's current Hb level, trajectory, and variability; symptoms; cardiovascular risk; and other features of his/her clinical condition(s).
- If a dose increase or decrease is required to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL, inclusive, dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for epoetin alfa approximately 25%).
- In general, do not increase the dose more frequently than once every 4 weeks. A one-time dose increase after 2 weeks is allowed on only two occasions.
    - A subject's dose may be increased by 1 dose level if the subject has a decline in Hb ≥0.5 g/dL from Baseline/Day 1 in the first 2-week period (the initial period from Baseline/Day 1 to Week 2 following conversion from prior epoetin alfa therapy).
    - A subject's dose may also be increased by 1 dose level in the first 2-week period after initiation of TIW dosing (from Week 12 to Week 14) for subjects that meet criteria for transitioning from daily to TIW dosing.

- Reduce or interrupt the dose in the setting of a rapid rise in Hb (defined as >1.0 g/dL in any 2-week period)
- Reduce or interrupt the dose in the setting of Hb >11.0 g/dL
- Interrupt the dose in the setting of a Hb >12.0 g/dL until Hb value falls below 11.0 g/dL. After Hb falls below 11.0 g/dL, restart study drug and consider restarting at a lower dose.

Note: The minimum dose of vadadustat will be 150 mg daily or TIW (1 tablet daily/TIW) and the maximum dose will be 900 mg daily or TIW (6 tablets daily/TIW).

8.4.7 Late or Missed Doses

Subjects on vadadustat will be instructed to take the study drug at approximately the same time each day. If a dose is forgotten, subjects will be instructed to take the dose as soon as they remember during the same day.

- Daily dosing regimen: If a forgotten dose is not remembered on the same day, the subject will skip the dose and resume the normal dosing schedule the following day.
- TIW dosing regimen: If a forgotten dose is not remembered on the same day, the subject will take the dose on the following day (a non-dialysis day). If a forgotten dose is not remembered on the same day or the following day of a long interdialytic gap, the subject will take the dose on the subsequent day (the second non-dialysis day). Thereafter, the subject should resume the normal dosing schedule.
- Subjects will not double-up on missed doses.

Epoetin alfa dose (including handling of late or missed dose) will be administered at the site and titrated based on the subject's central laboratory Hb value and the approved epoetin alfa US PI for adult patients with CKD on dialysis.

8.4.8 Iron Supplementation

IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol in Table 1.

TABLE 1 IRON SUPPLEMENTATION PROTOCOL

	Ferritin <200 ng/mL	**Ferritin 200-500 ng/mL**	**Ferritin >500 ng/mL**
TSAT <20%	IV Iron 100 mg every treatment (max 400 mg/month)	IV Iron 50 mg weekly	Hold
TSAT 20-50%	IV Iron 100 mg every week	IV Iron 50 mg weekly	Hold
TSAT >50%	Hold	Hold	Hold

IV: intravenous; TSAT: transferrin saturation

Subjects already receiving oral iron supplementation as part of their treatment plan may continue their current treatment regimen. 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 oral medications containing iron.

Subjects will be instructed to take any oral medications containing iron at least 2 hours after the dose of vadadustat.

8.4.9 Rescue Therapy

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

8.4.9.1 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 will 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 medical necessity. Study drug (vadadustat or epoetin alfa) may be continued during the transfusion period.

Reasons for RBC transfusion will be captured in the appropriate CRF.

8.4.9.2 ESA Use

ESA administration will be allowed when medically necessary at the discretion of the investigator. In general, ESA will not be administered in subjects with Hb ≥8.5 g/dL, and ESA will be stopped when Hb ≥9.0 g/dL. ESA therapy will be administered using an approved ESA and dosing as per the local institution's guidelines and per the approved product label.

While receiving ESA therapy, subjects randomized to vadadustat must temporarily interrupt vadadustat. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA, and treatment will be resumed after the following intervals:

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

Following ESA administration, vadadustat will be resumed at the same dose as previously used or with one additional tablet (+150 mg) at the discretion of the investigator.

Reasons for ESA use will be captured in the appropriate CRF.

8.4.10 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 clinical judgment. The method of phlebotomy will be in accordance with the study site's standard clinical practice.

8.4.11 Treatment Compliance

Throughout the study, subjects in the vadadustat arm will be guided regarding dosing compliance using an eDiary or paper dosing reminders. The focus of the vadadustat eDiary is to guide subjects to remind them of the dose, instruct them to hold their dose for the PK/PD sample dates and guide them if they have transitioned from daily dosing to TIW dosing. Subjects will also be questioned at study visits on whether they have questions or have experienced any problems related to the dosing of vadadustat. The investigator will also maintain drug accountability logs itemizing all study drugs dispensed to and returned from each subject during the study. Treatment compliance will be determined from these logs, subject questioning, and the study drug Case Report Form (CRF).

For epoetin alfa, the dose that is administered is required to be entered in the electronic data capture (EDC) system, and the EDC system will be used to determine dosing compliance.

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

8.4.12 Continuation of Treatment

Subjects in the vadadustat dosing groups will not receive vadadustat beyond the Treatment Period of approximately 20 weeks. However, enrollment may be increased by up to approximately 20 additional subjects in the Main study and up to approximately 30 additional subjects in the ESA hyporesponder parallel study to ensure adequate data are captured for the primary, PK/PD, and safety endpoints. Subjects in the vadadustat dosing groups who complete Visit 14 (Week 20), or discontinue early, will resume dosing with epoetin alfa (or another ESA) as per standard of care after all EOT procedures are completed.

8.5 Prior and Concomitant Therapy

8.5.1 General

Any medicinal product, prescribed or non-prescribed (including vitamins, minerals, natural and herbal remedies, topicals, inhaled, intranasal and dietary supplements) taken before entering the study is considered prior medication. All medicinal products other than the study drug, including prescribed or non-prescribed treatments used during the Treatment Period will be considered concomitant medication.

8.5.2 ESAs

Co-administration of any ESA with vadadustat is 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 8.4.9.2, ESA Use) if deemed medically necessary at the discretion of the investigator. Guidelines for ESA administration as rescue therapy are provided in Section 8.4.9.2, ESA Use. All efforts will be made to avoid inadvertent administration of ESAs resulting from adherence to ESA hemodialysis center protocols (e.g., DaVita ESA protocols for patients 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. A minimum interval will be observed prior to restarting vadadustat after the last dose of ESA. Vadadustat treatment may be resumed after the following intervals:

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

8.5.3 HMG-CoA Reductase Inhibitors (Statins)

Exposures to atorvastatin and an active metabolite (para-hydroxy) 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 done with caution.

8.5.4 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 resistance protein (BCRP) substrates should be used with caution when taken concomitantly with vadadustat.

8.5.5 Phosphate Binders

Subjects will be instructed to take phosphate binders (iron-containing and non-iron-containing phosphate binders) at least 2 hours after the dose of vadadustat.

8.5.6 Dialysis Treatment and Renal Replacement Therapy

Information on dialysis treatment including dialysis vascular access type, dialysis adequacy, and history of and changes in renal replacement therapies will be collected as described in Section 9, Study Procedures and Schedule of Activities and Appendix A: Schedule of Activities.

8.5.7 Investigational Medications

Study subjects are not to have received any investigational medications within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to randomization. In addition, subjects cannot have had any prior use of a HIF-PH inhibitor.

Additionally, subjects are not to 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:

- Eligibility Screening Period (from Day -28 to Baseline/Day 1)

  The Screening Period starts at the time the informed consent is signed and will be a maximum of 28-days in duration. Two Screening visits (SV1 and SV2, with a minimum of 4 days in between) must be performed within the Screening Period and prior to dosing (Baseline/Day 1).

