Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Vadadustat

REVISED CLINICAL PROTOCOL

Phase 3b, Randomized, Open-label, Active-controlled Trial Evaluating the Efficacy and Safety of Oral Vadadustat Once Daily (QD) and Three Times Weekly (TIW) for the Maintenance Treatment of Anemia in Hemodialysis Subjects Converting from Erythropoiesis-Stimulating Agents (ESAs)

Protocol No. 404-201-00012
IND No. 102,465
EudraCT No. 2019-004851-36

CONFIDENTIAL — PROPRIETARY INFORMATION

Drug Development Phase:	3b
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) 2440 Research Boulevard Rockville, Maryland 20850, United States
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Reporting Adverse Events:	Reported via electronic data capture (EDC) If EDC is unavailable, send paper Serious Adverse Event (SAE) Form, Pregnancy Form or Special Situations Form to: IQVIA™ Safety Mailbox: [redacted]
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1 Protocol Summary

1.1 Synopsis

Name of Sponsor:

Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)

Name of Investigational Medicinal Product:

Vadadustat

Protocol No.:

404-201-00012

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Protocol Title:

Phase 3b, Randomized, Open-label, Active-controlled Trial Evaluating the Efficacy and Safety of Oral Vadadustat Once Daily (QD) and Three Times Weekly (TIW) for the Maintenance Treatment of Anemia in Hemodialysis Subjects Converting from Erythropoiesis-stimulating Agents (ESAs)

Clinical Phase:

3b

Treatment/Indication:

Anemia of chronic kidney disease (CKD)

Objectives and Endpoints:

The primary objective of the trial is to demonstrate the efficacy and safety of vadadustat compared to darbepoetin alfa for the maintenance treatment of anemia in hemodialysis subjects after conversion from current ESA therapy.

Primary efficacy endpoints of the trial include efficacy parameters for change in hemoglobin (Hb) between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).

Key secondary efficacy endpoints of the trial include efficacy parameters for change in Hb value between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 46 to 52).

Other efficacy endpoints of the trial include the following:

- Proportion of subjects having average Hb values within the target range during the primary evaluation period (Weeks 20 to 26).
- Proportion of subjects having average Hb values within the target range during the secondary evaluation period (Weeks 46 to 52).
- Proportion of subjects receiving intravenous (IV) iron therapy from Baseline to Week 52.
- Average monthly dose of IV elemental iron administered from Baseline to Week 52 in subjects who have received IV elemental iron.
- Receipt of ESA rescue.
- Proportion of subjects receiving red blood cell (RBC) transfusions from Baseline to Week 26.
- Proportion of subjects receiving RBC transfusions from Baseline to Week 52.
- Change from Screening Visit 2 36-Item Short Form (SF-36v2) Health-related Quality of Life (HRQOL) scores.
- Change from Screening Visit 2 to the average value in Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score.
- Change from Screening Visit 2 to the average value in Total FACT-An Score.
- Change from Screening Visit 2 in score of Patient Global Impression of Severity (PGI-S).
- Score of Patient Global Impression of Change (PGI-C).

Safety endpoints of the trial include adverse events (AEs) and serious adverse events (SAEs), vital sign measurements, electrocardiograms (ECGs) and clinical laboratory values, episodes of Hb > 12.0 g/dL, > 13.0 g/dL, or > 14.0 g/dL, and the number of episodes of Hb increase > 1.0 g/dL within any 2-week interval or > 2.0 g/dL within any 4-week interval.

Pharmacokinetic (PK): no PK analysis will be conducted. Vadadustat plasma concentrations may be included in a population PK analysis reported separately.

Pharmacodynamic (PD) endpoints of the trial include parameters erythropoietin (EPO), reticulocytes, and markers of iron metabolism (iron, ferritin, total iron binding capacity [TIBC], etc.).

[redacted]

Trial Design:

Phase 3b, randomized, open-label, active-controlled trial of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in hemodialysis subjects, after conversion from ESA therapy.

Following a Screening period of up to 8 weeks (56 days), subjects who meet all eligibility criteria will be randomized 1:1:1 to vadadustat QD, vadadustat TIW, or darbepoetin alfa. Target enrollment in this trial is an estimated 300 subjects at up to 150 investigative sites in the United States (US) and Europe.

Subjects will be randomized at the Baseline Visit using an Interactive Web Response (IWR) system to receive either vadadustat QD, vadadustat TIW, or darbepoetin alfa.

Randomization will be stratified with respect to:

- Geographic region (US versus Europe, approximately 90 subjects in Europe).
- Mean weekly darbepoetin alfa dose (or ESA equivalent) calculated over a period of 8 weeks prior to Screening Visit 2:
  - Low darbepoetin alfa dose group (≤ 0.45 μg/kg/week).
  - High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 μg/kg/week).

In each stratum, there will be 3 arms: vadadustat QD, vadadustat TIW, and darbepoetin alfa.

Following screening and randomization, there will be 2 periods during the trial:

- **Conversion and Maintenance Treatment Period (Weeks 0 to 52):** conversion to investigational medicinal product (IMP) for maintaining Hb (Weeks 0 to 20), primary efficacy evaluation (Weeks 20 to 26), and secondary efficacy evaluation (Weeks 46 to 52).
- **Safety Follow-up Period (Early Termination [ET] and Follow-up):** post-treatment Safety Follow-up Visit (ET/End of Treatment [EOT] + 4 weeks) (in person).

Individual subjects will participate in total trial duration of approximately 64 weeks.

A structured exit interview may be conducted at the EOT Visit at a subset of sites.

Trial Population:

An estimated 300 subjects with approximately:

- 100 subjects randomized to vadadustat QD arm.
- 100 subjects randomized to vadadustat TIW arm.
- 100 subjects randomized to darbepoetin alfa arm.

The trial population will consist of subjects ≥ 18 years of age receiving chronic, outpatient in-center hemodialysis TIW, with 2 screening Hb values between 8.0 and 11.0 g/dL (inclusive) in the US or between 9.0 and 12.0 g/dL (inclusive) in Europe, and on maintenance treatment with an ESA.

Inclusion Criteria:

Subjects are required to meet the following inclusion criteria:

1) ≥ 18 years of age.
2) Receiving chronic, outpatient TIW hemodialysis for end-stage renal disease for at least 12 weeks prior to Screening.
3) Hemodialysis adequacy as indicated by single-pool $K_t/V_{urea} \geq 1.2$ using the most recent historical measurement within 8 weeks prior to or during Screening.
4) Use of any approved ESA for at least the 8 weeks prior to Screening Visit 2.
5) Two Hb values, at least 4 days apart, measured by the central laboratory during Screening within the following prespecified ranges:
   a) Hb values between 8.0 and 11.0 g/dL (inclusive) in the US.
   b) Hb values between 9.0 and 12.0 g/dL (inclusive) in Europe.
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.

Exclusion Criteria:

Subjects will be excluded if they meet any of the following exclusion criteria:

1) Women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy of partner, tubal ligation, vaginal diaphragm, or intrauterine device.
2) 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.
3) Women who are breast feeding and/or who have a positive pregnancy test result prior to receiving IMP.
4) Subjects with contraindication to required trial assessment.
5) Subjects who, is in opinion of the investigator or medical monitor, have a medical history or medical findings inconsistent with safety or trial compliance.

6) Anemia due to a cause other than CKD (eg, sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia).
7) Subjects meeting cut-off of the following equivalent mean weekly doses calculated over 8 weeks prior to Screening Visit 2:
    a) Methoxy polyethylene glycol-epoetin beta > 50 µg/week.
    b) Darbepoetin alfa > 100 µg/week.
    c) Epoetin analogues > 23000 IU/week.
8) Active bleeding or recent blood loss within 8 weeks prior to randomization.
9) Red blood cell transfusion within 8 weeks prior to randomization.
10) Anticipated to discontinue hemodialysis during the trial.
11) Judged by the investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the trial.
12) History of chronic liver disease (eg, chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis, or fibrosis of the liver).
13) 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.
14) Current uncontrolled hypertension as determined by the investigator that would contraindicate the use of an ESA.
15) 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.
16) 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.
17) History of a new or recurrent episode of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening.
18) History of hemosiderosis or hemochromatosis.
19) History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded).
20) 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.
21) History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded).
22) Known hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients.

23) Use of an investigational medication within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to screening or during screening and any prior use of a hypoxia-inducible factor prolyl hydroxylase inhibitor. Subjects may participate in another concurrent trial only if that trial is a non-interventional, observational investigation.
24) Subjects with bilateral native nephrectomy.
25) Treated with probenecid within the 28-day Screening Period prior to randomization or during the study treatment duration.
26) Any other reason, which in the opinion of the investigator, would make the subject not suitable for participation in the trial.

Retesting/Rescreening

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

Subjects who fail to qualify for the trial 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 trial. Each screening attempt includes the potential of a retest. Additionally, subjects who fail to qualify for the trial based on inclusion criteria values for TSAT, ferritin, folate, or B_{12} values may be considered for rescreening after receiving replacement therapy. A minimum of 3 weeks from IV iron replacement therapy (for low TSAT and ferritin values) must be observed prior to collecting next trial visit Hb value.

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.

Trial Sites:

Targeting up to 150 investigative sites in the US and Europe.

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

Vadadustat will be provided as 150 and 450 mg tablets, to be taken orally. Darbepoetin alfa will be dispensed as a solution in single-dose prefilled syringes, to be given by IV injection through dialysis vascular access.

Subjects will be randomized 1:1:1 to vadadustat QD or vadadustat TIW or darbepoetin alfa.

Randomization will be stratified by mean weekly darbepoetin alfa dose (or equivalent) calculated over a period of 8 weeks prior to Screening Visit 2:

Low darbepoetin alfa dose group (≤ 0.45 µg/kg/week) or

High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 µg/kg/week)

- In the low darbepoetin alfa dose group, subjects will be randomized in a 1:1:1 ratio to receive either an initial vadadustat daily dose of 300 mg daily or 600 mg TIW, or darbepoetin alfa.
- In the high darbepoetin alfa dose group, subjects will be randomized in a 1:1:1 ratio to receive either an initial vadadustat daily dose of 450 mg daily, 750 mg TIW, or darbepoetin alfa.

Refer to the trial-specific Dosing Guideline for instructions on ESA medications conversion to an equivalent darbepoetin alfa dose for stratification and randomization.

Dosing will be initiated at the Baseline/Day 1 Visit and the first dose of vadadustat will be administered at the trial site after other Baseline/Day 1 procedures have been completed. Thereafter, vadadustat will be taken QD or TIW (on dialysis days) on an outpatient basis. Subjects may take vadadustat with or without food and should be instructed to swallow the tablet(s) whole, without chewing. Subjects will be instructed to take vadadustat at roughly the same time each day. Darbepoetin alfa will be initiated at Baseline/Day 1. For subjects who were receiving darbepoetin alfa during screening and randomized to the darbepoetin alfa arm, the initial dosing regimen in the trial (starting from Baseline/Day 1) will be approximately the same weekly dose that subjects were receiving prior to randomization. For subjects receiving darbepoetin alfa for the first time, the initial dosing regimen (starting from Baseline/Day 1) will be determined by the US Package Insert (USPI) or European Union (EU) Summary of Product Characteristics (SmPC), per the medical judgment of the investigator. Dose adjustments will be guided by the USPI or EU SmPC (Section 6.1.1.4).

For all subjects, it is recommended that no additional ESA doses be administered after Screening Visit 2 and prior to the Baseline Visit (Day 1).

For all subjects, it is required that a minimum period as outlined below be observed between the last dose of ESA administered during Screening and Randomization Visit:

- 2 days after last dose of epoetin analogues.
- 7 days after last dose of darbepoetin alfa.

- 14 days after last dose of methoxy polyethylene glycol-epoetin beta.

After discussion with the Medical Monitor, screening may be extended for an additional 2 to 4 weeks based on the subject's Hb level or Hb trajectory or based on timing of the last ESA dose given during screening.

Dose Adjustment

Vadadustat dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment.

Darbepoetin alfa dose adjustments are based on the USPI or EU SmPC per the medical judgment of the investigator, incorporating the Guidelines for Dose Adjustment as well as the subject's current Hb level, trajectory, and variability; symptoms; cardiovascular risk; and other features of his/her clinical condition(s).

Hemoglobin will be monitored via central laboratory throughout the trial to determine if the dose of IMP (vadadustat or darbepoetin alfa) will be adjusted, interrupted, or maintained as per the Guidelines for Dose Adjustment as follows:

Guideline for Dose Adjustment	
Status of Hb Levels	**Dose Adjustment[a]**
Hb levels are to be maintained in the following target ranges: US only: 10.0 to 11.0 g/dL, inclusive. Europe only: 10.0 to 12.0 g/dL, inclusive.	A dose increase or decrease is required to achieve and maintain Hb levels within the target range. Dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for darbepoetin alfa approximately 25%)
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 ESA) and if Hb is < 10.0 g/dL.	A subject's dose may be increased by 1 dose level.
A rapid rise in Hb is observed (defined as follows): > 1.0 g/dL in any 2-week period or > 2.0 g/dL in any 4-week period.	Reduce or interrupt the dose.[b]
Hb levels are in the following setting: US only: Hb > 11.0 g/dL. Europe only: > 12.0 g/dL.	Reduce or interrupt the dose. After Hb falls below 11.0 g/dL (US) or 12.0 g/dL (Europe), restart IMP and consider restarting at a lower dose.

[a]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 one occasion. Dose adjustment should be based on the investigator's clinical discretion.
[b]See Section 7.3.1 (Treatment Interruption).

The minimum dose of vadadustat will be 150 mg daily and the maximum dose will be 900 mg QD or 1200 mg TIW.

Trial Assessments:

Assessments for subject reported outcomes: The SF-36v2 HRQOL, PGI-S, PGI-C, and FACT-An.

Assessments for PK: Plasma samples for PK evaluation will be collected only for subjects randomized to vadadustat to analyze for both the parent compound (vadadustat) and its metabolites. Collection time points for PK will include Week 12 Visit at predose and 0.5, 1, 2, and 3 hours postdose.

Assessments for PD: Blood samples for EPO, reticulocytes, and other iron indices (ferritin, iron, TIBC, and TSAT) will be obtained.

[redacted]

Assessments for Safety: AEs and SAEs, clinical laboratory tests, medical history, demographic information, physical examination findings including dry weight, concomitant medication recording, vital signs, ECG, major adverse cardiovascular events (MACE), RBC transfusions, ESA rescue, and therapeutic phlebotomy.

[redacted]

Statistical Methods:

For the primary efficacy analysis, it will be assumed that the difference in mean change from Baseline in Hb for vadadustat will be the same as the active control, darbepoetin alfa, and the common standard deviation for the mean change from Baseline will be assumed to be 1.2 g/dL. The noninferiority margin of -0.75 g/dL will be used (for vadadustat minus darbepoetin alfa). With these assumptions and approximately 100 subjects per treatment group, the noninferiority test will have > 90% power with consideration of 30% drop out rate.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is defined as the Hb change from Baseline (average pretreatment Hb) to the average Hb from Weeks 20 to 26 (inclusive).

The primary analysis of the primary endpoint will use the randomized population with an analysis of covariance, with randomization stratification factors and Baseline Hb as covariates.

