CLINICAL PROTOCOL

A RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF DOSE CONVERSION FROM A LONG-ACTING ERYTHROPOIESIS-STIMULATING AGENT (MIRCERA®) TO THREE TIMES WEEKLY ORAL VADADUSTAT FOR THE MAINTENANCE TREATMENT OF ANEMIA IN HEMODIALYSIS SUBJECTS

Compound:	Vadadustat (AKB-6548)
Protocol Number:	AKB-6548-CI-0039
Regulatory Agency ID Number(s):	IND: 102,465
Study Phase:	Phase 3b
Protocol Version/Date:	Original Version 1.0/16 September 2020
Sponsor:	Akebia Therapeutics, Inc. 245 First Street Cambridge, MA 02142 United States of America

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SIGNATURE PAGES

Protocol Approval

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Investigator Agreement

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guidance for Industry, Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I will make a copy of the protocol and any amendments available to all study personnel under my supervision for the conduct of the study. I will discuss the materials with them to ensure that they are fully informed and understand this study and are able to comply.

_____ _____

Principal Investigator Name (printed) Signature

_____

Date

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Synopsis	
Protocol Title	A Randomized, Open-label, Active-controlled Study Evaluating the Efficacy and Safety of Dose Conversion from a Long-acting Erythropoiesis-stimulating Agent (Mircera®) to Three Times Weekly Oral Vadadustat for the Maintenance Treatment of Anemia in Hemodialysis Subjects
Protocol Number	AKB-6548-CI-0039
Phase of Development	3b
Indication	Anemia associated with chronic kidney disease (CKD)
Investigational Product	Vadadustat; 300 mg tablets
Reference Therapy, as applicable	Methoxy polyethylene glycol-epoetin beta (Mircera), F. Hoffman-La Roche Ltd.
Study Population	The study population will consist of subjects ≥18 years of age and receiving chronic, outpatient in-center hemodialysis three times weekly (TIW), requiring erythropoiesis-stimulating agent (ESA) treatment and are on maintenance treatment currently receiving Mircera and with mean of 2 Screening hemoglobin (Hb) values between 8.5 and 11.0 g/dL (inclusive).
Number of Study Sites	Approximately 50 investigative sites in the United States (US) at outpatient hemodialysis center.
Planned Number of Subjects	Approximately 450 subjects.
Rationale	During prior clinical trials, vadadustat has demonstrated dose proportional pharmacokinetic (PK) and dose dependent pharmacodynamics (PD). Vadadustat showed dose-dependent increases in erythropoietin (EPO) concentrations in Phase 1 and Phase 2 studies. The changes in EPO have been accompanied by an increase in reticulocytes and Hb as well as increases in total iron binding capacity (TIBC) and decreases in hepcidin and ferritin. Overall, the safety profile for vadadustat has been acceptable and has supported further development. Akebia is developing vadadustat as a treatment for anemia associated with CKD in adult patients. The development program to date included a number of phase 1, 2, and 3 clinical trials in both populations. A majority of trials studied once daily (QD) dosing. TIW dosing is supported by an earlier completed clinical trial involving TIW dosing and PK-PD modelling data. The rationale for this trial is to obtain safety and efficacy data that supports DD-CKD patients switching from Mircera to vadadustat TIW.
Primary Objectives	The primary objective of the study is to demonstrate the efficacy and safety of vadadustat administered TIW compared to long acting ESA (Mircera) for the maintenance treatment of anemia in hemodialysis subjects.
Efficacy Endpoints	**Primary:** • Primary efficacy endpoint is mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive). **Secondary:** Secondary efficacy endpoint is mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 46 to 52, inclusive).