  - Screening Visit 1 (SV1)
  - Screening Visit 2 (SV2)
- Study Treatment Period will consist of study visits from Baseline/Day 1 through Week 20 visit. In weeks where there is no schedule study visit a subject will have a status check performed during one of their dialysis treatment appointments.
  - Baseline/Day 1, Visit 1
  - Visit 2, Week 1 +5 days
  - Visit 3, Week 2 ± 3 days
  - Visit 4, Week 4 ± 3 days
  - Visit 5, Week 6 ± 3 days
  - Visit 6, Week 8 ± 3 days
  - Visit 7, Week 10 ± 3 days
  - Visit 8, Week 11 ± 3 days
  - Visit 9, Week 12 ± 3 days (Transition to TIW dosing if all Week 12 criteria are met)
  - Visit 10, Week 13 +5 days
  - Visit 11, Week 14 ± 3 days
  - Visit 12, Week 16 ± 3 days
  - Visit 13, Week 18 ± 3 days
  - Visit 14, Week 20 ± 3 days (EOT visit)
- Safety Follow-Up Period (from Week 20 to 24)
  - Visit 15, Week 24 visit ± 5 days

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

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent will be obtained and legally signed prior to the subject entering into the study and before any protocol-directed procedures (including Screening activities) are performed (see Section 15.3, Subject Information and Consent). After providing informed consent and receiving a unique subject identification number, subjects will undergo various Screening activities.

9.1.2 eDiary

An eDiary will be utilized throughout the study for completion of SF-36v2 and PGI assessments. Paper dosing reminders will also be provided to subjects randomized to the vadadustat treatment arm. In addition, the eDiary will guide dosing for subjects in the vadadustat arm. The focus of the eDiary is to guide subjects to remind them of when to take the dose, or instruct them to hold their dose for the PK/PD sample dates and provide reminders if they have transitioned from daily dosing to TIW dosing. Once eligibility has been confirmed at Baseline/Day 1, subjects will be instructed on data entry procedures for the eDiary and will complete the SF-36v2, PGI-S in the eDiary and the EQ-5D-5L paper form prior to dialysis and any other study procedures being performed.

Thereafter, the SF-36v2, PGI-C, and PGI-S will be completed in the eDiary and the EQ-5D-5L will be completed on paper at appropriate visits prior to dialysis and any study procedures being performed.

9.1.3 Documentation of Screen Failures

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

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

9.1.4 Status Check

In weeks where there is no scheduled study visit, a subject will have a status check performed during one of their dialysis treatment appointments in the week. It will include a review of the subject's vital signs and a review of current health status for identification of any issues that may require follow-up by the investigator or delegated staff personnel. Documentation of the review must be done in the subject's source documentation. If an AE is identified at the status check or other actions result from the status check, these will be captured per the protocol.

9.1.5 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 of vadadustat in the rat are ongoing, and there are no data on the transmission of vadadustat in breast milk or the effect of vadadustat on infants.

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 drug.

Adequate contraception for subjects is defined as follows:

- For females of non-childbearing potential
  - Confirmation of surgical sterility (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) at least 1 month prior to Screening, or

- Post-menopausal (no menses for >1 year with FSH >40 U/L at Screening)

- For females of childbearing potential
  - Subjects must confirm the use of acceptable forms of contraception*, for a minimum of one complete menstrual cycle prior to Screening.
  - Must have a negative serum pregnancy test at SV2.
  - Starting Baseline/Day 1, subjects must use two acceptable forms of contraception* (at least one of which must be a barrier method) throughout the Treatment Period and for 30 days after the final study drug administration
- For males subjects who have not had a vasectomy must agree to the following: use of an acceptable form of contraception* during the study and for 30 days after the last dose of the study drug; to not donate sperm during the study and for at least 30 days after the last dose of vadadustat.

* *Acceptable forms of contraception include:*
- *Established use of oral, injected or implanted hormonal methods of contraception.*
- *Placement of an intrauterine device or intrauterine system.*
- *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.*

9.1.6 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. If the evaluations occur on a hemodialysis day, the evaluations will be completed before dialysis, if applicable.

- 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 will be documented. After SV2, an abbreviated, symptom-directed physical examination will be performed at the discretion of the investigator, as clinically indicated.
- Dialysis Adequacy: Dialysis adequacy, as available from local collection, will be recorded at SV1 and Visits 9 and 14 (EOT).
- SF-36v2 HRQOL: The SF-36v2, a patient-reported survey of patient health status (See Appendix C: SF-36v2 Standard). It will be completed within the eDiary at the beginning of the study visit, prior to dialysis and any study procedures being performed. It will be administered at Baseline/Day 1, and Visits 9, 14 (EOT), and 15.

- PGI-S: The PGI-S is a global index that is used to rate the severity of disease (See Appendix D: Patient Global Impression of Severity [PGI-S]). It will be completed within the eDiary at the beginning of the study visit, prior to dialysis and any study procedures being performed. It will be administered at Baseline/Day 1, and Visits 9, 14 (EOT), and 15.
- PGI-C: The PGI-C is a scale that evaluates all aspects of a subject's health and assesses if there has been an improvement or decline in clinical status (see Appendix E: Patient Global Impression of Change [PGI-C]). It will be completed within the eDiary at the beginning of the Safety Follow-Up (Visit 15), prior to dialysis and any study procedures and assessments being performed.
- EQ-5D-5L HRQOL: The EQ-5D-5L is a patient reported outcomes measurement of health status on the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (See Appendix F: EuroQol 5 Dimensions 5 Levels [EQ-5D-5L]). It is a paper assessment that will be completed at the beginning of the study visit, prior to dialysis and any procedures being performed. It will be administered at Baseline/Day 1, and Visits 9, 14 (EOT), and 15.
- Vital Sign Measurements: Vital signs will include temperature, heart rate (HR), BP, respiratory rate (RR), and dry weight. Temperature, HR, BP, and RR will be assessed in the seated position after 5 minutes of rest. For BP, a total of two measurements at intervals of at least 2 minutes should be performed. Temperature, HR, BP, and RR will be collected at SV1, SV2, Baseline/Day 1, during all study visits, and Visit 14 (EOT). Measurements will be taken prior to blood draws when possible.

  Dry weight will be collected for all subjects at SV2, Baseline/Day 1, Visit 9 and 14 (EOT). For subjects on epoetin alfa, subjects will be weighed for dosing as per the local standard of care.
- 12-Lead ECG: A standard 12-lead ECG will be performed at Baseline/Day 1, which may be obtained up to 3 days prior to Baseline/Day 1. The ECG will be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and will be taken prior to vital sign assessments and blood draws when possible. 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.
- AE Assessments: AE collection will begin from time of randomization through 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 (study end date) or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
- Prior and Concomitant Medication Recording: All prior and concomitant medications (except those routinely administered as part of the hemodialysis procedures, such as heparin or saline flushes used for routine catheter maintenance, unless relevant for an AE or SAE) taken within 30 days prior to Baseline/Day 1 and through the final study visit will be recorded on the appropriate CRF.

Iron treatment regimen 30 days prior to Baseline/Day 1 and through the final study visit will be recorded on the appropriate CRF. In addition, to ensure adequate collection of prior ESA dosing history, a minimum of 8 weeks of ESA therapy prior to start of study drug will be recorded on the appropriate CRF page.

At each study visit, subjects will be asked whether they have started, changed or discontinued any medication since their previous study visit. This includes single use or as needed medication use. All medications and changes in dosage and frequency will be recorded on the appropriate CRF Page. Documentation for all medicinal products will include the medication name, indication, dose, dosing frequency and dates of administration.

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. If blood is collected on a dialysis day, blood draws will be done prior to dialysis, if applicable. The investigator is responsible for reviewing laboratory results for clinical significance.

For eligibility purposes, one retest for each parameter may be performed during the Screening window. Refer to Section 7.4.1, Retesting and Section 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening Period.

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 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 drug. A FSH test will be performed at SV2 for post-menopausal females.
- Complete Blood Count (CBC): A CBC with differential will be performed at Baseline/Day 1 and at Visit 14 (EOT). At all other noted visits in Appendix A: Schedule of Activities, including SV1 and SV2 (with a minimum of 4 days in between), a CBC without differential will be performed. The CBC without differential will include: Hb, hematocrit, RBCs, mean corpuscular Hb, mean corpuscular Hb concentration, red cell width distribution, white blood cell count and platelets. The CBC with differential will include the same parameters as CBC without differential with the addition of white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

  Hb will be monitored throughout the study via central laboratory to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive. Refer to Section 8.4.3, Measurement of Hb Levels for Dose Adjustment Consideration. Hb levels can be measured more frequently based on investigator's clinical judgment.
- Reticulocyte Count: An automated reticulocyte count (both absolute and percent) will be performed at Baseline/Day 1 and at Visits 2, 4, 6, 8, 9, 10, 12, and 14 (EOT).
- Folate and Vitamin B_{12}: A blood sample will be drawn at SV1 to assess the folate and Vitamin B_{12} levels.