A 2-sided, 95% confidence interval (CI) will be calculated for the difference in mean change in Hb from Baseline to the primary evaluation period between the vadadustat

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

A hierarchical testing scheme will be used to correct for the multiplicity of the 2 primary endpoints: comparison between vadadustat QD vs. darbepoetin alfa and comparison between vadadustat TIW vs. darbepoetin alfa.

- Step 1: comparison between vadadustat QD vs. darbepoetin alfa
- If the noninferiority of vadadustat is established in step 1, then move to the step 2;
- Step 2: comparison between vadadustat TIW vs. darbepoetin alfa

Blinded summary safety data will be provided for all subjects who had the opportunity to complete the Week 12 Visit by a cut-off date, with the cut-off date to be determined at a later date to support potential regulatory filing.

Trial Duration:

Each subject in this trial is expected to participate in the following periods of the trial (approximate durations listed):

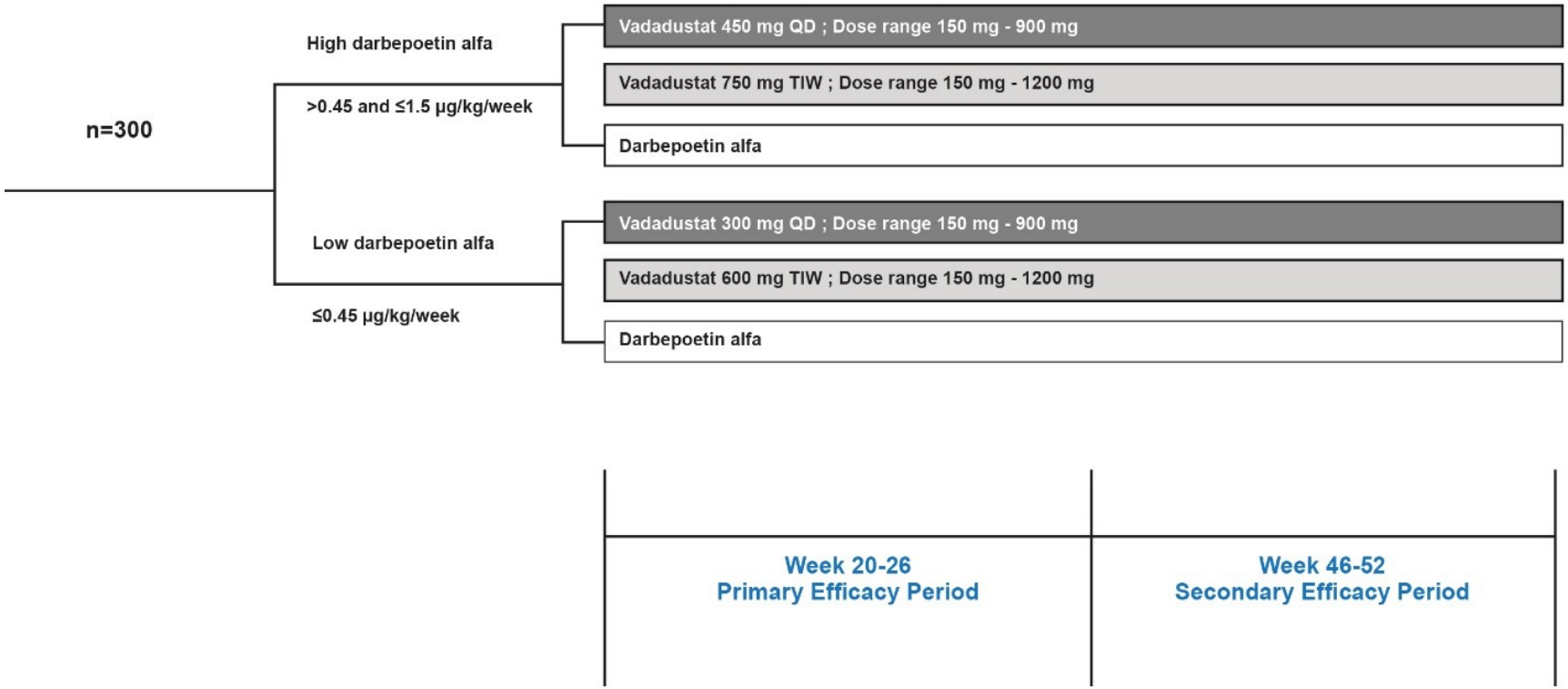
- Two Screening Visits (Screening Visit 1 and Screening Visit 2) (Weeks -8 to 0)
- Baseline/Randomization Visit (Week 0/Day 1)
- Treatment Period (Conversion and Maintenance) Trial Visits/Evaluations while receiving IMP: Weeks 2, 4, 6, 8, 10, 12, (± 3 days) 16, 20, 24, (± 5 days), 26 (± 3 days), 30, 34, 38, 42, 46, 50, (± 5 days) 52/EOT (± 3 days).
- ET Visit (+ 7 days)
- Follow-up Visit/EOT (4 weeks after the ET [+ 7 days] visit).
- Unscheduled visit(s)

Trial Completion: The trial will be considered completed after all randomized subjects have completed their final trial visit (ET, Week 52/EOT, or Safety Follow-up).

Subject Completion: A subject will be considered as having completed the trial after completion of their final trial visit (ET or Week 52/EOT). Safety Follow-up Visit data summarization and analysis will be performed separately.

The trial duration for an individual subject from the time the informed consent form (ICF) is signed to the final subject assessment is expected to be approximately 64 weeks.

1.2 Schema



n = number of subjects; QD = once daily; TIW = three times weekly

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Trial Period	Screening		Treatment (Conversion and Maintenance)																		Safety Follow-up	
Visit Type	SV1	SV2	BL								Primary Efficacy Evaluation							Secondary Efficacy Evaluation			ET	Follow-up
Week	-8 to 0		0	2	4	6	8	10	12	16	20	24	26	30	34	38	42	46	50	52/ EOT	ET	ET/EOT +4 weeks
Visit Window (Days)				± 3						± 5			± 3	± 5						± 3	+ 7	
Procedures/Assessments																						
Informed Consent	X																					
I/E Criteria	X	X	X																			
Vital signs [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X																				
Actual Dry Weight After Dialysis		X							X				X							X	X	X
Demographics, Medical History		X																				
Physical Exam [b]		X																		X	X	
12-Lead ECG [c]			X																	X	X	
Randomization			X																			
SF-36v2 HRQOL		X							X				X							X	X	
FACT-An		X							X				X							X	X	
PGI-S		X							X				X							X	X	
PGI-C									X				X							X	X	
Exit interviews [d]																						X
Laboratory Procedures (note: the procedures grayed out and bolded can be retested)																						
Pregnancy Test [e]		X																				
Folate and Vitamin B_{12}[f]	**X**																					
C-Reactive Protein			X						X											X	X	
CBC without diff	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CBC with diff [g]			X																	X	X	
Iron Indices [h,f]	**X**		**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Serum Chemistry [i,f]	**X**		**X**						**X**											**X**	**X**	
Liver Function Tests [j,f]	**X**		**X**		**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Lipid Panel [k]			X										X							X	X	
[redacted]			[redacted]						[redacted]											[redacted]	[redacted]	

Trial Period	Screening		Treatment (Conversion and Maintenance)																		Safety Follow-up	
Visit Type	SV1	SV2	BL								Primary Efficacy Evaluation							Secondary Efficacy Evaluation				Follow-up
Week	-8 to 0		0	2	4	6	8	10	12	16	20	24	26	30	34	38	42	46	50	52/ EOT	ET	ET/EOT +4 weeks
Visit Window (Days)				± 3						± 5			± 3	± 5						± 3	+ 7	
[redacted]			[redacted]		[redacted]				[redacted]				[redacted]							[redacted]	[redacted]	
Reticulocyte Count			X		X				X				X							X	X	
Erythropoietin			X		X				X				X							X	X	
[redacted]			[redacted]										[redacted]							[redacted]	[redacted]	
[redacted]			[redacted]										[redacted]							[redacted]	[redacted]	
Dialysis adequacy	X	X	To be reported every 3 months																			
Safety Assessments																						
MACE Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RBC Transfusions and ESA Rescue				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Therapeutic Phlebotomy				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Assessments and Procedures																						
Concomitant Medicine Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vadadustat/Darbepoetin alfa Medication Dispensing [n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vadadustat Medication Dosing			Daily or TIW dosing (see Section 6)																			
Darbepoetin alfa Dosing			Dosing according to USPI or EU SmPC																			
PK Sampling																						
PK Evaluation (Vadadustat dosing arms only)									X													

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; CBC = complete blood count; ECG = electrocardiogram; EOT = end-of-treatment; ESA = erythropoiesis-stimulating agent; ET = early termination; FACT-An = Functional Assessment of Cancer Therapy-Anemia; [redacted] Hb = hemoglobin; HDL = high density lipoprotein; HRQOL = Health-related Quality of Life; I/E = inclusion/exclusion; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MACE = major adverse cardiovascular event; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; [redacted] PK = pharmacokinetic; RBC = red blood cell; SF-36v2 = 36-Item Short-Form; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; SV1 = Screening Visit 1; SV2 = Screening Visit 2; TIBC = total iron binding capacity; TIW = three times per week; TSAT = transferrin saturation; US = United States; [redacted]

[a] Vital signs to be assessed in the seated position after 5 minutes of rest before dialysis occurs.

[b] During the Treatment period, an abbreviated physical examination should be performed at the discretion of the investigator, as clinically indicated.

[c] An ECG should be performed prior to serum chemistry blood draw when possible and obtained after the subject has been resting for approximately 5 minutes. The clinical evaluations should be completed before dialysis occurs. ECGs may be measured up to 3 days before BL.

[d] A structured exit interview may be conducted at the EOT Visit at a subset of sites.

Trial Period	Screening		Treatment (Conversion and Maintenance)																	Safety Follow-up	
Visit Type	SV1	SV2	BL								Primary Efficacy Evaluation							Secondary Efficacy Evaluation			Follow-up
Week	-8 to 0		0	2	4	6	8	10	12	16	20	24	26	30	34	38	42	46	50	52/ EOT	ET	ET/EOT +4 weeks
Visit Window (Days)				± 3						± 5			± 3	± 5						± 3	+ 7	

[e] Serum pregnancy will be tested in women of childbearing potential at SV2. Additional serum or local urine pregnancy tests should be conducted throughout the trial in sufficient number, as determined by the investigator or required by local regulations, to establish the absence of pregnancy during the trial. If positive at SV2, the subject is not eligible to enter the trial. If a subject becomes pregnant during the trial, the subject must permanently discontinue investigational medicinal product (IMP) and should attend all subsequent trial visits and be continually monitored according to the Schedule of Activities for the duration of the trial.

[f] Subjects may be retested.

[g] For eligibility, 2 Hb values measured by the central laboratory during Screening (SV1, SV2 or retest) must be between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) Europe.

[h] Iron indices: ferritin, iron, TIBC, and TSAT.

[i] If blood is collected on a hemodialysis day, the blood draw should be completed before dialysis occurs.

[j] Liver function tests: total bilirubin, alkaline phosphatase, ALT/SGPT, AST/SGOT, and LDH.

[k] Lipids: total cholesterol, LDL, HDL, and triglycerides.

[redacted]

D[redacted]

[n] Subjects will be provided with a supply of vadadustat at the Baseline Visit and will be resupplied at subsequent visits as needed. Please refer to the drug dispensing instructions for further details.

2 Introduction

2.1 Background Information

Chronic kidney disease (CKD), defined as the presence of kidney damage or a decreased level of kidney function for > 3 months, is a major public health problem worldwide. Globally, CKD is estimated to affect between 8% to 16% of the population.[1,2] At the most advanced stages of CKD, end-stage renal disease, patients require chronic dialysis, or kidney transplantation to sustain life. Chronic kidney disease is not only a cause of end-stage renal disease, but is also a significant risk factor for cardiovascular (CV) disease, infection, cancer, and mortality.[3]

The prevalence and severity of renal anemia in CKD increases as renal function deteriorates.[4,5] 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.[6] Anemia generally exists when hemoglobin (Hb) is less than 13.0 g/dL in men or less than 12.0 g/dL in women.[7] 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.[3,8]
- 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).[8,9] 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.[5] 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 (HF).[10] 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.[3,11] Overall, anemia contributes to a poorer prognosis in patients with CKD.[3,8]

The risks associated with erythropoiesis-stimulating agents (ESAs), currently the standard of care, including an increased risk of death and CV events[12,13,14,15,16] highlight the need for additional therapies that might minimize or avoid these risks. 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.

2.2 Hypoxia-Inducible Factor Prolyl-Hydroxylase Inhibitors

Please see the vadadustat Investigator's Brochure (IB) for additional discussion and information for the following section.[17]

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}] = 8 nM) than of PHD2 (IC_{50} = 12 nμM). 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 possibly other organs), and this increase in EPO results in an increase in RBC production in the bone marrow. In clinical studies, vadadustat has been shown to facilitate iron homeostasis by decreasing hepcidin and increasing transferrin levels in healthy adult male subjects 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.

[redacted]

[redacted]

[redacted]

[redacted]

2.4 Known and Potential Risks and Benefits

Please see the vadadustat IB for additional information.

Trials of injectable ESAs in patients with anemia secondary to NDD-CKD or DD-CKD have demonstrated an increased risk of CV events associated with higher Hb targets.[12,14,16] 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.[18,19] 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 studies 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).[20] 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 subjects, there were low numbers of treatment-emergent AEs. The most frequently reported AEs were in the gastrointestinal disorders (ie, nausea, diarrhea, abdominal pain, flatulence, dyspepsia) and nervous system disorders (ie, 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), CV 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.

Important identified risks of hepatotoxicity and drug-drug interactions associated with vadadustat therapy have been confirmed. There have been reports of drug-induced liver injury possibly or probably related to vadadustat. All subjects recovered without sequelae. Other non-important identified risks include nausea, diarrhea, vomiting, abdominal pain, headache, and increased blood uric acid.

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.

2.5 Trial Rationale

This trial will evaluate efficacy and safety of different vadadustat dosing strategies in hemodialysis subjects converting from ESAs to further characterize the optimal vadadustat regimen. See Section 4.2 for additional rationale for the trial design elements.

Trial sites will receive updated versions of the IB[17] when available, and trial sites should refer to the most current version as needed.

3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To demonstrate the efficacy and safety of vadadustat compared to darbepoetin alfa for the maintenance treatment of anemia in hemodialysis subjects after conversion from current ESA therapy.	Primary Efficacy: Change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).
	Key Secondary Efficacy: Change in Hb value between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 46 to 52). Other Efficacy: • Proportion of subjects having average Hb values within the target range during the primary evaluation period (Weeks 20 to 26). • Proportion of subjects having average Hb values within the target range during the secondary evaluation period (Weeks 46 to 52). • Proportion of subjects receiving IV iron therapy from Baseline to Week 52. • Average monthly dose of IV elemental iron administered from Baseline to Week 52 in subjects who have received IV elemental iron. • Receipt of ESA rescue. • Proportion of subjects receiving RBC transfusions from Baseline to Week 26. • Proportion of subjects receiving RBC transfusions from Baseline to Week 52. • Change from Screening Visit 2 36-Item Short Form (SF-36v2) Health-related Quality of Life (HRQOL) scores. • Change from Screening Visit 2 to the average value in Anemia Subscale ("Additional Concerns") of Functional Assessment of Cancer Therapy-Anemia (FACT-An) Score. • Change from Screening Visit 2 to the average value in Total FACT-An Score. • Change from Screening Visit 2 in score of Patient Global Impression of Severity (PGI-S).