Other Endpoints	• Proportion of subjects having a Hb value within the target range (10.0 to 11.0 g/dL) during the primary evaluation period (Weeks 20 to 26). • Proportion of subjects having a Hb value within the target range (10.0 to 11.0 g/dL) during the secondary evaluation period (Weeks 46 to 52).
Safety Endpoints	• Treatment-emergent adverse events (AEs) and Serious Adverse Events (SAEs). • Proportion of subjects receiving red blood cell (RBC) transfusions from Baseline to Week 26 • Proportion of subjects receiving RBC transfusions from after Week 26 to Week 52. • Proportion of subjects with Hb >11.0, Hb >12.0, >13.0, or >14.0 g/dL. • Proportion of subjects with Hb <7.0, <8.0, <9.0, or <10.0 g/dL. • Proportion of subjects with Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval.
PK/PD Endpoints	The PK endpoints include the following: • Maximum observed concentration (C_{max}) • Pre-dose trough concentration (C_{tau}) The PD endpoints include the following: • EPO • Reticulocyte count • Markers of iron metabolism (including iron, ferritin, total iron binding capacity [TIBC]).
[redacted]	[redacted]
Methodology (study design)	A multi-center, randomized, open-label, active-controlled study of the efficacy and safety of conversion from long-acting ESA (Mircera) to vadadustat TIW for the maintenance treatment of anemia in hemodialysis patients. Following a Screening period of up to 8 weeks (56 days), subjects who meet all inclusion and none of the exclusion criteria, Mircera will be discontinued and subjects will be randomized 1:1:1 to vadadustat 600 mg TIW, vadadustat 900 mg TIW, or to remain on Mircera according to the dialysis center's protocol. Randomization will be stratified by dialysis organization: Following randomization, there will be 2 periods during the study: • **Conversion and Maintenance Period (Weeks 0 to 52):** conversion to vadadustat TIW or to remain on Mircera (Weeks 0 to 20). There will be a primary efficacy evaluation period (Weeks 20 to 26) and a secondary efficacy evaluation period (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) either in person or via telephone.
Study Duration	Individual subjects will participate in the study for up to 64 weeks, including a Screening Period of up to 8 weeks, a 52-week Treatment Period and a 4-week Safety Follow-Up Period.
Key Inclusion and Exclusion Criteria	Subjects must meet the following inclusion criteria: 1. ≥18 years of age. 2. Receiving chronic, outpatient in-center hemodialysis TIW for end-stage kidney disease for at least 12 weeks prior to Screening Visit (SV)1. 3. Currently maintained on Mircera (≤250 µg/month) with at least 2 doses

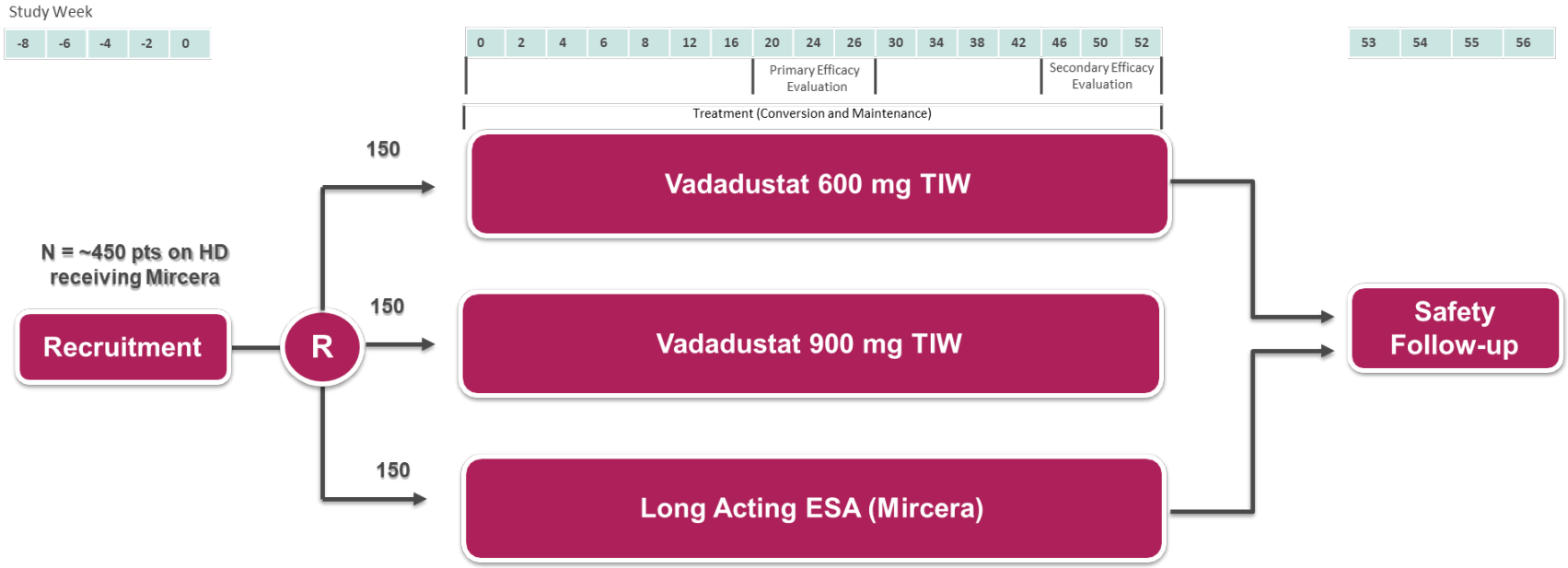
	received within 8 weeks prior to SV2. 4. Mean screening Hb between 8.5 and 11.0 g/dL (inclusive), as determined by the average of 2 Hb values measured by the central laboratory at least 4 days apart between SV1 and SV2. 5. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening. 6. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening. Subjects must not meet any of the following exclusion criteria: 1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia). 2. Clinically meaningful bleeding event in opinion of investigator within 8 weeks prior to Baseline. 3. RBC transfusion within 8 weeks prior to Baseline. 4. Having received any doses of darbepoetin alfa (Aranesp®) within the past 4 weeks prior to Baseline. 5. Having any epoetin alfa (Epogen®) within the past 1 week prior to Baseline. 6. Anticipated to discontinue hemodialysis during the study. 7. Judged by the Investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study. 8. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver). 9. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded. 10. Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of an ESA. 11. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for heart failure (HF) or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening. 12. History of new, active 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 treated cervical carcinoma in situ are not excluded. 13. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening 14. History of hemosiderosis or hemochromatosis. 15. History of prior organ transplantation (subjects with a history of failed