- CRP: A blood sample for CRP will be collected at the Baseline/Day 1, Visit 9 and 14 (EOT).
- Serum Chemistry: Blood samples to assess serum chemistry will be collected at SV1, Baseline/Day 1, Visit 9 and 14 (EOT). The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, blood urea nitrogen, creatine phosphokinase, uric acid, albumin, and total protein.
- Liver Function Tests (LFTs): Blood samples to assess liver function will be collected at SV1, Baseline/Day 1, and every 2 weeks at Visits 3, 4, 5, 6, 7, 9, 11, 12, 13, and 14 (EOT). LFTs will include: total bilirubin, alkaline phosphatase (ALP), ALT/SGPT, AST/SGOT, and lactate dehydrogenase.
- Iron Indices: Blood samples to assess the iron indices will be collected at SV1, Baseline/Day 1, Visit 4, 6, 9, 12 and 14 (EOT). Assessments will include the following indices: ferritin, iron, transferrin, TIBC, and TSAT.
- Lipid Profile: Blood samples will be collected at the Baseline/Day 1 and Visit 14 (EOT) to assess the cholesterol levels and will be tested for the following types of lipids: total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides.
- Biomarkers (including, but not limited to, vascular endothelial growth factor [VEGF], and hepcidin): Samples for VEGF and hepcidin biomarker analyses will be drawn at the Baseline/Day 1, Visit 9 and 14 (EOT).

9.2.2.1 PK/PD Sampling for Subjects Randomized to Vadadustat

Refer to Appendix B for a schematic overview of the PK/PD samples for the vadadustat arm.

Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below. Preferably, PK/PD samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).

At Baseline/Day 1, PK/PD samples will be collected prior to dialysis and administration of vadadustat.

At Week 1 (after at least a full week of vadadustat treatment), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

On the following non-dialysis day, blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes post-dose

At Week 11, vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

At Week 13 (after at least one week on TIW vadadustat dosing regimen), vadadustat will be administered between 15 minutes to one hour prior to the start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

Note: Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Week 13 PK/PD sampling.

9.2.2.2 PK Sampling for Subjects Randomized to Epoetin Alfa

Refer to Appendix B for a schematic overview of the PK samples for the epoetin alfa arm.

Blood for measurement of EPO level in the epoetin alfa arm, in both the Main study and ESA hyporesponder parallel study, will be collected as outlined below. Preferably, PK samples are to be taken on the day of hemodialysis after the first short interdialytic interval (e.g., at the second session of the week).

At Baseline/Day 1, a sample will be collected prior to dialysis and administration of epoetin alfa.

At Week 1 (after at least a full week of study epoetin alfa treatment), epoetin alfa will be administered within 1 hour after start of dialysis. Blood samples will be collected as follows:

- 15 minutes pre-dose, and 2 hours ± 15 minutes, 3.5 hours ± 15 minutes, and 5 hours ± 30 minutes post-dose
- From subjects enrolled at a subset of study sites only, additional samples will be collected at 7 hours ± 30 minutes and 10.5 hours ± 1.5 hours post-dose

On the following **dialysis day**, one blood sample will be collected 15 minutes prior to administration of epoetin alfa.

9.2.2.3 PK/PD Sampling

For all PK and PD sampling the time of the previous dose of study drug (vadadustat or epoetin alfa) is to be collected for the pre-dose sample and the timing of administration of study drug (epoetin alfa and vadadustat) and the start and stop time of the dialysis session will be recorded.

9.3 Schedule of Activities

The Schedule of Activities (see Appendix A: Schedule of Activities) shows the timing of planned study procedures. Every effort will be made to adhere to this procedure schedule and all assessments will be completed at each study visit. Where possible, study visits will be performed and scheduled as part of a patients regularly scheduled dialysis session.

9.3.1 Screening Visits

Subjects will need to sign a full consent form prior to SV1 procedures. The consent form may be signed in advance of the SV1 procedures. The Screening Period starts at the time the informed consent is signed and will be a maximum of 28-days in duration. Two Screening visits (SV1 and SV2, with a minimum of 4 days in between) must be performed within the Screening Period and prior to dosing (Baseline/Day 1).

A subject may enter the washout period only after all eligibility criteria have been met following SV2. During the washout period, no epoetin alfa will be administered before Baseline/Day 1 for 5 days in the Main study and 2 days in the ESA hyporesponder parallel study.

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

9.3.1.1 SV1

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

- Informed consent
- Review of study eligibility criteria
- Review of acceptable methods of contraception
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws)
- Dialysis adequacy
- Laboratory procedures:
  - CBC (without differential)
  - Folate and vitamin B_{12} levels
  - Serum Chemistry
  - LFTs
  - Iron indices

  Refer to Section 7.4.1, Retesting and Section 7.4.2, Rescreening for further details regarding repeating laboratory measurements during the Screening Period.
- Visit registration in IWRS
- Review of prior medication
- Epoetin alfa dosing will continue

9.3.1.2 SV2

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

- Review of eligibility criteria
- Review of acceptable methods of contraception
- Physical examination (including height)
- Demographics and medical history
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws), and dry weight

- Laboratory procedures:
  - Serum pregnancy test for females of childbearing potential (eligible subjects will be advised to use an adequate contraceptive method see Section 9.2.2, Laboratory Evaluations for additional information). A FSH test will be performed at SV2 for post-menopausal females.
  - CBC (without differential)

    Subjects must have 2 Hb values measured by the central laboratory during Screening (at least 4 days apart between SV1 and SV2) as indicated below:
  - Main study: 2 Hb values between 8.5 and 11.0 g/dL, inclusive
  - ESA hyporesponder parallel study: 2 Hb values between 8.0 and 10.0 g/dL, inclusive

    If the subject's Hb does not qualify after SV1, SV2, or retest Hb, the subject will be considered a screen failure
- Visit registration in IWRS
- Prior and current medication use
- Epoetin alfa dosing will stop for a minimum of 5 days in the Main study or 2 days in the ESA hyporesponder parallel study until Baseline/Day 1

9.3.2 Baseline/Day 1 (Visit 1)

Epoetin alfa dosing will have been stopped for a minimum of 5 days in the Main study or 2 days in the ESA hyporesponder parallel study until Baseline/Day 1.

On Baseline/Day 1, blood sample collection and other Baseline/Day 1 procedures will be completed prior to dosing with study drug (vadadustat or epoetin alfa). On Baseline/Day 1, study drug will be administered at the study site, and will be administered after the PK sample is collected and prior to the dialysis session.

At Baseline/Day 1, the following activities/procedures will be performed:

- Review of study eligibility criteria
- Review of acceptable methods of contraception
- Review of medical history for new conditions since SV2
- Review of medication use since SV2
- Randomization
- Introduction to and instruction on the use of the eDiary and paper dosing reminders
- SF-36v2, PGI-S, and EQ-5D-5L assessments
- Abbreviated, symptom-directed physical examination, at the discretion of the investigator, as clinically indicated
- 12-lead ECG: ECGs will be completed prior to blood draws when possible and will be obtained after the subject has been resting supine comfortably for approximately 5 minutes; ECG may be completed and reviewed by the investigator on Baseline/Day 1 or if needed for scheduling reasons (e.g., dialysis treatment is scheduled for early morning of Baseline/Day 1), the ECG can be completed and reviewed up to 1-3 days prior to Baseline/Day 1.
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws), and dry weight

- Laboratory Procedures:
  - CBC (including differential)
  - Reticulocyte count
  - CRP
  - Serum chemistry
  - LFTs
  - Iron indices
  - Lipid profile
  - Biomarkers (VEGF, and Hepcidin)
  - PK prior to vadadustat or epoetin alfa dosing (see Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa) and prior to the dialysis session
- Study drug assessments and procedures:
  - Subject will take/receive their first dose of study drug at the study site during Baseline/Day 1
  - For subjects in the vadadustat treatment arm only:
    - Initiate vadadustat dosing
    - Vadadustat drug dispensation
    - Review vadadustat dosing instructions
  - Epoetin alfa dosing will continue for the subjects in the epoetin alfa arm
  - Iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation
  - Visit registration in IWRS
- Safety assessments:
  - AE review as needed
  - Review use of rescue therapy (RBC transfusions and ESA therapy)

9.3.3 Visit 2 to Visit 13 (Weeks 1 to 20)

At the Baseline/Day 1, Visit 7, and Visit 9, subjects in the vadadustat treatment arm will be reminded and instructed to hold their vadadustat dose on the day of Visit 2, Visit 8, and if applicable Visit 10, respectively, as blood sample for PK analysis will be collected on the day of Visit 2, Visit 8, and Visit 10 prior to vadadustat administration at the study site.