Table 3-1 Trial Objectives and Endpoints	
Objectives	**Endpoints**
	• Score of Patient Global Impression of Change (PGI-C).
	Safety endpoints: AEs and SAEs, vital sign measurements, ECGs and clinical laboratory values, episodes of Hb > 12.0 g/dL, > 13.0 g/dL, or > 14.0 g/dL, and number of episodes of Hb increase > 1.0 g/dL within any 2-week interval or > 2.0 g/dL within any 4-week interval. Pharmacokinetic: No PK analysis will be conducted. Vadadustat plasma concentrations may be included in a population PK analysis reported separately (Table 8.2-1). Pharmacodynamic: EPO, reticulocytes, and markers of iron metabolism (iron, ferritin, TIBC, etc.). [redacted]

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a phase 3b, randomized, open-label, active-controlled trial of vadadustat versus darbepoetin alfa for the maintenance treatment of anemia in hemodialysis subjects, after conversion from ESA therapy.

Following a Screening period of up to 8 weeks (56 days), subjects who meet all eligibility criteria will be randomized 1:1:1 to vadadustat QD, vadadustat TIW, or darbepoetin alfa. Target enrollment in this trial is an estimated 300 subjects at up to 150 investigative sites in the US and Europe (Figure 1.2-1).

Subjects will be randomized at the Baseline Visit using an Interactive Web Response (IWR) system to receive either vadadustat QD, vadadustat TIW, or darbepoetin alfa.

Randomization will be stratified with respect to:

- Geographic region (US versus Europe, approximately 90 subjects in Europe).
- Mean weekly darbepoetin alfa dose (or ESA equivalent) calculated over a period of 8 weeks prior to Screening Visit 2:
  - Low darbepoetin alfa dose group (≤ 0.45 µg/kg/week).
  - High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 µg/kg/week).

In each stratum, there will be 3 arms: vadadustat QD, vadadustat TIW, and darbepoetin alfa.

Following screening and randomization, there will be 2 periods during the trial:

- **Conversion and Maintenance Treatment Period (Weeks 0 to 52):** conversion to investigational medicinal product (IMP) for maintaining Hb (Weeks 0 to 20), primary efficacy evaluation (Weeks 20 to 26), and secondary efficacy evaluation (Weeks 46 to 52).
- **Safety Follow-up Period (Early Termination [ET] and Follow-up):** post-treatment Safety Follow-up Visit (ET/End of Treatment [EOT] + 4 weeks) (in person).

Individual subjects will participate in total trial duration of approximately 64 weeks.

A structured exit interview may be conducted at the EOT Visit at a subset of sites.Hemoglobin will be assessed with a complete blood count (CBC) through the central laboratory for dose adjustments and efficacy and safety evaluations.

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

For subjects assigned to vadadustat, the initial dose of vadadustat will depend on mean weekly darbepoetin alfa dose (or equivalent) calculated over a period of 8 weeks prior to Screening Visit 2 as follows:

- Low darbepoetin alfa dose group (≤ 0.45 µg/kg/week): vadadustat 300 mg QD, 600 mg TIW.
- High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 µg/kg/week): vadadustat 450 mg QD, 750 mg TIW.

Refer to the trial-specific Dosing Guideline for instructions on ESA medications conversion to an equivalent darbepoetin alfa dose for stratification and randomization.

Adjustments to doses for vadadustat will be guided by Hb concentration and Dose Adjustment Algorithms (Section 6.1.1).

For subjects who were receiving darbepoetin alfa during screening and randomized to the darbepoetin alfa treatment arm, the initial dosing regimen in the trial (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization. Darbepoetin alfa dose will be administered IV at the hemodialysis clinic. For subjects receiving darbepoetin alfa for the first time, the initial dosing regimen (starting from Baseline/Day 1) will be determined by the US Package Insert (USPI) or European Union (EU) Summary of Product Characteristics (SmPC), per the medical

judgement of the investigator. Dose adjustments will be guided by the USPI or EU SmPC (Section 6.1.1.4). ESA dosing is independent of the visit schedule, and the dosing schedule may shift per local standard of care and investigator discretion.

Investigators will prescribe iron supplementation (IV, oral, or intradialytic) as needed during the trial to maintain ferritin ≥100 ng/mL or transferrin saturation (TSAT) ≥20% (see Section 6.5.2.1 for details regarding iron supplementation during the trial). 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 IMP 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 vadadustat at least 1 hour before oral medications containing iron (Section 6.5.2.1).

Clinical and safety assessments will be performed as indicated at Screening, during the Conversion and Maintenance Period, and during the Follow-up Period (4 weeks after the EOT) as shown in the Schedule of Assessments (Table 1.3-1).

The trial will be considered completed (end of trial) after all randomized subjects have completed their final trial visit (ET, Week 52/EOT, or Safety Follow-up) or have prematurely withdrawn from the trial (lost to follow-up). A subject is considered as having completed the trial after completion of their final trial visit (ET or Week 52/EOT). Safety Follow-up Visit data summarization and analysis will be performed separately.

4.2 Scientific Rationale for Trial Design

This trial 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, inflammation, and a greater risk of adverse outcomes.[12,19,21] As described above (Section 2.3) in a phase 2 hemodialysis trial (AKB-6548-Cl-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.

Two levels of pre-baseline ESA dose will be evaluated. Subjects will be randomized to one of 2 cohorts based on pre-baseline darbepoetin alfa dose (≤ 0.45 µg/kg/week and between > 0.45 and ≤ 1.5 µg/kg/week) or equivalent. This dose threshold of 0.45 µg/kg/week was determined by converting the ESA threshold of 90 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 Trial, which ranged from approximately 90 to 110 U/kg/week.

In this trial, darbepoetin alfa was chosen as an active comparator as it is marketed and available globally and has an extensive safety profile. This is particularly relevant in the current medical and regulatory climate given the accumulating trial findings that resulted in the FDA revising the prescribing information for the currently marketed ESAs. These trial results indicate an increased risk of death and adverse CV events, such as stroke and HF, particularly when using ESAs to achieve a higher Hb concentration. In addition, post-hoc analysis has also shown that higher ESA doses carry a higher risk for CV outcomes regardless of Hb. In the US, the mortality and CV risks associated with ESAs are outlined in a boxed warning in the prescribing information of ESAs, with a recommendation to use the lowest dose possible to avoid transfusions. While no similar major warnings exist in the EU SmPC, there is caution suggested with use of ESAs, and recommendation to keep Hb levels below 12.0 g/dL. Recent clinical practice guidelines[22] recommend that risk factors for stroke and malignancy should also be taken into account when making treatment decisions to use ESAs for the treatment of anemia.

This trial incorporates 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 in the US and 10.0 to 12.0 g/dL in Europe, inclusive (see Section 6.1.1.1). The approach to vadadustat dose adjustment in this phase 3b trial 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 trial, dose increases for vadadustat will be allowed at 4-week intervals, with the exception of the initial 2 weeks of treatment. An additional dose increase may occur after 2 weeks of treatment initiation based on the Hb trajectory, in the daily and TIW dosing arms, in subjects with a Hb decline ≥ 0.5 g/dL from Baseline/Day 1 to Week 2 following conversion from prior ESA and if Hb is < 10 g/dL. This approach is commonly used in clinical practice to treat patients with declining or low Hb values.[14,16] Risk of abrupt or excessive increases in Hb is minimized due to the underlying Hb trajectory and is further mitigated by close Hb monitoring.

This trial will evaluate efficacy and safety of different vadadustat dosing strategies in hemodialysis subjects converting from ESA to further characterize the optimal vadadustat regimen. This trial will be performed as an open-label trial. Because Hb values are objective and will be measured via a central laboratory for all efficacy endpoints, efficacy assessments are not considered to be subject to bias with an open-label design.

4.3 Dosing Rationale

In this trial, vadadustat starting daily doses will be determined by pre-baseline ESA dose (Section 6.1.1.1). In this trial starting doses of vadadustat will be 300 mg QD or 600 mg TIW in subjects converting from darbepoetin alfa doses ≤ 0.45 µg/kg/week (or ESA equivalent) and 450 mg QD and 750 mg TIW in subjects converting from darbepoetin alfa doses > 0.45 and ≤ 1.5 µg/kg/week (or ESA equivalent).

The maximum vadadustat dose evaluated in completed phase 1 studies in healthy subjects was 1200 mg (single dose) and 900 mg (10 days). Vadadustat 750 mg and 900 mg QD as titration doses are being studied in an ongoing phase 2 trial in DD-CKD subjects and in an ongoing phase 1b trial, DD-CKD subjects have been dosed 900 mg QD. As described above (Section 2.3), the maximum vadadustat starting dose evaluated in completed phase 2 NDD-CKD studies was 630 or 600 mg QD, and in completed phase 2 DD-CKD studies was 450 or 600 mg.

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 in the US and 10.0 to 12.0 g/dL inclusive in Europe. The dose range for titration is 150 to 900 mg QD and 150 to 1200 mg TIW.

Doses of 150 to 630 mg QD have been evaluated in studies evaluating subjects with NDD-CKD and DD-CKD. Evaluation of higher doses is justified because 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 subjects, 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. 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. 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.

As described above (Section 2.3), the 16-week phase 2 hemodialysis trial 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 TIW dosing regimen of 450 mg TIW maintained Hb levels through 16 weeks, similar to 300 mg or 450 mg QD dosing regimens. However, six of the 31 patients in TIW arm were withdrawn from the trial because of worsening of anemia. Upon further analysis of

these patients, it was observed that these patients had higher baseline-ESA doses. It is postulated that these patients could have benefited with higher TIW starting and maximum dose of vadadustat to yield an increase in erythropoietic effect to overcome worsening of anemia. To maximize the probability that subjects treated with vadadustat TIW will maintain Hb levels within the target range, this trial will allow for earlier dose increase after 2 weeks of initial treatment and permit dose increases up to 1200 mg TIW.

The maximum dose of vadadustat in this trial is 900 mg daily and 1200 mg TIW. No accumulation was evident after repeat dosing with vadadustat exposure and therefore, the exposures with 1200 mg single dose was likely to be similar to 1200 mg TIW. Per total weekly dosing, 1200 mg TIW (3600 mg/week) is a lower dosing regimen compared 900 mg QD (6300 mg/week) and no C_{max} related AEs were evident throughout clinical development of vadadustat.

From a safety and tolerability standpoint, as described above (Section 2.3), multiple doses of 700 and 900 mg daily for up to 10 days and single doses of 1200 mg have been examined in healthy subjects. 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.[23] 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 trial withdrawal, and no SAEs were reported. No clinically meaningful changes or abnormalities in vital signs, safety laboratory studies, or ECG parameters were reported.

The starting dose of vadadustat for the high darbepoetin alfa group TIW arm will be 750 mg and for the low darbepoetin alfa TIW arm will be 600 mg. In the ongoing global phase 3 program, subjects are getting higher total weekly doses as subjects treated in the high darbepoetin alfa group may be administered 600 mg vadadustat daily for a total weekly dose of 4200 mg; no significant dose-related safety concerns have been identified by the Independent Data Monitoring Committee (IDMC) in these trials.

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

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 in the US and 10 to 12 g/dL in Europe.

- 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.

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

4.4 End of Trial Definition

The end of trial date is defined as the last date of contact or the date of final contact attempt from the safety follow-up electronic case report form (eCRF) page for the last subject completing or withdrawing from the trial.

The trial will be considered completed (end of trial) after all randomized subjects have completed their final trial visit (ET, Week 52/EOT, or Safety Follow-up).

4.5 Definition of Completed Subjects

A subject will be considered as having completed the trial after completion of their final trial visit (ET, or Week 52/EOT). Safety Follow-up Visit data summarization and analysis will be performed separately.

Subjects who discontinue prematurely from the trial will complete the ET Visit assessments and will complete the Safety Follow-up Visit, 4 weeks after their last dose of IMP.

The need for rescue therapy does not constitute trial completion unless it meets the criteria stated in Section 7.3.2. Also, the occurrence of a safety endpoint does not constitute trial completion and is not a criterion for subject withdrawal from the trial or IMP (vadadustat or darbepoetin alfa).

5 Trial Population

An estimated 300 subjects with approximately:

- 100 subjects randomized to vadadustat QD arm.
- 100 subjects randomized to vadadustat TIW arm.
- 100 subjects randomized to darbepoetin alfa arm.

The trial population will consist of subjects ≥ 18 years of age receiving chronic, outpatient in-center hemodialysis TIW, with 2 screening Hb values between 8.0 and 11.0 g/dL (inclusive) in the US or between 9.0 and 12.0 g/dL (inclusive) in Europe, and on maintenance treatment with an ESA.

5.1 Subject Selection and Numbering

All subjects will be assigned a unique subject number.

Demographic information (collection date, date of birth, sex, childbearing potential, race, and ethnicity) and medical history will be recorded in eCRF at Screening Visit.

Eligible subjects who are enrolled in the trial will be assigned a unique subject randomization number for treatment sequence assignment (see Section 6.3.1). Results of the eligibility assessment, date of randomization (or date of treatment assignment) and randomization number (or treatment group) will be recorded in the eCRF.

5.2 Eligibility Criteria

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

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) ≥ 18 years of age.
2) Receiving chronic, outpatient TIW in-center hemodialysis for end-stage renal disease for at least 12 weeks prior to Screening.
3) Hemodialysis adequacy as indicated by single-pool $K_t/V_{urea} \geq 1.2$ using the most recent historical measurement within 8 weeks prior to or during Screening.
4) Use of any approved ESA for at least the 8 weeks prior to Screening Visit 2.
5) Two Hb values, at least 4 days apart, measured by the central laboratory during Screening within the following prespecified ranges:
   a) Hb values between 8.0 and 11.0 g/dL (inclusive) in the US.
   b) Hb values between 9.0 and 12.0 g/dL (inclusive) in Europe.
6) Serum ferritin ≥ 100 ng/mL and TSAT ≥ 20% during Screening.
7) Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) Women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of investigational medicinal product (IMP). If employing birth control, 2 of the following precautions must be used: vasectomy of partner, tubal ligation, vaginal diaphragm, or intrauterine device (see Section 10.3).
2) 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 (see Section 10.3) 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.
3) Women who are breast feeding and/or who have a positive pregnancy test result prior to receiving IMP.
4) Subjects with contraindication to required trial assessment.
5) Subjects who, is in opinion of the investigator or medical monitor, have a medical history or medical findings inconsistent with safety or trial compliance.
6) Anemia due to a cause other than CKD (eg, sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia).
7) Subjects meeting cut-off of the following equivalent mean weekly doses calculated over 8 weeks prior to Screening Visit 2:
    a) Methoxy polyethylene glycol-epoetin beta > 50 µg/week.
    b) Darbepoetin alfa > 100 µg/week.
    c) Epoetin analogues > 23000 IU/week.
8) Active bleeding or recent blood loss within 8 weeks prior to randomization.
9) Red blood cell transfusion within 8 weeks prior to randomization.
10) Anticipated to discontinue hemodialysis during the trial.
11) Judged by the investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the trial.
12) History of chronic liver disease (eg, chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis, or fibrosis of the liver).
13) 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.
14) Current uncontrolled hypertension as determined by the investigator that would contraindicate the use of an ESA.
15) Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for HF or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening.