	kidney transplant or corneal transplants are not excluded). 16. 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. 17. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded). 18. Known hypersensitivity to vadadustat, Mircera, or any of their excipients. 19. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to Screening (subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation). 20. Current exposure to any hypoxia-inducible factor prolyl-hydroxylase (HIF-PH) inhibitor or prior exposure to vadadustat. 21. Subjects with bilateral native nephrectomy. 22. Noncompliance with dialysis session attendance defined as missing more than 1 dialysis session within 8 weeks prior to Baseline. 23. Active Severe Acute Respiratory Syndrome-Related Coronavirus (SARS-CoV-2) during Screening. 24. Females who are pregnant or breastfeeding during Screening or are planning to become pregnant and breastfeeding during the study period, and for 30 days after the final study drug administration. 25. Women of childbearing potential who are unable or unwilling to use 2 acceptable methods of contraception* starting at Screening, throughout the study period and for 45 days after the final study drug administration. 26. Female subjects of childbearing potential who plan to donate ova during the study, and for 30 days after the last dose of study drug. 27. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception* from time of first dose of study drug until 30 days after the last dose of the study drug. 28. Male subjects who plan to donate sperm during the study and for at least 30 days after the last dose of study drug. 29. Any other reason, which in the opinion of the Investigator, would make the subject not suitable for participation in the study. **Acceptable forms of contraception include:* • *Established use of oral, injected or implanted hormonal methods of contraception* • *Placement of an intrauterine device or intrauterine system* • *Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.*
Safety Oversight	An Independent Data Monitoring Committee (IDMC) will be established to review and discuss the available study data as subjects are enrolled and followed. The IDMC will meet approximately twice per year throughout the course of the study. The IDMC will be unblinded and will include, at a minimum 2 physicians and a biostatistician. The discussions of the IDMC will include a review of key safety data (i.e., AEs, vital sign measurements, and laboratory assessments). Hepatic cases will be adjudicated by a hepatic panel of experts.
Statistical considerations	The primary efficacy endpoint is defined as the mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).