The following activities/procedures will be performed at Visit 2 to Visit 13, unless noted otherwise:

- SF-36v2, PGI-S, and EQ-5D-5L assessments (Visit 9 only)
- Abbreviated, symptom-directed physical examination, at the discretion of the investigator, as clinically indicated
- Vital signs including temperature, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws). Dry weight will be collected at Visit 9 only.

  - A status check (BP, vital signs, and review of current health status) will be performed during weeks with no scheduled study visit.
- Dialysis adequacy, as available from local information (Visit 9 only)
- Safety assessments:
  - AE review
  - Review use of rescue therapy (RBC transfusions and ESA therapy)
  - Review of therapeutic phlebotomy
- Laboratory procedures (if blood samples are collected on a day of dialysis, blood draws will be done prior to dialysis, if applicable):
  - CBC
  - Reticulocyte count (Visits 2, 4, 6, 8, 9, 10 and 12 only)
  - CRP (Visit 9 only)
  - Serum chemistry (Visit 9 only)
  - LFTs (Visits 3, 4, 5, 6, 7, 9, 11, 12, and 13)
  - Iron indices (Visits 4, 6, 9 and 12 only)
  - Biomarkers (VEGF and Hepcidin, Visit 9 only)
  - Vadadustat PK/PD sampling (Visits 2, 8 and 10 only) for details, see Section 9.2.2.1, PK/PD Sampling for Subjects Randomized to Vadadustat and Section 9.2.2.3, PK/PD Sampling)
  - Epoetin alfa PK sampling (Visit 2 only) for details, see Section 9.2.2.2, PK Sampling for Subjects Randomized to Epoetin Alfa and Section 9.2.2.3, PK/PD Sampling)
- Medication assessments and procedures:
  - Assessment for meeting criteria to switch from daily to TIW dosing (vadadustat arm)
  - Review of concomitant medications
  - Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa
  - For subjects in the vadadustat treatment arm only:
    - Visit registration in IWRS (for bottle dispensing only)
    - Vadadustat drug dispensation (scheduled Visits 4, 6, 9, and 12)
    - Review vadadustat dosing instructions
    - Review of vadadustat dosing compliance
    - Vadadustat reconciliation
  - Review of iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation)

9.3.4 EOT Visit 14 (Week 20)

EOT evaluations will be performed when the Treatment Period (Baseline/Day 1 to Visit 13) is completed. Subjects who prematurely discontinue study drug for any reason will also attend this visit.

At Visit 14 (EOT), the following activities/procedures will be performed:

- SF-36v2, PGI-S, and EQ-5D-5L assessments
- Vital signs including, HR, BP, and RR (assessed in seated position after 5 minutes of rest and prior to blood draws), as well as temperature and dry weight
- Dialysis adequacy, as available from local information
- Safety assessments:
  - AE review
  - Review use of rescue therapy (RBC transfusions and ESA therapy)
  - Review of therapeutic phlebotomy
- Laboratory Procedures:
  - CBC (with differential)
  - Reticulocyte count
  - CRP
  - Serum chemistry
  - LFTs
  - Iron indices
  - Lipid panel
  - Biomarkers (VEGF and Hepcidin)
- Medication assessments and procedures:
  - Review of concomitant medications
  - Subjects in epoetin alfa treatment arm will continue to receive epoetin alfa.
  - For subjects in the vadadustat treatment arm only:
    - Review of vadadustat dosing compliance
    - Vadadustat reconciliation
    - Resume dosing with epoetin alfa (or another ESA): After the end of vadadustat treatment at Visit 14 (or following early discontinuation of vadadustat), subjects may resume dosing with epoetin alfa (or another ESA), based on standard of care.
  - Visit registration in IWRS
  - Review of iron supplementation as needed to maintain ferritin ≥100 ng/mL or TSAT ≥20% (per local product label; see Section 8.4.8, Iron Supplementation)

9.3.5 Safety Follow-Up Visit 15 (Week 24)

At the Visit 15, the following activities/procedures will be performed:

- SF-36v2, EQ-5D-5L, PGI-S, and PGI-C assessments
- AE review
- Review use of rescue therapy (RBC transfusions and ESA therapy)
- Review use of therapeutic phlebotomy
- Concomitant medication review

9.3.6 Unscheduled Visits

Unscheduled assessments may be conducted at any time as medically warranted. All laboratory assessments required in the study are included in the central laboratory Unscheduled Visit kits to allow for re-testing of any study laboratory parameters. Additionally, the Unscheduled Visit kits include a coagulation panel (international normalized ratio [INR], prothrombin time (PT), and activated partial thromboplastin time [aPTT]) for testing INR (see Section 9.4, Study Medication Stopping Rules).

Starting from Baseline/Day 1, the following activities/procedures will be performed at an Unscheduled Visit at minimum:

- Safety assessments:
  - AE review
  - Review use of rescue therapy (RBC transfusions and ESA therapy)
  - Review of Therapeutic phlebotomy
- Medication assessments and procedures:
  - Review of concomitant medications
- Any other procedures that are medically warranted at the discretion of the investigator.

9.4 Study Medication Stopping Rules

Study medication must be permanently discontinued if a subject meets one of the following 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 (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash) **or** eosinophilia	Permanently Discontinue Treatment

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; ULN: upper limit of normal

See Section 10.1.1, AEs 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 AEs

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.

AEs therefore include the following:

- All AEs, whether suspected to be causally related to study drug or otherwise.
- All AEs secondary to any medication overdose, medication error, abuse, withdrawal, sensitivity, or toxicity.
- Illnesses apparently unrelated to study drug, including the worsening of a pre-existing illness (see paragraph below on Pre-existing Conditions).
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) will 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 (e.g., elevated liver enzymes in a subject with jaundice) will 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 will 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 will be the reported AE term, instead of fever and dyspnea, when the diagnosis has been established. Signs and symptoms will 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, will not be reported as AEs. However, the medical condition for which the procedure was performed will be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period will 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 will not be reported as AEs.

Pre-existing Conditions – In this study, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical examination form) will 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 will 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 will also be reported as AEs. Any abnormal laboratory value which requires treatment or further diagnostic testing and/or results in discontinuation from study will 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 Contract Research Organization (CRO) designee within 24 hours of awareness as an 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 and without meeting any criteria listed in Table 2 are identified, the following steps are to be taken:

- Temporary discontinuation of study medication;
- 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;
- Study medication 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 will not be considered an AE unless the worsening of anemia is associated with a cause *other than* the subject's CKD.

Transplantation – During this study, it is anticipated that subjects may receive a kidney transplant. These events will not be recorded as AEs. Subjects will discontinue study drug for receipt of a kidney, other solid organ, hematopoietic stem cell or bone marrow transplant, will complete the EOT visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14 as described in Section 7.6.3, Early Discontinuation from Study.

10.1.2 SAEs

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
  - Life-threatening is defined as 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.
- In-patient hospitalization or prolongation of existing 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 (e.g., 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).
- Persistent or significant disability/incapacity
  - Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.
- Congenital anomaly/birth defect
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject, or may require medical or surgical intervention to prevent one of the criteria listed in this definition.

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

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:

- Malignancies – Newly diagnosed malignancies or a recurrence of a malignancy will 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 of skin, 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 Akebia specific designated medical events (DME) that they will always classify as SAEs. If an event on the DME list is reported as an AE, the investigator will be notified and additional information on the event (e.g., investigator confirmation of seriousness, causality) will be requested from the investigator. The DME list will be available upon request.