16) 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.
17) History of a new or recurrent episode of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening.
18) History of hemosiderosis or hemochromatosis.
19) History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded).
20) 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.
21) History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded).
22) Known hypersensitivity to vadadustat, darbepoetin alfa, or any of their excipients.
23) Use of an investigational medication within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to screening or during screening and any prior use of a hypoxia-inducible factor prolyl hydroxylase inhibitor. Subjects may participate in another concurrent trial only if that trial is a non-interventional, observational investigation.
24) Subjects with bilateral native nephrectomy.
25) Treated with probenecid within the 28-day Screening Period prior to randomization or during the study treatment duration.
26) Any other reason, which in the opinion of the investigator, would make the subject not suitable for participation in the trial.

A definition of childbearing potential can be found in Section 10.3.

Subjects must agree to restrictions to medications described in Section 6.5.1.

5.3 Lifestyle Considerations

Not applicable.

5.3.1 Meals and Dietary Restrictions

Not applicable.

5.3.2 Caffeine, Alcohol, and Tobacco

Not applicable.

5.3.3 Activity

Not applicable.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an informed consent form [ICF]), but who is not randomized or assigned trial treatment.

If the subject meets the definition of a screen failure in this trial, the following information (at a minimum) will be recorded in the eCRF:

- Date of informed consent.
- Visit date (Screening Visit).
- Demographics (collection date, birth date, sex, race, ethnicity, country).
- Result of eligibility assessment.
- Screen failure date.
- Reason for screen failure.

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

Screening numbers assigned to subjects who fail Screening will not be reused.

Subjects who fail to qualify for the trial at the initial Screening Visit will receive a new subject number for each rescreening attempt (see Section 5.4.1). If rescreened, the subject will also sign a new ICF and will repeat all Screening procedures.

5.4.1 Retesting and Rescreening

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

Subjects who fail to qualify for the trial 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 trial. Each screening attempt

includes the potential of a retest. Additionally, subjects who fail to qualify for the trial based on inclusion criteria values for TSAT, ferritin, folate, or B_{12} values may be considered for rescreening after receiving replacement therapy. A minimum of 3 weeks from IV iron replacement therapy (for low TSAT and ferritin values) must be observed prior to collecting next trial visit Hb value.

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.

6 Trial Treatments

6.1 Trial Treatments Administered

The investigator or designated trial personnel will be responsible for preparing IMP for dispensing to the subject (Section 6.2) and for IMP supply accountability (Section 6.2.3).

For information regarding the dose regimen and treatment period(s), including any follow-up period(s) for each treatment group/arm of the trial, see Section 4.1.

6.1.1 Dosing and Dose Adjustment Guidelines

Dosing and dose adjustments are described below for vadadustat (Section 6.1.1.3) and darbepoetin alfa (Section 6.1.1.4).

6.1.1.1 ESA Equivalent Dose Calculation

Following a Screening Period of up to 8 weeks, subjects who meet all eligibility criteria will be randomized 1:1:1 to vadadustat QD, vadadustat TIW, or darbepoetin alfa. Mean weekly darbepoetin alfa dose (or ESA equivalent) will be calculated over a period of 8 weeks prior to Screening Visit 2 and stratified into 2 groups:

- Low darbepoetin alfa dose group (≤ 0.45 µg/kg/week).
- High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 µg/kg/week).

Refer to the trial-specific Dosing Guideline for instructions on ESA medications conversion to an equivalent darbepoetin alfa dose for stratification and randomization.

6.1.1.2 Dose Adjustment Algorithm

This protocol provides guidance for the treatment of subjects with anemia associated with CKD in order to achieve and maintain Hb levels within the target Hb range. Dose adjustment should be based on the investigator's clinical discretion, incorporating the protocol guidance, and considering the subject's clinical condition, Hb rate of rise, Hb rate of decline, Hb variability, and IMP responsiveness. In cases where the investigator

does not follow the dosing algorithm, the clinical circumstances must be documented in the subject's source or dosing approach may be considered a protocol deviation.

Hemoglobin will be monitored via central laboratory throughout the trial to determine if the dose of IMP (vadadustat or darbepoetin alfa) will be adjusted, interrupted, or maintained and is used for the Guidelines for Dose Adjustment (see Table 6.1.1.2-1).

Table 6.1.1.2-1 Guidelines for Dose Adjustment

Status of Hb Levels	Dose Adjustment[a]
Hb levels are to be maintained in the following target ranges: US only: 10.0 to 11.0 g/dL, inclusive. Europe only: 10.0 to 12.0 g/dL, inclusive.	A dose increase or decrease is required to achieve and maintain Hb levels within the target range. Dose is adjusted by 1 dose level (for vadadustat 1 tablet [150 mg], for darbepoetin alfa approximately 25%)
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 ESA) and if Hb is < 10.0 g/dL.	A subject's dose may be increased by 1 dose level.
A rapid rise in Hb is observed (defined as follows): > 1.0 g/dL in any 2-week period or > 2.0 g/dL in any 4-week period.	Reduce or interrupt the dose.[b]
Hb levels are in the following setting: US only: Hb > 11.0 g/dL. Europe only: > 12.0 g/dL.	Reduce or interrupt the dose. After Hb falls below 11.0 g/dL (US) or 12.0 g/dL (Europe), restart IMP and consider restarting at a lower dose.

[a]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 one occasion. Dose adjustment should be based on the investigator's clinical discretion.

[b]See Section 7.3.1 (Treatment Interruption).

6.1.1.3 Vadadustat Dosing

For subjects assigned to vadadustat, the initial dose of vadadustat will depend on mean weekly darbepoetin alfa dose (or ESA equivalent) calculated over a period of 8 weeks prior to Screening Visit 2 (see Section 6.1.1.1) as follows:

- Low darbepoetin alfa dose group (≤ 0.45 µg/kg/week) will receive either an initial vadadustat dose of 300 mg QD or 600 mg TIW or
- High darbepoetin alfa dose group (> 0.45 and ≤ 1.5 µg/kg/week) will receive either an initial vadadustat dose of 450 mg QD or 750 mg TIW.

Dosing will be initiated at the Baseline/Day 1 Visit and the first dose of vadadustat will be administered at the trial site after other Baseline/Day 1 Visit procedures have been completed. Thereafter, vadadustat will be taken QD or TIW (on dialysis days) on an outpatient basis. Subjects may take vadadustat with or without food and should be

instructed to swallow the tablet(s) whole, without chewing. Subjects should be instructed to take vadadustat at roughly the same time each day.

During the trial, vadadustat should be dosed according to the Dose Adjustment Algorithm (Section 6.1.1.2), and dose adjustments will be guided by Hb concentrations and the Guidelines for Dose Adjustment (see Table 6.1.1.2-1).

The minimum dose of vadadustat will be 150 mg and the maximum dose will be 900 mg QD or 1200 mg TIW.

6.1.1.4 Darbepoetin Alfa Dosing

For subjects who were receiving darbepoetin alfa during screening and randomized to the darbepoetin alfa treatment arm, the initial dosing regimen in the trial (starting from Baseline/Day 1) will be approximately the same weekly dose that they were receiving prior to randomization. For subjects receiving darbepoetin alfa for the first time, the initial dosing regimen (starting from Baseline/Day 1) will be determined by the USPI or EU SmPC, per the medical judgment of the investigator. Darbepoetin alfa will be dispensed as a solution in single-dose prefilled syringes, to be given by IV injection through dialysis vascular access.

6.1.2 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.

6.1.3 Late or Missed Doses

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

Subjects on TIW dosing regimen should be instructed to take the dose on dialysis days. If a dose is forgotten, subjects should be instructed to take the dose as soon as they remember during the same day or the next non-dialysis day. Subjects should not double-up on missed doses.

Site personnel who are administering darbepoetin alfa should be instructed to administer the IMP, including handling of late or missed dosed, as described in the USPI or EU SmPC.

Subjects should be questioned regarding dosing compliance at every visit and whether they have questions or have experienced any problems related to the dosing of IMP (vadadustat only).

6.2 Management of Investigational Medicinal Product

The investigator will maintain record of all vadadustat tablets and darbepoetin alfa injections dispensed to and returned from each subject during the trial. Subjects will receive either vadadustat or darbepoetin alfa according to the randomization assignments provided via the IWR system (see Section 6.3.1).

Subjects will be provided with a supply of vadadustat at the Baseline Visit according to the IWR system assignment. Resupply of additional vadadustat at subsequent visits will be managed via the IWR system and will be dependent on the current dose level of vadadustat and the number of tablets remaining in the subject's current vadadustat supply at a given trial visit (Section 6.1.1.1).

Subjects should be instructed to bring unused vadadustat and empty bottles to each trial visit for product accountability. Empty bottles will be collected at these trial visits. If the subject moves from 300 mg to 450 mg, the subject should return the 150 mg bottles to the site for accountability.

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

Darbepoetin alfa will be dispensed according to the IWR system assignment.

- For subjects already on darbepoetin alfa, the initial dosing regimen in the trial should be based on the prior dosing regimen.
- For subjects on epoetin analogues or methoxy polyethylene glycol-epoetin beta, who are randomized to darbepoetin alfa arm, the starting dose of darbepoetin alfa will be determined by USPI or EU SmPC.

Dispensing of additional darbepoetin alfa at subsequent dosing visits will be managed by the IWR system (Section 6.1.1.4).

For full details on IMP management, please refer to the vadadustat IB.[17]

6.2.1 Packaging and Labeling

Vadadustat for oral administration and darbepoetin alfa for injection will be provided and shipped by the sponsor or its designated supplier/distributor. Both vadadustat and darbepoetin alfa will be supplied as open label supplies.

Vadadustat will be provided as 150 mg white, round, film-coated, or 450 mg pink, oval, 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.

Darbepoetin alfa will be provided in its commercially-approved primary packaging.

Investigational medicinal product will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. Labeling will be in accordance with current Good Manufacturing Practices (GMP) and local regulatory requirements and each IMP used in the dosing period will be labeled to clearly disclose the subject identifier (ID), compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

6.2.2 Storage

All IMP supplies must be kept in a temperature controlled, locked facility, accessible only to authorized trial personnel. Access will be limited to investigators and their designees.

Vadadustat should be stored at controlled room temperature of 15°C to 30°C (59°F to 86°F). Please consult the Pharmacy Manual for details on storage and managing temperature excursions.

Darbepoetin alfa will be stored per the USPI for US sites or EU SmPC for EU sites.

The clinical site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP received, dispensed, administered, and returned. Neither the investigator nor any designees may provide IMP to any subject not participating in this protocol.

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

Proper drug accountability includes, but is not limited to:

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

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

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

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

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

6.2.4 Returns and Destruction

All unused and/or partially used vadadustat or darbepoetin alfa should be returned to the sponsor or destroyed at the investigational site, as specified by the sponsor. Appropriate records of the disposal will be documented and maintained. No unused vadadustat or darbepoetin alfa may be disposed of until fully accounted for by the sponsor's monitor (or designee). Empty containers may be disposed of according to local procedures.

6.3 Measures to Minimize/Avoid Bias

6.3.1 Randomization

This trial will be open to an estimated 300 subjects ≥ 18 years of age receiving chronic, outpatient in-center hemodialysis TIW with 2 screening Hb values (at least 4 days apart) between 8.0 and 11.0 g/dL (inclusive) in the US and between 9.0 and 12.0 g/dL (inclusive) in Europe, and on maintenance treatment with an ESA.

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

To maintain balance between vadadustat QD-treated, vadadustat TIW-treated and darbepoetin alfa-treated subjects, randomization will be stratified with respect to:

- Geographic region (US versus Europe, approximately 90 subjects in Europe).
- Mean weekly darbepoetin alfa dose (or ESA equivalent) calculated over a period of 8 weeks prior to Screening Visit 2:
  - Low darbepoetin alfa dose group ($\leq$ 0.45 µg/kg/week)
  - High darbepoetin alfa dose group (> 0.45 and $\leq$ 1.5 µg/kg/week)
- In the low darbepoetin alfa dose group, subjects will be randomized in a 1:1:1 ratio to receive either an initial vadadustat daily dose of 300 mg daily or 600 mg TIW, or darbepoetin alfa.
- In the high darbepoetin alfa dose group, subjects will be randomized in a 1:1:1 ratio to receive either an initial vadadustat daily dose of 450 mg daily, 750 mg TIW, or darbepoetin alfa.

Refer to the trial-specific Dosing Guide for instructions on ESA medications conversion to darbepoetin alfa equivalent dose for stratification.

6.3.2 Blinding

This will be an open-label trial. Treatment assignment will be done through the IWR system and the investigator, sponsor, and contract research organization (CRO) trial teams will not be aware of which treatment will be assigned next. Treatments will be administered in an open-label fashion. The sponsor and CRO trial teams will be blinded to "by treatment" aggregated analyses except for the unblinded personnel. Because Hb values are objective and will be measured via a central laboratory for all efficacy endpoints, efficacy assessments are not considered to be subject to bias with an open-label design. In addition, the trial will involve the use of an IDMC, and an identical schedule of visits, procedures, and assessments for all treatment groups in order to reduce the potential for bias. Adjustments to doses for vadadustat will be based on Hb concentration and Dose Adjustment Algorithms and darbepoetin alfa will be based on USPI or EU SmPC.

As described in Section 9.5, the Safety Event Adjudication Committee (SEAC) will remain blinded throughout the full course of the trial.

6.4 Subject Compliance

Subjects will be questioned regarding dosing compliance at every visit and whether they have questions or have experienced any problems related to the dosing of the IMP (vadadustat or darbepoetin alfa). Treatment compliance will be determined from drug accountability logs along with the subject questioning and the IMP eCRFs. Dosing compliance for vadadustat or darbepoetin alfa is defined as 80% to 120% over the course of the Treatment Period.

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

6.5 Concomitant Medications or Therapies

The investigator will record all medications and therapies taken by the subject from 8 weeks prior to signing of informed consent through the Safety Follow-up Visit on the eCRF. The investigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eCRF.

Erythropoiesis-stimulating agents (ESAs), blood transfusions, and iron treatment regimen prior to randomization and the date of last dose will be recorded on a separate disease-related concomitant therapy eCRF pages.

6.5.1 Prohibited Medications

6.5.1.1 Erythropoiesis-stimulating Agents

Co-administration of any ESA with vadadustat is prohibited. If ESA rescue therapy is deemed medically necessary, vadadustat treatment must be stopped during ESA administration (see Section 6.5.3.2 for guidelines). All efforts will be made to avoid inadvertent administration of ESA resulting from adherence to ESA hemodialysis center protocols (eg, ESA protocols for subjects on hemodialysis). If ESA is inadvertently administered to subjects actively receiving vadadustat treatment, vadadustat treatment will be stopped and the event will be reported as a protocol deviation.[17]

For all subjects, it is required that a minimum period as outlined below be observed between the last dose of ESA administered during Screening and Randomization Visit:

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

Non-protocol ESAs are prohibited from randomization until the end of the trial, unless the subject is receiving ESA rescue therapy, interrupts IMP for other reasons, or permanently discontinues the IMP. Reasons for ESA use will be captured in the appropriate eCRF (eg, AE, inadvertent administration, etc.).