a. General analysis plan b. Rationale for number of subjects	The primary analysis of the primary endpoint will use the randomized population. Analysis of covariance (ANCOVA) with multiple imputation for missing data will be used to calculate the 95% confidence interval (CI) of the difference in mean change in Hb from baseline to the primary evaluation period between the vadadustat group and Mircera® control group, with a randomization stratification factor and Baseline Hb as covariates. 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 comparisons of the primary efficacy endpoint: comparison between vadadustat TIW 600 mg versus Mircera and comparison between vadadustat TIW 900 mg versus Mircera . • Step 1: comparison between vadadustat TIW 900 mg versus. Mircera If the noninferiority of vadadustat is established in step 1, then move to the step 2; • Step 2: comparison between vadadustat TIW 600 mg versus Mircera 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, Mircera, 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 Mircera). With the 1:1:1 randomization ratio of vadadustat 600 mg TIW, vadadustat 900 mg TIW, and Mircera, approximately 150 subjects in each arm, the noninferiority test will have >90% power with consideration of a 30% drop out rate. In addition to the final analysis which will take place when all subjects have completed study and will include all data collected, the 26-week efficacy and safety data may be summarized after the last patient completes the primary efficacy period (Week 26). As the study conduct and final analyses of primary efficacy endpoint will not be modified by this analysis, no alpha adjustment is proposed. The decision about whether this 26-week analysis would be conducted and details about the analysis will be described in the statistical analysis plan (SAP).

1.2 Schema

Figure 1 Study Schema



ESA: erythropoiesis stimulating agent; HD: hemodialysis; R: randomized;
TIW: three times weekly

1 CONFIDENTIAL

1.3 Schedule of Activities

Table 1 Schedule of Activities

Study Period	Screening		Treatment (Conversion and Maintenance)																		Safety Follow-up[a]
Visit Type	SV1	SV2	BL							Primary Efficacy Evaluation							Secondary Efficacy Evaluation				
Week	-8 to 0		0	2	4	6	8	12	16	20	24	26	30	34	38	42	46	50	52 (EOT) /ET[b]	56 (EOT or ET +4 weeks)
Visit Window (Days)				±3				±5				±3	±5						±3	+7
General and Clinical Assessments																				
Informed Consent	X																			
I/E Criteria	X	X	X																	
Randomization			X																	
Demographics, Medical History		X																		
Physical Exam[c]		X										X							X	
Height		X																		
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]			[redacted]					[redacted]				[redacted]							[redacted]	
Laboratory Assessments [f]																				
Pregnancy Test[g]		X																		
C-Reactive Protein			X									X							X	
CBC without differential[h]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CBC with differential			X																X	
Iron Indices[i]	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry	X		X					X				X							X	
Liver Function Tests[j]	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipid Panel[k]			X									X							X	
Reticulocyte count			X									X							X	
Coagulation Tests [l]																				
[redacted]			[redacted]		[redacted]			[redacted]				[redacted]							[redacted]	
Erythropoietin			X		X			X				X							X	
PGx and future biospecimen research[n]			X																X	
Dialysis Assessments																				
Dialysis Adequacy [o]			X									X							X	
Dialysis Access Type			X	Document any change to dialysis access type during Treatment Period																X
Safety Assessments																				

Study Period	Screening		Treatment (Conversion and Maintenance)																		
Visit Type	SV1	SV2	BL							Primary Efficacy Evaluation							Secondary Efficacy Evaluation			Safety Follow-up[a]
Week	-8 to 0		0	2	4	6	8	12	16	20	24	26	30	34	38	42	46	50	52 (EOT) /ET[b]	56 (EOT or ET +4 weeks)
Visit Window (Days)				±3				±5				±3	±5						±3	+7
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusions and ESA Rescue				Document any transfusions or ESA rescue during Treatment Period																
Therapeutic Phlebotomy				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
Vadadustat Dispensing [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vadadustat Reconciliation				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vadadustat Medication Dosing			X	TIW dosing																
Mircera Dosing			X	Dosing according to the dialysis center's protocol																
Iron Supplementation			As needed to maintain ferritin ≥100 ng/mL and TSAT ≥20% As needed IV iron dosing according to the dialysis center's protocol																	
PK Sampling																				
PK Evaluation (Vadadustat dosing arm only)[q]								X												