10.1.3 Adverse Events of Special Interest

The following are considered to be AEs of special interest for this study:

- Malignancy (see Section 10.1.2, SAEs)
- Elevation in ALT or AST >3 times ULN (see Section 10.1.1, AEs)
- Pulmonary hypertension
- Pregnancy (see Section 10.4, Exposure In-Utero)

Reporting and classification of these events as AEs (see Section 10.1.1, AEs) or SAEs (see Section 10.1.2, SAEs) will be as per investigator decision.

10.2 Eliciting AE 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 randomization.

10.3 Reporting

Each AE is to be classified by the investigator as SERIOUS or NONSERIOUS based on the criteria in Section 10.1.2, SAEs.

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

10.3.1 Reporting Period

The AE reporting period for this study begins from time of randomization and ends at the final protocol-required Safety Follow-Up (Visit 15).

In addition, any SAE that occurs subsequent to the AE reporting period that the investigator assesses as related to the study drug will also be reported as an SAE.

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, will 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 will contain, at a minimum items number 1 to 6:

1. Subject number/ID, sex, and age/date of birth
2. The date of report
3. Name of the reporter
4. Name of the suspected medicinal product

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

If the causality assessment is not provided in the initial report an updated report with the causality must be provided within 24 hours, once assessed.

Information about all SAEs (either initial or follow-up information) will be collected and recorded in English on the electronic SAE Report Form within the EDC system. The investigator will assess the relationship to each specific component of the study treatment. If the event meets serious criteria and it is not possible to access the EDC system, a paper SAE Report Form will 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 again, the SAE information will be entered within 24 hours of the system becoming available.

The investigator will report follow-up information relating to an SAE to the sponsor's Medical Monitor or CRO designee within 24 hours of awareness 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 will be entered within 24 hours. The subject will 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 IRB 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 study site.

10.3.4 Relationship to Study Drug

The causal relationship of the AE to study drug (vadadustat or epoetin alfa) will be assessed by both the investigator and the sponsor.

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

Examples of evidence that would suggest a causal relationship between the study drug and the AE include the occurrence of an AE that is uncommon and known to be strongly associated with drug exposure (e.g., 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 drug are generally uninformative and do not contribute meaningfully to the development of the safety profile of the drug or to subject protection.

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

10.3.5 Severity

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

MILD: Does not interfere with subject's usual function

MODERATE: Interferes to some extent with subject's usual function

SEVERE: Interferes significantly with subject's usual function

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

10.3.6 Follow-up of Unresolved Events

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

In addition, all SAEs and those nonserious events assessed by the investigator as related to the study drug will continue to be followed even after the subject's participation in the trial is over. Such events will 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 will be confirmed by a positive serum β human chorionic gonadotropin test.

The study drug will 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 drug (vadadustat or epoetin alfa) or within 30 days of discontinuing the study drug, the pregnancy will be recorded on the Pregnancy Reporting Form/Exposure in Utero Form in 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 will also be reported.

The Pregnancy Reporting Form/Exposure in Utero Form will be completed with all known information regarding the pregnancy at the time of reporting. Study 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 an SAE (i.e., 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 an SAE within 24 hours of awareness. A pregnancy in and of itself is not considered an AE; however, unexpected complications are considered AEs.

Additional information about pregnancy outcomes follows:

- Note that "spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth will be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as related or unrelated to the in utero exposure to the study drug will also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

10.5 Special Situations

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

- Overdose of the medicinal product
  - Epoetin alfa overdose – The US PI will be referenced for information on epoetin alfa overdosing.
  - Vadadustat overdose – There is no known antidote for vadadustat. In cases of suspected overdose, subjects will 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 will be discontinued and standard treatment for polycythemic hyperviscosity syndrome will 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 exposure to the sponsor's medicinal product [e.g., name confusion])
- Drug-drug interaction.

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

10.6 Safety Monitoring

This is an open label study allowing the study team full access to safety data which will be reviewed on a regular basis, throughout the course of the study. Safety monitoring will be performed as described in the Medical Monitor Plan.

11 DATA ANALYSIS

Data collected throughout the study will be summarized using descriptive statistics and listed in the by-subject listings. Continuous variables will be summarized using number of subjects with mean, standard deviation (SD), 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.

11.1 Sample Size Estimation

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

Sample size reflects the exploratory nature of this study.

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

11.2 Study Analysis Populations

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects. Analyses of this population will be based on the randomized treatment.
- Full Analysis Population (FAS): all subjects in the randomized population who received at least one dose of study drug and had at least one Hb assessment during the primary efficacy evaluation period. Analyses of this population will be based on the randomized treatment.
- Safety Population: all subjects in the randomized population who received at least one dose of study treatment. Analysis of this population will be based on the actual treatment received. Subjects who received in error some vadadustat and some epoetin alfa will be classified by the more frequently received drug.
- Per protocol (PP) population: all randomized subjects who received study drug during the primary evaluation period, had at least one Hb assessment during the primary efficacy evaluation period, received no rescue therapy (with ESA or transfusion) prior to the evaluation period, and had no major protocol deviation affecting the primary endpoint analyses. Major protocol deviations leading to exclusion from the PP population will be specified prior to database lock and recorded in a separate document. Analyses of this population will be based on actual treatment received.

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 Randomized Population and other analysis populations which will be defined in detail in the Statistical Analysis Plan.

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

11.4 Disposition of Subjects

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

The number of randomized subjects who completed the study, discontinued early from study drug, completed or discontinued from the study, and reasons for discontinuation will be summarized by treatment group and overall.

11.5 Missing Data

It is expected that few subjects will discontinue Follow-Up. The reasons for any missing data will be summarized by treatment arm. Missing Hb values will be imputed using last observation carried forward (LOCF).

11.6 Efficacy Analyses

The primary efficacy endpoint as well as all other secondary endpoints will be summarized using descriptive statistics (means or proportions) by treatment groups and in total, 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.

11.7 Safety Analyses

Safety analyses will be descriptive in nature.

All AEs will be coded using MedDRA. Treatment-emergent and post-treatment AEs will be summarized by SOC and preferred term for each treatment group. AEs will also be summarized by their maximum severity.

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

- SAEs
- AEs of Special Interest (See Section 10.1.3, Adverse Events of Special Interest)
- Related AEs, as determined by the investigator
- AEs leading to early discontinuation of study drug

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

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

PK and PD parameters will be summarized using descriptive statistics: number of subjects, mean, median, SD, minimum, maximum, and coefficient of variation, geometric mean and geometric mean SD.

11.8.1 PK Assessments

Plasma concentrations will be summarized using descriptive statistics. Mean and individual subject vadadustat concentrations and O-glucuronide (primary metabolite of vadadustat) concentrations will be plotted versus time on linear and semi-logarithmic axes. The following PK parameters for vadadustat and O-glucuronide will be estimated as deemed appropriate from the plasma concentrations using standard methods of non-compartmental analyses: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, elimination rate constant (λz), and $t_{1/2}$. CL/F and V_d/F will be estimated for vadadustat. PK analysis will be reported separately.

11.8.2 PD Assessments

A by-subject listing of all PD variables will be provided including the changes from Baseline/Day 1. The observed and change from Baseline/Day 1 values of all PD assessments will be summarized using descriptive statistics. An exposure-response analysis of vadadustat, EPO and other PD measures will be conducted as deemed appropriate. PD analysis may be reported separately.

11.8.3 Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug dictionary. Refer to Section 8.5, Prior and Concomitant Therapy.

11.8.4 Biomarkers

Biomarkers (including, but not limited to, hepcidin and VEGF) will be summarized descriptively at Baseline/Day 1 and by visit post-Baseline/Day 1.

12 DATA HANDLING AND RECORD KEEPING

12.1 CRFs/EDC

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. CRFs available through this system are required and will be completed for each randomized subject.

Any form of data from the electronic system are the sole property of the sponsor and will 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 will 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 will 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, e.g., 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 (e.g., letters, meeting minutes, and telephone calls reports). The records will be retained by the investigator according to the International Council for Harmonisation of Technical Requires for Pharmaceuticals for Human Use (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 (e.g., retirement and relocation), the sponsor will be prospectively notified. The study records will be transferred to a designee acceptable to the sponsor, such as another investigator, another institution, or to the sponsor. The investigator will obtain sponsor's written permission before disposing of any records, even if retention requirements have been met.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study 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 study site may also be subject to Quality Assurance audits performed by the sponsor or companies working with or on behalf of the sponsor, and/or review by the IRB, 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

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the Trial Master File.