6.5.1.2 Sulfasalazine and Other BCRP Substrates and Probenecid

Exposure to sulfasalazine was moderately increased with co-administration of vadadustat based on a trial 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. If there are questions regarding a specific concomitant medication, please consult with the Trial Team Medical Monitor.

Probenecid, an inhibitor of uridine 5'-diphospho-glucuronosyltransferase and the organic anion transporter 1/3 transporters, increased vadadustat area under the curve and is prohibited during the trial.

6.5.2 Permitted Medications

6.5.2.1 Iron Supplementation

Investigators will prescribe iron supplementation (IV, oral, or intradialytic) during the trial to maintain ferritin ≥ 100 ng/mL or TSAT ≥ 20%. The use of iron-based phosphate binders (eg, ferric citrate) is permitted.

Important: 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 IMP is not to be administered concurrently with an oral iron supplement (including multivitamins containing iron), iron-containing and non-iron-containing phosphate binders, or any oral medications containing iron.

Subjects will be instructed to take vadadustat at least 1 hour before oral medications containing iron. Iron supplementation details will be captured in the appropriate eCRF.

6.5.2.2 Phosphate Binders

Subjects will be instructed to take vadadustat at least 1 hour before or 2 hours after non-iron-containing phosphate binders.

6.5.2.3 HMG-CoA Reductase Inhibitors (Statins)

Numerous drug-drug interactions have been reported following concomitant administration of vadadustat with various statins and the following guidelines regarding the concomitant use of statins during the trial should be considered.

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

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

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

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

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

A summary of results and management of concomitant administration of vadadustat with the various statins is provided in Table 6.5.2.3-1.

Table 6.5.2.3-1 Results and Management of Concomitant Administration of Vadadustat with Statins		
Statin	**Change in Statin Exposure When Dosed with Vadadustat[a]**	**Recommended Statin Dosing in Subjects Receiving Concomitant Vadadustat**
Atorvastatin	Mild increase	No dose adjustment
Pravastatin	No increase	No dose adjustment
Rosuvastatin	Moderate increase	Maximum daily dose of 10 mg
Simvastatin	Mild-to-moderate increase	Maximum daily dose of 20 mg
Other statins	Not studied	Upward titration to higher doses should be done with caution

[a]Based on FDA guidance, inhibitor potency is based on an increase in exposure of ≥ 1.25- to < 2-fold, ≥ 2- to < 5-fold, or ≥ 5-fold for weak, moderate, or strong interactions, respectively.[24]

6.5.3 Rescue Medications

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

6.5.3.1 RBC Transfusion

Investigators will use their local institution's transfusion guidelines when determining whether to transfuse a trial subject. In general, in the event of an acute or severe loss of blood, an 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. Trial medication (vadadustat or darbepoetin alfa) may be continued during the transfusion period.

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

6.5.3.2 ESA Use

ESA administration will be allowed when medically necessary at the discretion of the investigator. 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 if deemed medically necessary at the discretion of the investigator. In general, ESA rescue will be allowed in subjects with Hb < 9.5 g/dL, and ESA will be stopped when Hb ≥ 10.0 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 rescue therapy, subjects randomized to vadadustat must temporarily interrupt vadadustat. A minimum interval must be observed prior to restarting vadadustat after the last dose of ESA rescue medication, and treatment may be resumed after the following intervals:

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

Please refer to local prescribing information.

Following ESA rescue 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 eCRF.

6.5.3.3 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 trial site's standard clinical practice.

6.6 Intervention after the End of the Trial

Subjects will be treated based on the investigator's clinical judgment.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, Institutional Review Board (IRBs)/Independent Ethics Committee (IECs), and regulatory authorities in accordance with regulatory requirements.

The entire trial may be suspended or terminated by the sponsor, or the IRB for safety or other unanticipated reasons or upon request of regulatory agencies. If this occurs, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

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

7.1.1 Criteria for Premature Termination or Suspension of the Trial

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

New information regarding the safety or efficacy of the IMP 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 trial.

Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary trial objectives or compromises subject safety.

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years following the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Up to 25 years or longer according to region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either

1) Written permission from the sponsor or
2) Provision of an opportunity for sponsor to collect such records.

The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

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

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

A trial site may be terminated prematurely or suspended if the trial 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 trial.

In the event that the sponsor elects to terminate or suspend the trial or the participation of an investigational trial site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational trial sites during the course of termination or trial suspension.

7.3 Individual Subject Discontinuation

During this trial, it is anticipated that some subjects may permanently discontinue IMP (vadadustat or darbepoetin alfa).

Subjects who discontinue IMP prematurely and the investigator determines that the subject will be permanently discontinued from the trial (see Section 7.3.1), will complete the ET Visit assessments and the Safety Follow-up Visit, 4 weeks after ET Visit.

Subjects may discontinue prematurely from the trial for any of the following reasons:

- Adverse Event.
- Subject withdrawal of consent.
- Investigator's discretion.
- Lack of efficacy, defined as inadequate response to darbepoetin alfa or vadadustat in the investigator's opinion.
- Lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Receipt of a solid organ (including kidney), hematopoietic stem cell, or bone marrow transplantation.
- Meeting criteria for Trial Medication Stopping Rules (see Section 7.3.2).
- Change in dialysis modality (ie, from hemodialysis to peritoneal dialysis or change from in center hemodialysis to home/nocturnal hemodialysis).
- Permanent change in frequency of in-center hemodialysis from three-times per week.
- Death.
- Other reasons (pregnancy [see Section 10.3], specific reasons to be documented by the investigator).

A subject has the right to withdraw consent for participation in the trial at any time (Section 7.3.4).

See Table 7.3.2-1 for additional details on the management of subjects with ALT and AST abnormalities.

7.3.1 Treatment Interruption

Subjects who temporarily interrupt IMP (vadadustat or darbepoetin alfa) treatment after the first dose and prior to completion of the trial will continue with trial visits and assessments. Unless contraindicated, treatment with IMP should be resumed within a 30-day time period from the start date of interruption and routinely considered at every visit following IMP interruption. If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

During the trial, a subject may interrupt the IMP (vadadustat or darbepoetin alfa) for any of the following reasons:

- Adverse event.
- Missed dialysis visit (darbepoetin alfa arm).
- Investigator's discretion.
- Rapid rise in Hb (defined as > 1.0 g/dL in any 2-week period or > 2.0 g/dL in any 4-week period).
- Hb above 11.0 g/dL (US) or above 12 g/dL (Europe).
- New elevations in ALT or AST > 3x ULN, without elevation in total bilirubin.
- Vadadustat arm: ESA use.
- Darbepoetin alfa arm: ESA use other than darbepoetin alfa IMP.

While receiving ESA rescue, subjects must temporarily discontinue IMP. Unless contraindicated, treatment with IMP should be resumed within a 30-day time period from the start date of the interruption. Re-start of IMP should be assessed at every visit following IMP interruption.

If a subject is receiving a tolerated dose of IMP prior to interruption, the subject may interrupt IMP for a maximum duration of 30 days. Re-start of IMP should be assessed at every visit following IMP interruption. Prior to the end of the 30-day time period from the start date of interruption, the investigator, in consultation with the sponsor's Medical Monitor or CRO designee, should assess either if the subject can or cannot be re-started on the IMP. If by Day 30 the subject will not be re-starting IMP, they will be

permanently discontinued from the trial and will complete the ET Visit and the Safety Follow-up Visit assessments.

7.3.2 Treatment Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible. If, after discussion with the investigator about possible mitigations for AEs, etc., the subject still chooses to discontinue IMP, the subject will permanently discontinue IMP and will complete the ET Visit assessments and will complete the Safety Follow-Up Visit, 4 weeks after last dose of IMP and the subject will not be allowed to re-start the IMP.

Trial medication is to be permanently discontinued if ESA rescue (other than darbepoetin alfa in comparator arm, any ESA in vadadustat arm) is not in the setting of acute bleeding (ie, gastrointestinal bleed, surgery, excess bleeding) and one of the following:

- The first cycle of ESA rescue lasts >30 days or
- Subject requires a second cycle of ESA for rescue (that must be related to anemia) at any time.

Trial medication must be permanently discontinued if a subject meets one of the criteria in Table 7.3.2-1.

Table 7.3.2-1 Trial 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[a]	Permanently Discontinue Treatment
ALT or AST > 3x ULN with symptoms including eg, fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia	Permanently Discontinue Treatment

INR: international normalized ratio; ULN: upper limit of normal

[a]Re-challenge generally should be avoided with ALT or AST > 5x ULN unless there are no other good therapeutic options.

See Section 8.8 for reporting requirements related to a subject being permanently discontinued based on meeting the laboratory abnormalities list above in Table 7.3.2-1.

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

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A subject may temporarily interrupt or discontinue IMP for the reasons listed in Section 7.3.1 and Section 7.3.2.

If the subject temporarily interrupts or discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.1 and Section 7.3.2 must be followed.

7.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary.

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial.

[redacted]

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the Safety Follow-up Visit after the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up". Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact

the subject via certified mail or an alternative similar method, where appropriate, before assigning a “lost to follow-up” status.

If the subject was classified as “lost to follow-up”, “Were you able to contact the subject?”, “Date of contact/Date of final contact attempt” and “Contact method” will be recorded in the source documents.

8 Trial Procedures

The Schedule of Assessments (Table 1.3-1) shows the timing of planned trial procedures. Every effort should be made to adhere to this procedure schedule and all assessments should be completed at each trial visit. Where possible, trial visits should be performed and scheduled as part of a subjects regularly scheduled dialysis session.

Subjects are to be assessed by the same investigator or investigative site personnel whenever possible.

Screening Visits

The ICF will be signed at Screening Visit 1. Subjects will need to sign the ICF prior to any Screening Visit 1 procedures. The Screening period starts at the time the ICF is signed and will be up to 8 weeks in duration. Two Screening visits must be performed within 8 weeks prior to dosing (Baseline Visit/Day 1). There must be a minimum of 4 days between the 2 Screening Visits and a minimum of 4 days (based on last ESA use) between Screening Visit 2 or last retest and the Baseline Visit.

The investigator will maintain a log of subjects and indicate who of the Screened subjects were enrolled or excluded and the reason for exclusion.

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

Two Hb values, at least 4 days apart, measured by the central laboratory during Screening must be between 8.0 and 11.0 g/dL (inclusive) in the US or between 9.0 and 12.0 g/dL (inclusive) in Europe to qualify for inclusion into the trial. If the subject’s Hb does not qualify after Screening Visit 1, Screening Visit 2, or retest Hb, the subject should be considered a Screen failure. Refer to Section 5.4.1 for further details regarding repeating laboratory measurements during the Screening period.

For all subjects, it is recommended that no additional ESA doses be administered after Screening Visit 2 and prior to the Baseline Visit (Day 1).

For all subjects, it is required that a minimum period as outlined below be observed between the last dose of ESA administered during Screening and Randomization Visit:

- 2 days after last dose of epoetin analogues.

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

After discussion with the Medical Monitor, screening may be extended for an additional 2 to 4 weeks based on the subject's Hb level or Hb trajectory or based on timing of the last ESA dose given during screening.

Baseline Visit (Day 1)

The Baseline Visit must be performed after a minimum period as outlined above. Subject will take their first dose of IMP at the investigative site during the Baseline Visit.

Iron supplementation as needed to maintain ferritin ≥ 100 ng/mL or TSAT ≥ 20% (per local product label; see Section 6.5.2.1). Subjects will be instructed to take vadadustat at least 1 hour before oral medications containing iron. AEs should be assessed after receiving the first dose of IMP.

Treatment Period Visits (Week 2 through Week 52)

Treatment Period Visits will occur from Weeks 2 to 52. The primary efficacy evaluation period will occur from Weeks 20 to 26, and the secondary efficacy evaluation period will occur from Week 46 to 52.

End of Treatment Visit/Early Termination Visit

The EOT Visit will be conducted on Week 52 for subjects that complete the 52-week treatment period (± 3 days). For subjects that end treatment prior to Week 52, the ET assessments should be performed within 7 days after stopping IMP.

Exit Interview

Using a semi-structured interview guide, a contributing CRO will conduct a single individual telephone interview with subjects at a subset of sites. The purpose of the exit interview is to document the subject's evaluation of the treatment received as well as their overall experience of the clinical trial. The information obtained during the exit interview will help to gain a better understanding of the both the disease and treatment from the subject's perspective. It is anticipated that each interview will be approximately 60 minutes. All exit interviews will be conducted by the CRO, audio recorded, and transcribed for analysis during the 4-week follow-up period.

A sample size of 60 subjects in the US and up to 30 subjects from Europe is targeted and sufficient to address trial objectives. The sample size was selected based on the subject diversity in the trial population; the minimum sample size required for exit interviews is

20 subjects. Interviews will be conducted using English or translated versions of the interview guide as appropriate.

The interview guide will begin with a very brief overview of the interview process and very general questions intended to get the subjects talking about their experiences associated with anemia due to CKD (the symptoms and impact of anemia) prior to entering the trial, most important or most bothersome aspects of the disease, and expectations of treatment prior to the trial. As the discussion continues, the semi-structured interview will focus on identifying and understanding the breadth and magnitude of subjects' perceived treatment benefits, including general experiences with trial treatment; anticipated or unanticipated benefits, impact of those benefits; impact of treatment on daily life/functioning; how well treatment addresses most important/bothersome symptoms; treatment satisfaction and reasons for satisfaction.

Follow-up Visit

The Follow-up Visit will be conducted 4 weeks after the EOT Visit, or 4 weeks after the last dose of IMP for ET.

Unscheduled Visits

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

- Adverse Event assessments.
- Major adverse cardiovascular events (MACE) assessment.
- Any other procedures that are medically warranted at the discretion of the investigator.

8.1 Subject Reported Outcome Assessments

8.1.1 36-Item Short Form Health-related Quality of Life

The SF-36v2 HRQOL is a subject-reported survey of subject health status which will be completed within the ePRO application during the dialysis visits, according to the Schedule of Assessments (Table 1.3-1).

8.1.2 Patient Global Impression of Severity Life

The PGI-S is a global index that is used to rate the severity of disease. It will be completed within the ePRO application during the dialysis visits, according to the Schedule of Assessments (Table 1.3-1).

8.1.3 Patient Global Impression of Change

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. It will be completed within the ePRO application during the dialysis visits, according to the Schedule of Assessments (Table 1.3-1).

8.1.4 Functional Assessment of Cancer Therapy-Anemia

The FACT-An is a subject-reported outcome measure which evaluates quality of life concerns related to anemia and fatigue. It will be completed within the ePRO application during the dialysis visits, according to the Schedule of Assessments (Table 1.3-1).

8.2 Pharmacokinetic Assessments

Plasma samples for PK evaluation will be collected only for subjects randomized to vadadustat to analyze for both the parent compound (vadadustat) and its metabolites.

Collection time points are as shown in Table 8.2-1 and Table 1.3-1 (Schedule of Assessments). Vadadustat may be dosed before or after the start of dialysis. The predose sample should be collected as close to the same time as the serum chemistry sample.

Blood samples will be collected and processed according to the Operations/Laboratory Manual. The actual date and time of the PK sample collection will be recorded in the eCRF. Additionally, the time of the dose of IMP will be recorded in the eCRF and the start and stop time of the dialysis session will be recorded in the eCRF.

Table 8.2-1 Vadadustat Pharmacokinetic Sampling Schema

	Week 12 Dialysis Day
Predose, within 60 minutes	X
0.5 hours ± 5 minutes (post-dose)	X
1 hour ± 10 minutes (post-dose)	X
2 hours ± 10 minutes (post-dose)	X
3 hours ± 15 minutes (post-dose)	X

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C or −20°C, unless otherwise instructed in the Operations/Laboratory Manual.

All plasma samples will be shipped to the bioanalytical laboratory for analysis. Information will be provided in the Operations/Laboratory Manual.

8.3 Pharmacodynamic Assessments

Blood samples for EPO, reticulocytes, and other iron indices (ferritin, iron, TIBC, and TSAT) analysis will be collected at the times noted in the Schedule of Assessments (Table 1.3-1). Blood samples will be collected and processed according to the Operations/Laboratory Manual. For all PD sampling, the time of the previous dose of IMP is to be recorded in the eCRF and the timing of administration of IMP and the start and stop time of the dialysis session will be recorded in the eCRF.

[redacted]

[redacted]

8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8. If the evaluations will occur on a hemodialysis day, the clinical evaluations should be completed before dialysis, if applicable.

8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the Schedule of Assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2.

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

Blood samples will be collected for the laboratory evaluations listed in Section 10.2 and will be conducted during the course of the trial. For details regarding the timing of these assessments refer to the Schedule of Assessments (Table 1.3-1).

- Pregnancy Test: A serum pregnancy test will be performed according to the Schedule of Assessments (Table 1.3-1) for females of childbearing potential. Additional serum or local urine (if possible) pregnancy tests may be conducted throughout the trial in sufficient number, as determined by the investigator or required by local regulations,

to establish the absence of pregnancy during the trial. These results must be available and must be negative before the subject takes the first dose of IMP.

8.7.2 Medical History, Demographics, and Physical Examination

Medical history, demographic information, and physical examination (including height) will be collected according to the Schedule of Assessments (Table 1.3-1). Relevant medical history (with particular emphasis on previous medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases should be documented. Dialysis events/issues (ie, the common issues that occur in a given dialysis patient such as pruritus, nausea, hypotension) should be recorded as medical history on the appropriate eCRF.

During the Treatment period, an abbreviated physical examination should be performed at the discretion of the investigator, as clinically indicated.

Dry weight will be collected for all subjects according to the Schedule of Assessments (Table 1.3-1). For subjects on ESA, subjects will be weighed for dosing as per the local standard of care.

8.7.3 Concomitant Medication Recording

All medications (both prescription and non-prescription, and including vitamins, herbals, topicals, inhaled, and intranasal), taken during the screening period and throughout the trial, ending at the final protocol required visit, should be recorded on the appropriate eCRF. At each trial visit, subjects will be asked whether they have started or discontinued any medication since their previous trial visit. This includes single-use or as-needed medication use. Any medications taken within 30 days of a reportable event must be reported on the Concomitant Medication eCRF.

All medications and treatments, including vitamin supplements, over the-counter medications and oral herbal preparations must be recorded in the eCRFs. Routine medications and treatments used during each hemodialysis session, such as heparin injections or saline flushes, are not required to be recorded unless relevant for an AE or SAE. In addition, the ESA, blood transfusion, and iron treatment regimen prior to randomization and date of last dose will be recorded.

8.7.4 Vital Signs

Vital signs will be collected at the time points described in the schedule of assessments (Table 1.3-1).

Vital sign measurements including temperature, heart rate, blood pressure, and respiratory rate will be assessed in the seated position after 5 minutes of rest prior to blood draws. For blood pressure, a total of 2 measurements at intervals of at least 2 minutes will be performed. Measurements will be taken prior to scheduled blood draws when possible.

8.7.5 Electrocardiogram

Electrocardiograms will be performed at the time points described in the schedule of assessments (Table 1.3-1).

A standard 12-lead ECG will be performed at Baseline, which may be obtained up to 3 days prior to the Baseline Visit. The ECG should be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes and should be taken prior to vital sign assessments and blood draws when possible. With the subject in a supine position, obtain the 12-lead tracing. All ECGs will be reviewed by the investigator for the presence of rhythms of potential clinical concern. A record of the tracing(s) will be made and retained with other source documents.

8.7.6 Other Safety Variables

8.7.6.1 Major Adverse Cardiovascular Events

At each post-randomization trial visit, the subject must specifically be questioned regarding the occurrence of any potential MACE (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for HF or thromboembolic event excluding vascular access thrombosis since the last trial visit. The eCRF must be completed in full at each visit even if no potential MACE (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for HF or thromboembolic event excluding vascular access thrombosis events have occurred.

8.8 Adverse Events

AE collection will begin from time of signing the ICF through the Safety Follow-up Visit. The investigator and trial personnel will review each subject's laboratory and clinical evaluation findings and query the site directly regarding AEs (see Section 8.8.1). Subjects must be followed for AEs until the final required protocol visit or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.

8.8.1 Definitions

An AE is defined as any untoward medical occurrence (including an abnormal laboratory finding) in a clinical trial subject administered an IMP that occurs in the protocol-specified AE reporting period and which does not necessarily have a causal relationship with this treatment or usage. Adverse events would not include information recorded as medical history at Screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

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

Adverse events therefore include the following:

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

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of open-label treatment. In more detail, TEAEs are all adverse events which started after start of open-label IMP treatment; or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption or reduction of IMP.

The sponsor maintains and updates a listing of any adverse event of special interest (AESI), serious or non-serious, which is of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate.

A SAE includes any event that results in any of the following outcomes:

- 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.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
  - Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the trial for a pre-existing condition that has not worsened during the AE reporting period does not constitute an SAE unless an untoward event occurs related to the procedure (eg, elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the course of the trial).
- 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 trial:

- **Malignancies** – If a subject develops basal cell carcinoma of skin, squamous cell carcinoma of skin, or cervical carcinoma in situ during the trial, or has worsening of these events from baseline, the event will be reported as an SAE by the investigator. 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.
- **Abnormalities in ALT or AST** – New elevations in ALT or AST > 3 times ULN, with or without an elevation of total serum bilirubin > 2 times ULN are to be reported to the sponsor's Medical Monitor or CRO designee within 24 hours of awareness as an SAE with "medically important" criteria selected. The following steps are to be taken for subjects who experience new elevations in ALT or AST > 3 times ULN, without an elevation of total serum bilirubin > 2 times ULN:
  - Temporary interruption of IMP.
  - Repeat testing of ALT, AST, alkaline phosphatase (ALP), and total bilirubin, to be completed within 48 to 72 hours to confirm the abnormalities and to determine trend.
  - Trial medication should not be resumed until monitoring indicates abnormalities have resolved or are stable.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of laboratory tests for each individual subject as they become available. This review will be documented by the investigator's dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eCRF. The severity of an adverse experience is defined as follows:

1 = Mild: Does not interfere with subject's usual function.

2 = Moderate: Interferes to some extent with subject's usual function.

3 = 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.

IMP Causality: The causal relationship of the AE to the IMP (vadadustat or darbepoetin alfa) will be assessed by both the investigator and the sponsor.

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

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

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

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

8.8.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and eCRF provided by the sponsor. Adverse event collection will begin from the time a subject signs the ICF.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail. Special attention should be paid to recording hospitalization and concomitant medications.

Adverse event start date and time, end date and time, seriousness, severity, relationship to trial treatment (IMP Causality), action taken with trial treatment and outcome will be recorded on the source documents and in the eCRF.

8.8.2.1 Guidelines for Reporting Adverse Events

Each AE is to be classified by the investigator as SERIOUS or NONSERIOUS and all AEs (serious and non-serious) are to be reported on the AE eCRFs.

All AEs that occur in trial subjects during the AE reporting period specified in this protocol must be reported, whether or not the event is considered related to IMP (vadadustat or darbepoetin alfa). In addition, each trial subject will be questioned about AEs at each visit following the initiation of treatment as described in Section 8.8.2.

The AE collection for this trial begins from time of ICF signing through the Safety Follow-up Visit.

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

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

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

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

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

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

Abnormal Test Findings – All laboratory test results will be reviewed by the investigator. The investigator will utilize his/her judgment in determining if out-of-range laboratory values are clinically significant (CS) and will denote this using the abbreviation "CS" on the laboratory report for source documentation. If there are significant changes in a laboratory report from a previous visit that are determined to be CS, these should also be reported as AEs. An expected laboratory abnormality from a condition that is part of the medical history is not considered CS for the purposes of the trial unless it represents a worsening of the condition.

Abnormalities in ALT, AST, and Total Bilirubin – Abnormalities in ALT, AST, and total bilirubin should be reported to the sponsor's Medical Monitor or CRO designee within 24 hours of awareness as 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

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

- Temporary interruption of IMP;
- Repeat testing of ALT, AST, ALP, and total bilirubin, should be completed within 48 to 72 hours to confirm the abnormalities and to determine trend;
- Trial medication should not be resumed until monitoring indicates abnormalities have resolved or are stable.
-

Details on the management of subjects with other ALT and AST abnormalities are further described in Table 7.3.2-1.

Worsening of Anemia – In this trial, it is possible that some subjects may experience a worsening of anemia. As the primary endpoint of this trial assesses Hb response, worsening of anemia is captured as part of this efficacy parameter. Worsening of anemia should not be considered an AE unless the worsening of anemia is associated with a cause other than the subject's CKD. However, if an event of worsening of anemia is due

to CKD and meets any serious criteria (see Section 8.8.1), it should be reported as an SAE.

Transplantation – During this long-term trial, it is anticipated that some subjects may receive a kidney transplant. These events will not be recorded as AEs. Subjects will discontinue IMP for receipt of a kidney, other solid organ, hematopoietic stem cell or bone marrow transplant and should continue with the Schedule of Assessments and safety assessments as described in Section 7.3.2.

Malignancy – During this long-term trial, some subjects may develop a newly diagnosed malignancy or a recurrence of a malignancy. At the discretion of the investigator, these subjects may continue IMP (vadadustat or darbepoetin alfa). For reporting of AEs of malignancy, see Section 8.8.1.

Reporting MACE – Investigators will be counseled to report any MACE (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for HF or thromboembolic event excluding vascular access thrombosis events that they assess as requiring adjudication. All events will be submitted in a blinded fashion to the SEAC for adjudication. To protect the integrity of the trial, already adjudicated events will not be unblinded or reported to either Health Authorities or investigators as safety reports unless otherwise requested or required by Health Authorities or Ethics Committees. After trial completion, these events will be included in the final analysis which will be unblinded and submitted to Health Authorities with the trial report.

8.8.2.2 Reporting Serious Adverse Events

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

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

- Subject number/identification, sex, and age/date of birth.
- The date of report.
- Name of the reporter.
- Name of the suspected medicinal product.
- A description of the event, including event term(s), seriousness criteria, and a clinical summary of the event.
- Causality assessment.

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

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

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

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

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

8.8.3 Procedure for Breaking the Blind

Blinding procedures are described in Section 6.3.2.

8.8.4 Follow-up of Adverse Events

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

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

8.8.4.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

8.9 Treatment of Overdose

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

- Overdose of the medicinal product
  - Darbepoetin alfa overdose – The USPI or SmPC should be referenced for information on darbepoetin alfa overdosing.
  - Vadadustat overdose - There is no known antidote for vadadustat. In cases of suspected overdose, subjects should be treated per standard medical practice based on the investigator's judgment and dose delays, reductions, or interruptions may be implemented as necessary. See Section 8.8 for guidance on AEs and SAEs.
  - 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 [eg, name confusion]).
  - Drug-drug interaction.

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

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

8.10 Subject Assessment Recording

Not applicable.

8.11 Other Assessments

8.11.1 Dialysis Adequacy and Treatment

Dialysis adequacy, as documented in the dialysis records, will be recorded in the eCRF. During screening, the most recent dialysis adequacy measurement within 8 weeks prior to or during screening should be recorded in the eCRF. Thereafter, dialysis adequacy should be assessed every 3 months.

Dialysis Treatment includes hemodialysis vascular access type use and any changes at baseline and monthly; and changes in renal replacement therapy (from in-center hemodialysis).

9 Statistical Considerations

Data collected throughout the trial will be summarized using descriptive statistics and listed in by-subject listings. Continuous variables will be summarized using number of subjects with data, mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated. Summaries will be provided by treatment group within appropriate analysis populations (as defined in Section 9.2) and by time point/time period, as appropriate.

For Hb, Baseline will be calculated as the average of the last 2 central laboratory Hb measurements of samples taken at or prior to the date of randomization. For other parameters, unless otherwise specified, Baseline will be defined as the last available value prior to the first dose of IMP.

Hemoglobin values will be assessed through the central laboratory for dose adjustments, efficacy, and safety evaluations.

9.1 Sample Size

The primary efficacy endpoint is defined as the Hb change from Baseline (average pretreatment Hb) to the average Hb from Weeks 20 to 26 (inclusive).

The primary efficacy objective of this trial is to first show that vadadustat QD is noninferior to darbepoetin alfa within the noninferiority margin. Noninferiority will be established based on a margin of -0.75 g/dL (for vadadustat minus darbepoetin alfa). If vadadustat QD meets the noninferiority margin, then the next objective is to show that vadadustat TIW is noninferior to darbepoetin alfa within the noninferiority margin.

For the primary efficacy analysis in this trial, it is assumed that the mean change from Baseline in Hb for vadadustat will be the same as for the active control darbepoetin alfa, and the common standard deviation for the mean change from Baseline is assumed to be

1.2 g/dL. Noninferiority will be established based on a 2-sided 95% confidence interval (CI) for the difference between the vadadustat group and darbepoetin alfa group and using a noninferiority margin of -0.75 g/dL.

With these assumptions and approximately 100 subjects per treatment group, the noninferiority test will have > 90% power with consideration of a 30% drop out rate.

9.2 Datasets for Analysis

The following analysis populations will be used in this trial:

- Randomized population: defined as all subjects randomized. Analyses of this population will be based on the randomized treatment.
- Full Analysis Set (FAS) population: defined as all subjects in the randomized population who received at least 1 dose of IMP and had at least 1 post dose Hb. Analyses of this population will be based on the randomized treatment.
- Per protocol (PP) population: defined as all randomized subjects who received IMP during the primary evaluation period, had at least 1 Hb assessments during the primary evaluation period, and had no critical or major protocol deviation affecting the primary endpoint analyses (ie, prior to Week 26). Analyses of this population will be based on actual treatment received, as described for the Safety population.
- Safety population: defined as all subjects in the randomized population who received at least 1 dose of IMP. Analysis of this population will be based on the actual treatment received. Subjects who received in error some vadadustat and some darbepoetin alfa (excluding rescue therapy) will be classified by the more frequently received drug.

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

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

It is expected that up to 30% of subjects will discontinue the trial. The reasons for discontinuation will be summarized by treatment arm. Missing Hb values will be imputed using multiple imputation.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

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

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is defined as the change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).