Note: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

14 STUDY DISCONTINUATION/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 will contact all participating subjects within a time period specified by the sponsor to inform them of the decision to discontinue the study.

14.1 Criteria for Premature Termination or Suspension of the Study

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

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

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

If the study has been suspended or terminated, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

14.2 Criteria for Premature Termination or Suspension of 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.

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

14.3 Procedures for Premature Termination or Suspension of the Study or Study 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 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 E6 guideline on GCP, and applicable local regulatory requirements and laws.

15.2 IRB

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

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

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

15.3 Subject Information and Consent

The investigator or designee will explain the nature of the study to the subject or their legally acceptable representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or their legally acceptable representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

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, will be prospectively approved by both the IRB 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 (i.e., clinical hold) by an applicable Competent Authority, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the sponsor will 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 (e.g., FDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

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

16 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between sponsor and the investigator and/or the investigator's institution. The sponsor will 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 will 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	**Screening [a]**		**Study Treatment Period**													**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [c]**	**15**
Weeks of study completed Study Day	**Day -28 to 0**		**Baseline/ Day 1 [b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57**	**Week 10 Day 71**	**Week 11 Day 78**	**Week 12 Day 85**	**Week 13 Day 92**	**Week 14 Day 99**	**Week 16 Day 113**	**Week 18 Day 127**	**EOT Week 20 Day 141**	**Week 24 Day 169**
Visit Window (Days)	—		—	+5	±3	±3	±3	±3	±3	±3	±3	+5	±3	±3	±3	±3	±5
Administrative Procedures																	
Informed consent	X																
Eligibility criteria [d]	X	X	X														
Review Contraception methods [e]	X	X	X														
Vital Signs [f]	X	X [g]	X [g]	X	X	X	X	X	X	X	X [g]	X	X	X	X	X [g]	
Demographics, Medical History [h]		X	X [i]														
Physical Exam [j]		X															
12-Lead ECG [k]			X														
Dialysis Adequacy (Kt/V)	X										X					X	
EQ-5D-5L			X								X					X	X
SF-36v2			X								X					X	X
PGI-S			X								X					X	X
PGI-C																	X
Randomization			X														
Assessment for meeting criteria to switch from daily to TIW dosing (vadadustat arm)											X						
Status check [l]																	
Safety Assessments																	

Study Period	**Screening [a]**		**Study Treatment Period**													**Safety Follow-Up**	
Visit	**SV1**	**SV2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 [c]**	**15**
Weeks of study completed Study Day	**Day -28 to 0**		**Baseline/ Day 1 [b]**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**Week 6 Day 43**	**Week 8 Day 57**	**Week 10 Day 71**	**Week 11 Day 78**	**Week 12 Day 85**	**Week 13 Day 92**	**Week 14 Day 99**	**Week 16 Day 113**	**Week 18 Day 127**	**EOT Week 20 Day 141**	**Week 24 Day 169**
AE review [m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review use of rescue therapy (RBC transfusions and ESA therapy)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of therapeutic phlebotomy				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluations																	
Serum Pregnancy test [n]		X															
CBC [o] [p]	X	X	X [q]	X	X	X	X	X	X	X	X	X	X	X	X	X [q]	
Reticulocyte count			X	X		X		X		X	X	X		X		X	
Folate and vitamin B12	X																
CRP			X								X					X	
Serum chemistry [r]	X		X								X					X	
LFTs [s]	X		X		X	X	X	X	X		X		X	X	X	X	
Iron indices [t]	X		X			X		X			X			X		X	
Lipid panel [u]			X													X	
Biomarkers (VEGF and Hepcidin) [v]			X								X					X	
PK/PD for vadadustat arm [w]			X	X						X		X [x]					
PK for epoetin alfa arm [y]			X	X													
Medication Assessments and Procedures																	
Concomitant medication review [z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Epoetin alfa dosing during Screening and resume standard of care after EOT	X [aa]															X [bb]	

Study Period	Screening [a]		Study Treatment Period													Safety Follow-Up	
Visit	SV1	SV2	1	2	3	4	5	6	7	8	9	10	11	12	13	14 [c]	15
Weeks of study completed Study Day	Day -28 to 0		Baseline/ Day 1 [b]	Week 1 Day 8	Week 2 Day 15	Week 4 Day 29	Week 6 Day 43	Week 8 Day 57	Week 10 Day 71	Week 11 Day 78	Week 12 Day 85	Week 13 Day 92	Week 14 Day 99	Week 16 Day 113	Week 18 Day 127	EOT Week 20 Day 141	Week 24 Day 169
Study Drug (vadadustat or epoetin alfa) dosing [cc]			X	X	X	X	X	X	X	X	X [dd]	X	X	X	X		
Vadadustat dispensation [ee]			X			X		X			X			X			
Review vadadustat dosing instructions and vadadustat dosing compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vadadustat reconciliation				X	X	X	X	X	X	X	X	X	X	X	X	X	
Review use of iron supplementation [ff]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visit Registration in IWRS	X	X	X			X [gg]		X [gg]			X [gg]			X [gg]		X	
eDiary instruction			X														

AE: adverse event; ALT/SGPT: alanine aminotransferase/serum glutamic pyruvic transaminase; aPTT: activated partial thromboplastin time; AST/SGOT: aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BUN: blood urea nitrogen; CBC: complete blood count; CPK: creatine phosphokinase; CRP: C-reactive protein; ECG: electrocardiogram; EOT: end-of-treatment; EPO: erythropoietin; EQ-5D-5L: EuroQol 5 Dimensions 5 Levels; ESA: erythropoiesis-stimulating agent; HDL: high density lipoprotein; INR: international normalized ratio; IWRS: Interactive Web Response System; LDL: low density lipoprotein; LFT: liver function test; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PD: pharmacodynamics; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PK: pharmacokinetic; PTT: partial thromboplastin time; RBC: red blood cell; RDW: red cell distribution width; SF-36v2: 36-Item Short-Form General Health Survey; SV1: Screening visit 1; SV2: Screening visit 2; TIBC: total iron binding capacity; TIW: three times per week; TSAT: transferrin saturation; VEGF: vascular endothelial growth factor; WBC: white blood cell; wks: weeks.

[a] The Screening Period is a maximum of 28 days in duration and starts at the time the informed consent is signed.
[b] The Screening Period starts at the time the informed consent is signed and will be a maximum of 28-days in duration. Two Screening visits (SV1 and SV2, with a minimum of 4 days in between) must be performed within the Screening Period and prior to dosing (Baseline/Day 1). A subject may enter the washout period only after all eligibility criteria have been met following SV2. During the washout period, no epoetin alfa will be administered before Baseline/Day 1 for 5 days in the Main study, and 2 days in the ESA hyporesponder parallel study.
[c] The EOT evaluations will be performed when the Treatment Period (Baseline/Day 1 to Week 20 [Visits 1 to 13]) is completed. Subjects who permanently discontinue study drug for any reason or discontinue prematurely from the study will complete the EOT visit (Visit 14) assessments and will complete the Safety Follow-Up (Visit 15) 4 weeks after Visit 14.
[d] Eligibility criteria will be reviewed at the SV1, SV2, and Baseline/Day 1.
[e] Contraception methods will be reviewed at Screening and Baseline/Day 1, as well as throughout the study as needed.
[f] Vital signs will include temperature, HR, BP, RR, and dry weight. Temperature, HR, BP, and RR will be assessed in the seated position after 5 minutes of rest. For BP, a total of two measurements at intervals of at least 2 minutes should be performed. Temperature, HR, BP, and RR will be collected at SV1, SV2, Baseline/Day 1, during all study visits, and Visit 14 (EOT). Measurements will be and will be taken prior to blood draws when possible.
[g] Dry weight will be collected as part of the vital signs for all subjects at SV2, Baseline/Day 1, Visit 9 and 14 (EOT). For subjects on epoetin alfa, subjects will be weighed for dosing as per the local standard of care.
[h] Relevant medical history (with particular emphasis on previous medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases will be documented.
[i] Review of medical history for new conditions since SV2.

[j] A physical examination (including height) is required at SV2. Thereafter, an abbreviated symptom-directed physical examination will be performed at the discretion of the investigator, as clinically indicated.
[k] A standard 12-lead ECG will be performed at Baseline/Day 1, which may be obtained up to 3 days prior to Baseline/Day 1. The ECG will be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and will be taken prior to vital sign assessments and blood draws when possible. 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.
[l] In weeks where there is no scheduled study visit (Weeks 3, 5, 7, 9, 15, and 17, and 19), a subject will have a status check performed during one of their dialysis treatment appointments in the week. It will include a review of the subject's vital signs and a review of current health status for identification of any issues that may require follow-up by the investigator or delegated staff personnel. Documentation of the review must be done in the subject's source documentation. If an AE is identified at the status check or other actions result from the status check, these will be captured per the protocol.
[m] AE collection will begin from time of randomization through 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. Subjects must be followed for AEs until the final required protocol visit (study end date) or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.
[n] A serum pregnancy test will be performed at SV2 for females of childbearing potential. Additional serum 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 drug. A FSH test will be performed at SV2 for post-menopausal females.
[o] A CBC without differential will be performed at all noted visits, except Baseline/Day 1 and Visit 14 (EOT). The CBC without differential will include: Hb, hematocrit, RBCs, MCV, MCH, MCHC, RDW, WBC count, and platelets.
[p] Hb will be monitored throughout the study via central laboratory to determine the dose of study drug (vadadustat or epoetin alfa) that subjects will receive. Hb levels can be measured more frequently based on investigator's clinical judgment. For eligibility purposes, one retest for Hb may be performed during the Screening Period. Two Hb values measured by the central laboratory at least 4 days apart between SV1 and SV2 must be between 8.5 and 11.0 g/dL, inclusive, for the Main study and 8.0 to 10.0 g/dL, inclusive, for the ESA hyporesponder parallel study.
[q] A CBC with differential will be performed at Baseline/Day 1 and Visit 14 (EOT). The CBC with differential will include the same parameters as CBC without differential with the addition of WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
[r] The serum chemistry will include the following assays: sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, glucose, creatinine, BUN, CPK, uric acid, albumin, and total protein.
[s] LFTs: total bilirubin, ALP, ALT/SGPT, AST/SGOT, and lactate dehydrogenase. Elevation in ALT or AST >3x ULN will require collection of Unscheduled Visit central laboratory coagulation panel (INR, PT, aPTT) to confirm INR value >1.5 and permanent discontinuation of study medication per Section 9.4.
[t] Iron Indices: ferritin, iron, transferrin, TIBC, and TSAT.
[u] Lipid Profile: total cholesterol, LDL, HDL, and triglycerides.
[v] The biomarkers will include, but are not limited to, VEGF and hepcidin. Samples for VEGF and hepcidin biomarker analyses will be drawn at Baseline/Day 1, Visit 9 and 14 (EOT).
[w] Blood for measurement of vadadustat, metabolites and EPO level in the vadadustat arm, in both the Main study and ESA hyporesponder parallel study will be collected at Baseline/Day 1, Week 1, and Week 11 as outlined in Section 9.2.2.1. For all PK and PD sampling, the time of the previous dose of vadadustat will be collected for the pre-dose sample and the timing of administration of vadadustat, and the start and stop time of the dialysis session will be recorded.
[x] Visit 10/Week 13 PK/PD sampling will only be done in subjects who transition to vadadustat TIW dosing regimen. Subjects who do not qualify for vadadustat TIW dosing and remain on daily dosing regimen will not have Visit 10/Week 13 PK/PD sampling.
[y] Blood for measurement of EPO level in the epoetin alfa arm, in both the Main study and ESA hyporesponder parallel study, will be collected at Baseline/Day 1 and Week 1 as outlined in Section 9.2.2.2. For all PK sampling the time of the previous dose of epoetin alfa is to be collected for the pre-dose sample and the timing of administration of epoetin alfa and the start and stop time of the dialysis session will be recorded.
[z] Concomitant medications should be collected and recorded at each visit as noted. All medications taken within 30 days prior to Baseline/Day 1 will be recorded.
[aa] Epoetin alfa dosing will stop for a minimum of 5 days before Baseline/Day 1 in the Main study or 2 days before Baseline/Day 1 in the ESA hyporesponder parallel study.
[bb] After the end of vadadustat treatment at Visit 14/Week 20 (or following early discontinuation of vadadustat), subjects will resume dosing with epoetin alfa (or another ESA), based on standard of care.
[cc] Subjects in the low epoetin alfa dose group randomized to vadadustat treatment will start at an initial dose of vadadustat 300 mg or 450 mg daily. Subjects in the high epoetin alfa dose group randomized to vadadustat treatment will receive an initial dose of 300 mg, 450 mg, or 600 mg daily. Subjects in the ESA hyporesponder parallel study randomized to vadadustat treatment will receive a starting dose of vadadustat 600 mg daily. For subjects who are randomized to the epoetin alfa treatment arm, the initial dosing regimen in the study (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization.
[dd] After completing the 12-week once daily dosing regimen, subjects randomized to vadadustat who meet criteria for switching from daily to TIW dosing will initiate TIW dosing at a starting dose 1 tablet greater (+150 mg) than the final dose in the daily dosing period. Central laboratory Hb values from Visit 8/Week 11 (11 weeks of treatment completed) will be used to determine if subjects meet Week 12 Transition criteria.
[ee] Subjects will be provided with a supply of vadadustat at Baseline/Day 1 and will be resupplied at Visit 4, 6, 9 and 12 or an unscheduled dispensing visit as needed. Subjects will be instructed to complete 1 bottle before opening a new bottle. The dose should be taken at approximately the same time each day.

[ff] IV iron will be administered based on ferritin and TSAT levels measured by the central laboratory according to the standardized, low-intensity, iron supplementation protocol in Section 8.4.8.
[gg] IWRS visit registration for vadadustat arm only for bottle dispensing.

APPENDIX B: PK/PD SAMPLING

PK/PD Sampling in Vadadustat Arm Subjects Who Transition to TIW Dosing at Week 12

	Baseline/Day 1 QD	Week 1 QD	Week 1 + 1 day	Week 11 QD		Week 13 TIW	
	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	●						
15 minutes (pre-dose)		●	●	●		●	
2 hours ± 15 minutes (post-dose)		●	●	●		●	
3.5 hours ± 15 minutes (post-dose)		●	●	●		●	
5 hours ± 30 minutes (post-dose)		●	●	●		●	
7 hours ± 30 minutes (post-dose)		●	●	●		●	
10.5 hours ± 1.5 hours (post-dose)		●		●		●	

Note: Gray shading indicates sample collection at a subset of study sites only.

PK/PD Sampling in Vadadustat Arm Subjects Who Do Not Transition to TIW Dosing at Week 12

	Baseline/Day 1 QD	Week 1 QD	Week 1 + 1 day	Week 11 QD	Week 13 TIW		
	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	•						
15 minutes (pre-dose)		•	•	•			
2 hours ± 15 minutes (post-dose)		•	•	•			
3.5 hours ± 15 minutes (post-dose)		•	•	•			
5 hours ± 30 minutes (post-dose)		•	•	•			
7 hours ± 30 minutes (post-dose)		•	•	•			
10.5 hours ± 1.5 hours (post-dose)		•		•			

Note: Gray shading indicates sample collection at a subset of study sites only.

PK Sampling in Epoetin Alfa Arm

	Baseline/Day 1 TIW	Week 1 TIW	Week 1 + 2 days	Week 11 TIW		Week 13 TIW	
	Dialysis Day	Dialysis Day	Dialysis Day	Dialysis Day	Non-Dialysis Day	Dialysis Day	Non-Dialysis Day
Baseline/Day 1 (Prior to first dose)	•						
15 minutes (pre-dose)		•	•				
2 hours ± 15 minutes (post-dose)		•					
3.5 hours ± 15 minutes (post-dose)		•					
5 hours ± 30 minutes (post-dose)		•					
7 hours ± 30 minutes (post-dose)		•					
10.5 hours ± 1.5 hours (post-dose)		•					

Note: Gray shading indicates sample collection at a subset of study sites only.