9.4.1.1.1 Primary Estimand

The primary estimand defining the treatment effect of interest in this trial uses the treatment policy strategy specified in the ICH E9 (R1) Addendum.[25] In this trial, the research question is to compare the assignment of darbepoetin alfa to vadadustat, regardless of intercurrent events. The primary analysis will be performed in the randomized population in accordance with intent-to-treat. This means the analysis will include individuals who never received treatment, discontinued treatment, were rescued with any therapy, and withdrew consent. The estimate of the treatment effect of interest will be the one regardless of whether the intercurrent event occurred.

The primary estimand for this trial is defined by the following components:

- Population: randomized population.
- Variable: change in Hb from Baseline (average pretreatment Hb) to the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).
- Intercurrent event: never received treatment, discontinued treatment, rescued with any therapy, or withdrew consent.
- Population-level summary: difference in mean change in Hb from baseline to the primary evaluation period between the vadadustat groups and darbepoetin alfa control group.

9.4.1.1.2 Primary Analysis of Primary Efficacy Endpoint

The primary analysis will use the randomized population with an analysis of covariance, with randomization stratification factors and Baseline Hb as covariates.

A 2-sided, 95% CI will be calculated for the difference in mean change in Hb from Baseline to the primary evaluation period between the vadadustat group and darbepoetin alfa control group. Noninferiority of vadadustat will be established if the lower limit of this CI is $\geq$ -0.75 g/dL.

A hierarchical testing scheme will be used to correct for the multiplicity of the 2 primary endpoints: comparison between vadadustat QD vs. darbepoetin alfa and comparison between vadadustat TIW vs. darbepoetin alfa.

- Step 1: comparison between vadadustat QD vs. darbepoetin alfa.
- If the noninferiority of vadadustat is established in step 1, then move to the step 2;

- Step 2: comparison between vadadustat TIW vs. darbepoetin alfa.

9.4.1.1.3 Sensitivity Analyses of Primary Efficacy Endpoint Screening

The following sensitivity analyses will be conducted:

- Primary analysis will be repeated using the FAS population.
- Primary analysis will be repeated using the PP population with the actual treatment received.
- Primary analysis will be repeated with imputation of data which may have been affected by a subject's having received any form of rescue (transfusion or ESA). Details are provided in the Statistical Analysis Plan (SAP).
- A mixed model for repeated measures will be fit to the observed data only.

9.4.1.1.4 Analyses of Primary Efficacy Endpoint When All Randomized Subjects Complete Week 26

Analyses of the primary efficacy endpoint may be conducted when all randomized subjects either complete their Week 26 evaluations or early discontinue the trial before Week 26.

9.4.1.2 Key Secondary Efficacy Endpoint Analysis

The key secondary endpoint will be formally analyzed once the non-inferiorities have been established in the primary endpoint for vadadustat QD and TIW regimens.

Mean change in Hb value between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 46 to 52) will be analyzed using the same methodology as specified for the primary efficacy endpoint. Sensitivity analyses similar to those of the primary efficacy endpoint will be performed and details will be provided in the SAP.

9.4.1.3 Other Efficacy Endpoint Analysis

Other efficacy endpoints analyses will be performed using the randomized and FAS population, using the assigned treatment as described in Section 9.2. Analysis for the key secondary efficacy endpoints will be repeated using the PP population with the actual treatment received.

9.4.1.4 Subgroups

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

- Low darbepoetin alfa dose group (≤ 0.45 µg/kg/week) or high darbepoetin alfa dose group (> 0.45 and ≤ 1.5 µg/kg/week).
- Due to use of different target Hb levels in the US versus non-US, the endpoints will also be analyzed for subsets based on the target Hb level:
  - The US subset will be assessed due to the target Hb range of 10.0 to 11.0 g/dL in the US.
  - The European subset will be assessed due to the target Hb range of 10.0 to 12.0 g/dL in the EU.
- Geographic region (US, Europe).
- Age.
- Gender.
- Race.

Blinded summary safety data will be provided for all subjects who had the opportunity to complete the Week 12 Visit by a cut-off date, with the cut-off date to be determined at a later date to support potential regulatory filing.

9.4.2 Safety Analysis

All analyses of safety data will use the safety population.

9.4.2.1 Adverse Events

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

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent and post-treatment AEs will be summarized by SOC and preferred term for each treatment group. Adverse events will also be summarized by their maximum severity.

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

- SAEs.
- Related AEs (including all categories for relationship to IMP other than “Unrelated”, as determined by the investigator).
- AEs leading to early discontinuation of IMP.
- Summaries on adjudicated events (see Section 9.5) will be provided by treatment group.

9.4.2.2 Remaining Safety Endpoints

The analysis of the safety endpoints will be detailed in the SAP.

Any Hb value postdose above a set threshold will be considered as a "yes" in the Hb related safety analysis. Subjects with no available data post Baseline will be excluded from this analysis. All other subjects will be classified to the "no" category.

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

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

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

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

9.4.3 Other Analyses

9.4.3.1 Disposition of Subjects

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

The number of randomized subjects who completed each period of IMP treatment (Conversion and Maintenance, and Long-term Treatment), discontinued from IMP early, and completed or discontinued from the trial and reasons for discontinuation will be summarized by treatment group and overall.

9.4.3.2 Analysis of Demographic and Baseline Characteristics

Descriptive statistics will be generated for demographic and pretreatment variables for each analysis population defined in Section 9.2.

Medical history terms will be coded using the MedDRA and summarized by SOC and preferred term for each treatment group based on the safety population.

9.4.3.3 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug dictionary.

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

9.4.3.4 Pharmacokinetic Analysis

Vadadustat plasma concentrations may be included in a population PK analysis that would be reported separately. Vadadustat and metabolite concentrations will be listed.

9.4.3.5 Pharmacodynamic Analysis

A by-subject listing of all PD variables (EPO, reticulocytes, and iron indices) 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. For PD variables analyzed after database lock, values will be reported separately.

9.4.3.6 Pharmacogenomic Analysis

No PGx analysis is planned.

9.4.3.7 Future Biospecimen Research Analysis

No FBR analysis is planned.

[redacted]

9.5 Data Monitoring, Safety Event Adjudication, and Independent Expert Panel Committees

An IDMC will be established to review and discuss trial safety data as subjects are enrolled and followed. The team will have no affiliation with any trial site, and will meet as per IDMC charter guidelines. The IDMC will be unblinded and will include, at a minimum, a nephrologist, a cardiologist, and a biostatistician. The discussions of the IDMC will include a review of key safety endpoint data (ie, AEs, SAEs, vital signs, ECGs, and laboratory assessments). Written records of the IDMC meetings, the materials reviewed, and the decisions made will be maintained. Details on the roles and

responsibilities of the IDMC and guidelines for monitoring trial safety data will be described further in the IDMC charter.

An independent SEAC that is composed of independent experts will be formed prior to trial commencement to adjudicate MACE (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for HF or thromboembolic event excluding vascular access thrombosis events. The committee will have no affiliation with any trial site and will be blinded throughout the course of the trial. Details on the responsibilities of the SEAC will be described further in the SEAC charter.

An Independent Expert Panel Committee for Hepatic Events of Interest will also be formed prior to trial commencement to adjudicate hepatic events.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations International Council for Harmonisation (ICH) GCP: Consolidated Guideline (E6), international ethical principles derived from the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (2013) and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the eCRF, the investigator, subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

10.1.2 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, ICFs, and other relevant documents, (eg, recruitment advertisements, if applicable) from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to the sponsor or its designee.

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

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

10.1.3 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian as applicable for local laws) prior to inclusion in the trial. The ICF will be approved by the same IRB/IEC that approves this protocol.

Each ICF will comply with the ICH GCP: Consolidated Guideline E6[26] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions and have those questions answered, the IRB/IEC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator. Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

[redacted]

10.1.4 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel

(or their representatives or development partners) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject ID in eCRF. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

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

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

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the trial 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.

10.1.6 Quality Control and Quality Assurance

10.1.6.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH GCP: Consolidated Guideline (E6), and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.6.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and a review of the eCRF with source documents, as applicable. The investigator agrees to participate with audits. 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.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.7 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria, fraud or misconduct, increased health risk to the subject, or confounded interpretation of primary trial assessments), or except where necessary to eliminate an immediate hazard to trial subjects, the investigator or designee will contact the sponsor or designee (and IRB/IEC, as required) at the earliest possible time by telephone or via e-mail. If needed, the investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.8 Records Management

10.1.8.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, dialysis records or flow sheets, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.8.2 Data Collection

During each subject's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's EDC system that is 21 Code of Federal Regulations (CFR) Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on eCRF, such as data received from central laboratories will be reconciled using key data fields by the sponsor or the CRO with the eCRF data to ensure consistency.

10.1.8.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP: Consolidated Guideline (E6) and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.8.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10.1.8.5 Publication of Trial Results

No publication or disclosure of trial results will be permitted, except under the terms and conditions of a separate, written agreement between the sponsor (Otsuka Pharmaceutical Development & Commercialization, Inc. [OPDC] in collaboration with Akebia) and the investigator and/or the investigator's institution. The sponsor and Akebia must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this trial prior to submission for publication/presentation. Any information identified by the sponsor or Akebia as confidential must be deleted prior to submission.

For all publications relating to the trial, 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 (ICMJE).

10.1.8.5.1 Publication Authorship Requirements

Authorship for any Otsuka- or Akebia-sponsored publications resulting from the conduct of this trial will be based on ICMJE authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial subjects who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial subjects consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

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.

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Complete Blood Count	**Iron Indices**	**Serum Chemistry**
Hb	Ferritin	Sodium
Hematocrit	Iron	Potassium
RBC	TIBC	Bicarbonate
MCV	TSAT	Chloride
MCH		Calcium
MCHC		Magnesium
Platelets	**Lipid Profile**	Phosphorus
RDW	Total Cholesterol	Glucose
WBC	LDL	Creatinine
Differential WBC	HDL	BUN
Neutrophils	Triglycerides	CPK
Lymphocytes		Uric Acid
Monocytes	**Liver Function Tests**	Albumin
Eosinophils	Total bilirubin	Total Protein
Basophils	ALP	
Hematology panel without differential	ALT/SGPT	
Hb	AST/SGOT	
Hematocrit	LDH	
RBC		
MCH		
MCHC		
RDW		
RBC morphology and MCV		
Platelets		
WBC		
Additional Laboratory Tests		
β-HCG		
Reticulocyte Count[a]		
Folate		
Vitamin B_{12}		
CRP		
Erythropoietin		
INR[b]		
PT[b]		

β-HCG = beta human chorionic gonadotropin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CRP = C-reactive protein; Hb = hemoglobin; HDL = high density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV

= mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; RDW = red blood cell distribution; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TIBC = total iron-binding capacity; TSAT = transferrin saturation; WBC = white blood cell.

[a] An automated reticulocyte count should include both absolute and percent.

[b] INR and PT to be collected at the discretion of the investigator and sent to the central laboratory for analysis only if ALT or AST > 3x ULN to evaluate stopping criteria.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

In nonclinical animal embryo-fetal development and fertility studies, there was no evidence of teratogenicity, no skeletal or visceral malformations, and no changes in male or female reproductive and fertility indices, or in sperm parameters. In rats, decreased fetal body weight and reduced skeletal ossification were noted at the highest dose tested of 160 mg/kg/day. Peri-postnatal development studies have not yet been conducted with vadadustat, and there are no data on the transmission of vadadustat in breast milk or the effect of vadadustat on infants.

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

All WOCBP are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

For males and WOCBP, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is surgically sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a vasectomy), has negative pregnancy test results at Screening (serum), or remains abstinent during the trial and for 30 days after the last dose of IMP, 2 of the following approved methods of birth control must be used:

- Total abstinence from sexual intercourse (minimum one complete menstrual cycle prior to Screening Visit, throughout the trial, and for 30 days after the last dose of IMP).
- A partner who has had a vasectomy.
- Hormonal contraceptives (oral, parenteral, or transdermal) for at least 3 months prior to IMP administration or intrauterine contraception/device, throughout the trial, and for 30 days after the last dose of IMP.
- Double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap together with spermicidal foam/gel/film/suppository) starting at Screening Visit 1, throughout the trial, and for 30 days after the last dose of IMP.

The contraceptive method will be documented in the eCRF. Male subjects must also agree not to donate sperm from trial screening through 30 days after the last dose of IMP.

Before enrolling males and females in this clinical trial, investigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information.
- Informed consent form.
- Pregnancy prevention information.
- Drug interactions with hormonal contraceptives.
- Contraceptives in current use.
- Follow-up of a reported pregnancy.

Before trial enrollment, males and WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening on all WOCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP (vadadustat or ESA) or within 30 days of discontinuing the IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the Medical Monitor. If EDC is unavailable, send paper Pregnancy Form as indicated on the title page of this protocol.

Any pregnancy must 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 should also be reported. This will require agreement and separate written informed consent on the part of the pregnant female partner.

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

The investigator will follow the subject (or female partner of a male subject) until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death within 1 month of birth, or congenital anomaly [including 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 should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as related or unrelated to the in utero exposure to the IMP should also be reported.
- In the case of a live birth, the “normality” of the newborn can be assessed at time of birth.
- The “normality” of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Report Form/Exposure in Utero Form, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Abbreviations

Abbreviation	Definition
β-HCG	beta human chorionic gonadotropin
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BCRP	Breast cancer resistance protein
BL	Baseline
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Science
CKD	Chronic kidney disease
C_{max}	Maximum observed plasma concentration
CPK	Creatine phosphokinase
CRO	Contract research organization
CRP	C-reactive protein
CS	Clinically significant
CV	Cardiovascular
DD-CKD	Dialysis-dependent chronic kidney disease
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
ET	Early termination
EU	European Union
EudraCT	European Clinical Trial Data Base
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FAS	Full Analysis Set
FBR	Future biospecimen research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HF	Heart failure
Hb	Hemoglobin
HDL	High density lipoprotein
HIF	Hypoxia-inducible factor

Abbreviation	Definition
HIF-PH	Hypoxia-inducible factor prolyl-hydroxylase
HRQOL	Health-related Quality of Life
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identifier
IDMC	Independent Data Monitoring Committee
I/E	Inclusion/exclusion
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
IWR	Interactive Web Response
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
MACE	Major adverse cardiovascular events
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
MTPC	Mitsubishi Tanabe Pharma Corporation
n	Number of subjects
NDD-CKD	Non-dialysis-dependent chronic kidney disease
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamics(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PGx	Pharmacogenomic(s)
PHD	Prolyl 4-hydroxylase domain
PK	Pharmacokinetic(s)
PP	Per protocol
PT	Prothrombin time
QD	Once daily
RBC	Red blood cell
RDW	Red blood cell distribution
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SEAC	Safety Event Adjudication Committee
SF-36v2	36-Item Short Form

Abbreviation	Definition
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SmPC	Summary of product characteristics
SOC	System organ class
SV1	Screening Visit 1
SV2	Screening Visit 2
TEAE	Treatment-emergent adverse event
TIBC	Total iron binding capacity
TIW	Three times weekly
TSAT	Transferrin saturation
ULN	Upper limit of normal
US	United States
USPI	US Package Insert
[redacted]	[redacted]
WBC	White blood cell
WOCBP	Women of childbearing potential

10.5 Appendix 5: Institutions Concerned with the Trial

Akebia Therapeutics, Inc.