APPENDIX C: SF-36v2 Standard

Your Health and Well-Being

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

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

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

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

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

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

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

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

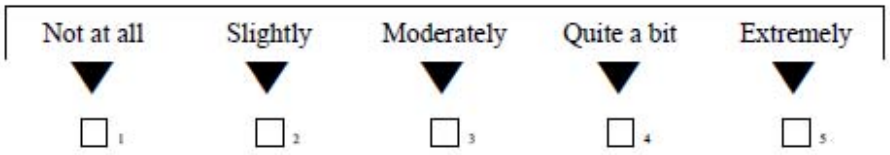
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

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

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

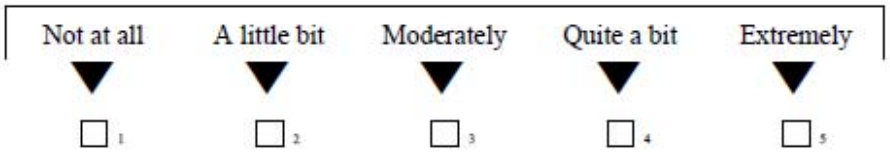
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐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

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



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

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



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

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

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

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

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

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

Thank you for completing these questions!

APPENDIX D: PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

Protocol Number: AKB-6548-CI-0025

Subject #_____-_____ **Subject Initials: _____**

Visit #: _____ **Date Completed:** dd / mmm / yyyy

Patient Global Impression of Severity: PGI-S

1. **How would you rate the impact of your anemia and its treatment on how you feel now?**

☐ 0 No Impact At All ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 As Bad As It Can Be

2. **How much does the treatment you currently take for anemia help you to perform your daily activities?**

☐ 0 Not At All ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 As Much As It Can Be

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APPENDIX E: PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

Protocol Number: AKB-6548-CI-0025

Subject #_____-_____ **Subject Initials: _____**

Visit #: _____ **Date Completed:** dd / mmm / yyyy

Patient Global Impression of Change: PGI-C

1. **How would you compare the impact of your anemia and its treatment on how you feel <u>now</u> to when you were on the previous treatment (or the period before your last visit)?**

- ☐ Very much worsened
- ☐ Much worsened
- ☐ Minimally worsened
- ☐ Not changed
- ☐ Minimally improved
- ☐ Much improved
- ☐ Very much improved

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APPENDIX F: EUROQOL 5 DIMENSIONS 5 LEVELS (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

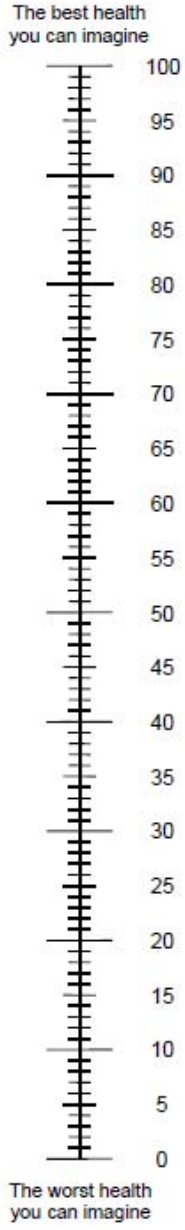
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX G: HISTORY OF AMENDMENTS TO THE PROTOCOL

Amendment 1 (Version 2.0; 11 September 2018)

Amendment 1 was issued based on sponsor assessment and external input.

The major changes introduced in the amendment are summarized below:

- Addition of an Exclusion Criterion of Subjects with bilateral native nephrectomy, to minimize potential variability in hemoglobin response observed in this Phase 2 PK/PD study that may arise from a decreased capacity to augment endogenous erythropoietin (EPO) production in the setting of bilateral nephrectomy.
- Addition of language to provide explicit guidance on early termination from the study for subjects who undergo a solid organ, hematopoietic stem cell, or bone marrow transplantation while participating in the study.
- Update to the description of the vadadustat tablet since new lots of vadadustat may include imprinting on the tablet. This is also referred to as a debossed tablet.
- Preliminary results of clinical drug-drug interaction studies showed a moderate interaction between vadadustat and rosuvastatin and no clinically significant interaction between vadadustat and pravastatin. Based on the data from these studies, guidance has been added to the protocol on how to manage the use of statins in combination with vadadustat.
- Removal of the requirement to assess and document oxygen saturation (SO_2) levels in study subjects for consistency with past and current Akebia DD-CKD protocols, and given that measurement of SO_2 levels is not required in the setting of vadadustat or epoetin alfa use or in the routine management of subjects with DD-CKD.
- AE reporting period clarified as starting at randomization in case there is a delay between date of randomization and date of first study drug dose.

Amendment 2 (Version 3.0; 05 April 2019)

Amendment 2 was issued based on sponsor assessment, external input, regulatory authority engagement, investigative site feedback, and results of a drug-drug interaction study.

The major changes are summarized below:

- Signature page: Dennis Vargo, Senior Director has replaced Geoffrey Ross as Vice President; Ajit Chavan, Senior Director has replaced Susan Paulson as Clinical Pharmacology.
- Section 4.2 Summary of Clinical Experience was updated to include the language of specific dose adjustment from 150 to 600 mg, and to highlight that this study is the first study to examine doses of 750 and 900 mg in DD-CKD subjects.
- Section 4.3: Potential Benefits and Risks: Addition of text to indicate hepatotoxicity as an identified important potential risk.
- Section 6.3 Dose Justification was updated to include additional details for the doses being used in the study.

- Section 7.3 Exclusion Criteria was updated to exclude persons who are concurrently participating in another study, or any prior use of a HIF-PH inhibitor.
- Section 7.6.3 Early Discontinuation From Study (Early Termination) was updated to include a reference to Study Medication Stopping Rules for management of subjects with ALT and AST abnormalities.
- Section 8.4.8 Iron Supplementation was updated to prohibit concurrent administration of oral iron supplementation of vadadustat and instruct them to take their iron supplementation at least 2 hours after dosing with vadadustat.
- Section 8.5.3 HMG-CoA Reductase Inhibitors (Statins) was updated to provide further guidance regarding concomitant use of HMG-CoA Reductase Inhibitor drug interactions with vadadustat.
- Section 8.5.4 Sulfasalazine and Other BCRP Substrates was added to provide guidance regarding concomitant use of Sulfasalazine and other BCRP substrates with vadadustat.
- Section 8.5.5 Phosphate Binders was added to provide guidance regarding concomitant use of Phosphate Binders with vadadustat.
- Section 9.1.2 eDiary was updated to also allow use of paper dosing reminders, and timing of completing questionnaires was clarified.
- Section 9.2.1 EQ-5D-5L was added as a patient reported outcomes measurement. Additional instructions have been provided to ensure consistency across all subjects in the timing of when the SF-36v2, HRQOL, PGI-S, and PGI-C.
- Section 9.2.2 Laboratory Evaluations were updated with additional Liver Function Test (LFT) timepoints, such that LFTs are performed every 2 weeks instead of every 4 weeks after Baseline/Day 1. Given expansion of potential risks to include hepatotoxicity associated with use of vadadustat.
- Section 9.3.1 Screening Visits was updated to remove the 4-day minimum requirement between SV2 and Baseline/Day 1 visits and to clarify that a subject may enter the washout period only after all eligibility criteria have been met following SV2. During the washout period, no epoetin alfa will be administered before Baseline/Day 1 for a minimum duration of 5 days in the Main study, and 2 days in the ESA hyporesponder parallel study.
- Section 9.3.2 Baseline/Day 1 (Visit 1) was updated to introduce the eDiary and HRQOL questionnaires at the Baseline/Day 1 visit instead of at SV2.
- Section 9.3.6 Unscheduled Visits was updated to clarify that a coagulation panel (INR, PT, aPTT) was added to the Unscheduled Visit central laboratory kit for testing INR (see Section 9.4 Study Medication Stopping Rules).
- 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 AEs 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 SAEs was updated to include information defining Designated Medical Events.
- Section 10.1.3 Adverse Events of Special Interest was added to include a classification for Malignancies, elevations of ALTs, ASTs, pregnancy, and pulmonary hypertension.