245 First Street

Cambridge, MA 02142

United States of America

Within Akebia, this protocol is referred to as Protocol #AKB-6548-CI-0036

10.6 Appendix 6: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

10.6.1 Protocol Amendment(s)/Administrative Change(s)

10.6.1.1 Protocol Amendment 1

Amendment 1 Approval Date: 17 Mar 2021

PURPOSE:

The purpose of this protocol amendment is to:

- Add that analyses of the primary efficacy endpoint may be conducted when all randomized subjects complete their Week 26 evaluations or early discontinue the trial before Week 26;
- Remove the PK endpoints of C_{max} and trough concentration;
- Adjust terminology applicable for the reporting of AEs by removing "immediately reportable event (IRE)" and "designated medical event (DME)" throughout the protocol;
- Change the definition of "subject completion" to after completion of their final visit (ET or Week 52/EOT). Safety Follow-up Visit data summarization and analysis will be performed separately.

Additional administrative and clarifying changes were made and are documented below. Finally, minor editorial revisions were made for consistency with Otsuka style and for internal consistency.

BACKGROUND:

These changes to clinical trial protocol 404-201-00012, originally issued on 17 Jan 2020, were made to add the possibility to conduct analyses on the primary efficacy endpoint at Week 26.

The PK endpoints of C_{max} and trough concentration were removed as analyses of concentration data from previous protocols indicated that these endpoints did not produce robust exposure estimates. Instead, concentrations may be included in a population PK analysis.

For the reporting of AEs, the terms immediately reportable event "IRE" and designated medical event "DME" (Otsuka's terminology) were removed throughout the protocol. This is an operational change that is specific to Otsuka processes only (not Akebia). From the onset of this trial, Akebia's pharmacovigilance processes have been followed. Removal of this terminology does not interfere with the current drug safety pharmacovigilance process. Removal of these terms ensures the protocol text for AE and SAE processes are consistent with Akebia's terminology and processes.

The definition of "subject completion" has been revised to after completion of their final visit (ET or Week 52/EOT) and will not include the Safety Follow-up. Safety Follow-up Visit data summarization and analysis will be performed separately.

MODIFICATIONS TO PROTOCOL:

General Revisions:

Table 10.6.1.1-1 General Revisions for Protocol Amendment 1

Location	Description of Text
Title Page	Updated "Director, Global Clinical Development" and contact information. Updated "Associate Director, Clinical Management" to "Director, Clinical Management."
Title Page, Section 8.8.1 (Definitions), Section 8.8.2 (Eliciting and Reporting Adverse Events), Section 8.8.2.1 (Guidelines for Reporting Adverse Events), Section 8.8.4.1 (Follow-up of Nonserious Adverse Events), Section 8.8.4.2 (Follow-up of Immediately Reportable Events), Section 8.8.4.3 (Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact), and Section 10.3 (Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information)	Adjusted terminology applicable for the reporting of AEs by deleting "immediately reportable event (IRE)" and "designated medical event (DME)" throughout the protocol.
Synopsis (Objectives and Endpoints), Table 3-1 (Trial Objectives and Endpoints), and Section 9.4.1.2 (Key Secondary Efficacy Endpoint Analysis)	Updated key secondary efficacy endpoints to clarify that Baseline refers to the "average pretreatment Hb."
Synopsis (Objectives and Endpoints) and Table 3-1 (Trial Objectives and Endpoints)	Clarified the safety "endpoints" (instead of "variables").
Synopsis (Objectives and Endpoints) and Table 3-1 (Trial Objectives and Endpoints)	Removed details on specific clinical laboratory values as these details are found in Appendix 10.2 and Table 1.3-1 (Schedule of Assessments).
Synopsis (Objectives and Endpoints) and Table 3-1 (Trial Objectives and Endpoints)	Updated PK endpoints to state that no PK analysis will be conducted and vadadustat plasma concentrations may be included in a population PK analysis reported separately.
Synopsis (Objectives and Endpoints and Trial Assessments), Table 1.3-1 (Schedule of Assessments), Table 3-1 (Trial Objectives and Endpoints), and Section 8 (Trial Procedures)	[redacted]
Synopsis (Objectives and Endpoints), Table 3-1 (Trial Objectives and Endpoints), and Section 9.4.3.5 (Pharmacodynamic Analysis)	Deleted exposure response analysis in PD endpoints.
Synopsis (Trial Design) and Section 4.1 (Type/Design of Trial)	Removed "sponsor-blind."

Table 10.6.1.1-1 General Revisions for Protocol Amendment 1

Location	Description of Text
Synopsis (Trial Design), Section 4.1 (Type/Design of Trial), and Section 6.3.1 (Randomization)	Replaced "at least" with "approximately" for the number of subjects in Europe.
Synopsis (Trial Design), Table 1.3-1 (Schedule of Assessments), Section 4.1 (Type/Design of Trial), and Section 8 (Trial Procedures)	Removed "/other" from the definition of secondary efficacy evaluation.
Synopsis (Trial Design), Table 1.3-1 (Schedule of Assessments), and Section 4.1 (Type/Design of Trial)	Clarified that a "structured" exit interview "may" be conducted.
Synopsis (Trial Population) and Section 5 (Trial Population)	Specified 100 subjects randomized to "vadadustat" QD arm, 100 subjects randomized to "vadadustat" TIW arm, and 100 subjects randomized to darbepoetin alfa arm.
Synopsis (Exclusion Criteria) and Section 5.2.2 (Exclusion Criteria)	Removed "birth control" as one of the precautions to be used in Exclusion Criteria No. 1.
Synopsis (Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration), Table 1.3-1 (Schedule of Assessments), Section 4.1 (Type/Design of Trial), Section 6.1.1.4 (Darbepoetin Alfa Dosing), Section 6.1.3 (Late or Missed Doses), Section 6.2 (Management of Investigational Medicinal Product), and Section 6.3.2 (Blinding)	Clarification on how darbepoetin alfa will be dispensed, initial dosing regimen, and/or information on dose adjustment was added/revised.
Synopsis (Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration), Section 4.1 (Type/Design of Trial), and Section 6.1.1.4 (Darbepoetin Alfa Dosing)	Removed "SC" as a route of administration for darbepoetin alfa.
Synopsis (Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration), Section 4.1 (Type/Design of Trial), Section 6.1.1.1 (ESA Equivalent Dose Calculation), and Section 6.3.1 (Randomization)	Removed details on "ESA medications conversions" as they are provided in the Dosing Guideline.
Synopsis (Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration) and Table 6.1.1.2-1	Added a table note to "See to Section 7.3.1 (Treatment Interruption)" in the Guideline for Dose Adjustment Table.
Synopsis (Trial Assessments), Table 1.3-1 (Schedule of Assessments), Section 8 (Trial Procedures), and Section 8.7.6.1 (Major Adverse Cardiovascular Events)	Removed "Endpoint Questionnaire" from MACE assessment.
Synopsis (Trial Assessments)	Added "RBC transfusions, ESA rescue, and therapeutic phlebotomy" to Assessments for Safety in-line with Table 1.3-1 (Schedule of Assessments).
Synopsis (Trial Duration), Section 4.1 (Type/Design of Trial), and Section 4.5 (Definition of Completed Subjects)	Changed the definition of "subject completion" to after completion of their final visit (ET or Week 52/EOT). Safety Follow-up Visit data summarization and analysis will be performed separately.

Table 10.6.1.1-1 General Revisions for Protocol Amendment 1

Location	Description of Text
Figure 1.2-1	Updated Trial Design Schematic for clarity of vadadustat dosing.
Section 2 (Introduction)	Updated text in-line with current vadadustat IB.
Section 4.1 (Type/Design of Trial), Section 6.5.2.1 (Iron Supplementation), and Section 8 (Trial Procedures).	Clarified that subjects will be instructed to take vadadustat at least 1 hour before oral medications containing iron.
Section 4.2 (Scientific Rationale for Trial Design)	Added clarification that higher ESA doses carry a higher risk for CV outcomes regardless of Hb and changed "black box" warning to "boxed" warning.
Section 6.1.3 (Late or Missed Doses)	Added that for subjects on TIW dosing, "subjects should not double-up on missed doses." Also, clarified that subjects should be questioned regarding dosing compliance at every visit.
Section 6.2.2 (Storage)	For darbepoetin alfa, removed "per local prescribing label for adult subjects with CKD on dialysis" as darbepoetin alfa will be stored per the USPI for US sites or EU SmPC for EU sites.
Section 6.3.2 (Blinding)	Updated to "unblinded personnel" instead of "unblinded statistician" as there will be unblinded programmers as well.
Section 6.4 (Subject Compliance)	Clarified that subjects will be questioned regarding dosing compliance at every visit.
Section 6.5.1.1 (Erythropoiesis-stimulating Agents)	Clarified that "co-administration of any ESA with vadadustat is prohibited. If ESA rescue therapy is deemed medically necessary, vadadustat treatment must be stopped during ESA administration."
Section 6.5.1.2 (Sulfasalazine and Other BCRP Substrates and Probenecid)	Heading title was revised. Removed "prohibited" and updated section to state that sulfasalazine and other BCRP substrates should be used with caution when taken concomitantly with vadadustat and added a sentence to clarify to consult the Medical Monitor if there are questions about a specific concomitant medication. A sentence was added to state that probenecid is prohibited during the trial.
Section 6.5.2 (Permitted Medications)	Changed section heading to "Permitted Medications" for clarity.
Section 6.5.2.1 (Iron Supplementation)	Changed "iron-containing phosphate binders" to "iron-containing and non-iron-containing phosphate binders."
Section 6.5.2.2 (Phosphate Binders)	Clarified that subjects will be instructed to take vadadustat at least 1 hour before or 2 hours after non-iron-containing phosphate binders.
Table 6.5.2.3-1 (Results and Management of Concomitant Administration of Vadadustat with Statins)	Clarified guidance on inhibitor potency.
Section 7.3 (Individual Subject Discontinuation)	Clarified that subjects who discontinue IMP prematurely and the investigator determines that the subject will be permanently discontinued from the trial will complete the ET Visit assessments and the Safety Follow-up Visit, 4 weeks after ET Visit.

Table 10.6.1.1-1 General Revisions for Protocol Amendment 1

Location	Description of Text
Section 7.3.1 (Treatment Interruption)	Clarified that, unless contraindicated, treatment with IMP should be resumed within a 30-day time period from the start date of interruption and routinely considered at every visit following IMP interruption. Updated text for clarification on re-start of IMP following treatment interruption.
Section 8 (Trial Procedures)	Clarified that the ICF will be signed at Screening Visit 1 prior to any Screening Visit 1 procedures. Under "Exit Interview," added the purpose of the exit interviews, removed "the United Kingdom, France, Germany, Italy, and Spain" (as countries may be deleted or other countries may be added), and added a sentence on how the sample size was selected.
Section 8.1 (Subject Reported Outcome Assessments)	Updated the timing of assessments to "during the dialysis visits" for all 4 assessments.
Section 8.2 (Pharmacokinetic Assessments)	Clarified that vadadustat may be dosed before or after the start of dialysis.
Section 8.7.1 (Clinical Laboratory Assessments)	Removed "the sponsor" from providing instructions for collection, processing, and shipment of laboratory samples as these will be provided by the central laboratory.
Section 8.7.3 (Concomitant Medication Recording)	Added a sentence to clarify reporting of concomitant medications.
Section 8.7.6.1 (Major Adverse Cardiovascular Events)	Added clarification of MACE (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for HF or thromboembolic event excluding vascular access thrombosis. The sentence referring to 'the endpoint packet checklist' was deleted.
Section 8.8.1 (Definitions)	Added a sentence on "AESIs" and clarified that malignancies will be reported as an SAE by the investigator.
Section 8.8.1 (Definitions) and Section 8.8.2.1 (Guidelines for Reporting Adverse Events)	Replaced "temporary discontinuation of trial medication" with "temporary interruption of IMP" for clarification.
Section 8.8.2 (Eliciting and Reporting Adverse Events) and Section 8.8.2.1 (Guidelines for Reporting Adverse Events)	Clarified that AE collection will be from the time of ICF signing through the Safety Follow-up Visit.
Section 8.8.2.1 (Guidelines for Reporting Adverse Events)	Changed "Reporting Trial Endpoints" to "Reporting MACE" and clarified that Investigators will be counseled to report any MACE (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for HF or thromboembolic event excluding vascular access thrombosis events that they assess as requiring adjudication. All events will be submitted in a blinded fashion to the SEAC for adjudication.

Table 10.6.1.1-1 General Revisions for Protocol Amendment 1	
Location	**Description of Text**
Section 8.9 (Treatment of Overdose)	Replaced "discontinuation" with "interruptions" for clarity and added a link to Section 8.8 for guidance on AEs and SAEs.
Section 9.2 (Datasets for Analysis)	Correction to "Week 26" from "Week 36" for the PP population definition.
Section 9.3 (Handling of Missing Data for Primary and Secondary Endpoint Analysis)	Clarified that the reasons for "discontinuation" will be summarized by treatment arm.
Section 9.4.1.1.1 (Primary Estimand) Section 11 (References)	New section added to outline the treatment policy strategy specified in ICH E9 (R1) Addendum and added associated literature reference.
Section 9.4.1.1.2 (Primary Analysis of Primary Efficacy Endpoint)	Deleted primary efficacy endpoint definition as it is previously stated in Section 9.4.1.1.
Section 9.4.1.1.4 (Analyses of Primary Efficacy Endpoint When All Randomized Subjects Complete Week 26)	New section added to add the possibility to conduct analyses on the primary efficacy endpoint at Week 26.
Section 9.4.3.4 (Pharmacokinetic Analysis)	Clarified that a population PK analysis may be reported separately.
Section 9.4.3.5 (Pharmacodynamic Analysis)	Updated how PD variables will be reported.
Section 9.4.3.7 (Future Biospecimen Research Analysis)	Add new section to state "No FBR analysis is planned."
Section 9.4.3.8 (Exploratory Endpoint Analysis)	[redacted]
Section 9.5 (Data Monitoring, Safety Event Adjudication, and Independent Expert Panel Committees)	The heading title was revised. The IDMC meeting frequency was removed. Added "SAEs" and "ECGs" to key safety endpoint data for clarification. Clarified that an independent SEAC will adjudicate MACE (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke) plus hospitalization for HF or thromboembolic event excluding vascular access thrombosis events. Clarified that an "Independent" Expert Panel Committee for Hepatic Events of Interest will also be formed prior to trial commencement to adjudicate hepatic events.
Section 10.1.7 (Protocol Deviations)	Clarified that "if needed," the investigator and sponsor will come as quickly as possible to a joint decision regarding subject's continuation in the trial.
Section 10.1.8.2 (Data Collection)	Removed "central ECG readers" as they will not be used.
Table 10.2-1 (Clinical Laboratory Assessments)	Updated "Complete Blood Count," "Iron Indices" and instructions for "INR and PT collection." Also added "Hematology panel without differential."
Section 11 (References)	The list of references was updated.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

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Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, vadadustat, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where vadadustat will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB/IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

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