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BL: baseline; CBC: complete blood count; EOT: end-of-treatment; ESA: erythropoiesis-stimulating agent; ET: early termination; [redacted]; Hb: hemoglobin; HDL: high density lipoprotein; I/E: inclusion/exclusion; [redacted] LDL: low density lipoprotein; [redacted] PGx: pharmacogenomics; PK: pharmacokinetic; 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 weekly; TSAT: transferrin saturation; [redacted].

a. The safety follow-up period includes the EOT visit and follow-up visit (4 weeks after EOT).

b. Subjects who permanently discontinue study medication prior to study completion will not continue in the study. These subjects are to have their ET visit at the time of permanently discontinuing study medication and perform a 4-week safety follow-up after ET visit.

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

d. Pre-dialysis vital signs including temperature, heart rate, blood pressure, respiratory rate, and weight. Dry weight will be collected for all subjects.

e. [redacted]

f. If blood is collected on a hemodialysis day, the blood draw should be completed before dialysis occurs. Subjects may be retested for iron indices, serum chemistry, and liver function tests.

g. Serum pregnancy will be tested in women of childbearing potential at SV2. Additional serum or local urine pregnancy tests may be conducted throughout the study as determined by the investigator to establish the absence of pregnancy during the study. If positive at SV2, the subject is not eligible to enter the study. If a subject becomes pregnant during the study, the subject must permanently discontinue study medication.

h. For eligibility, 2 Hb values measured by the central laboratory during Screening (SV1, SV2 or retest) must be between 8.5 and 11.0 g/dL (inclusive).

i. Iron indices: ferritin, iron, TIBC, and TSAT.

j. Liver function tests: total bilirubin, ALP, ALT/SGPT, AST/SGOT, and LDH.

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

l. The coagulation tests prothrombin time, partial thromboplastin time, and international normalized ratio will be performed for unscheduled visits only.

[redacted]

n. Optional additional blood samples will be collected for PGx and future biospecimen research for consenting subjects only.

o. Most recent dialysis adequacy assessment.

p. Subjects will be provided with a supply of vadadustat at the Baseline visit and will be resupplied at subsequent visits as needed. Refer to the study drug dispensing instructions for further details.

Study Period	Screening		Treatment (Conversion and Maintenance)																	Safety Follow-up[a]
Visit Type	SV1	SV2	BL							Primary Efficacy Evaluation							Secondary Efficacy Evaluation			
Week	-8 to 0		0	2	4	6	8	12	16	20	24	26	30	34	38	42	46	50	52 (EOT) /ET[b]	56 (EOT or ET +4 weeks)
Visit Window (Days)				±3				±5				±3	±5						±3	+7

q. Vadadustat PK samples will be taken predose (within 60 minutes) and 0.5 hours ±5 minutes, 1, 2 and 3 hours ±10 minutes postdose.

2.0 LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under concentration-time curve
BCRP	breast cancer resistance protein
β-HCG	β-human chorionic gonadotropin
C_{max}	maximum observed concentration
C_{tau}	pre-dose trough concentration
CERA	Continuous Erythropoietin Receptor Activator
CI	confidence interval
CKD	chronic kidney disease
CRF	case report form
CRO	Contract Research Organization
CSR	clinical study report
CV	cardiovascular
DD	dialysis-dependent
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of Treatment
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ET	Early Termination
EU	European Union
[redacted]	[redacted]
FBR	future biospecimen research

Abbreviation	Definition
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
Hb	hemoglobin
HF	heart failure
HIF	hypoxia-inducible factor
HIF-PHs	hypoxia-inducible factor prolyl-hydroxylases
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous(ly)
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
mRNA	messenger ribonucleic acid
MTPC	Mitsubishi Tanabe Pharma Corporation
NDD	non-dialysis-dependent
OAT	organic anion transporter
PD	pharmacodynamic
[redacted]	[redacted]
[redacted]	[redacted]
PGx	pharmacogenomic
PHD	prolyl 4-hydroxylase domains
PK	pharmacokinetic
PP	per protocol
PT	preferred term
QC	quality control
QD	once daily

Abbreviation	Definition
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Related Coronavirus
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOC	system organ class
SOP	Standard Operating Procedures
SV1	Screening Visit 1
SV2	Screening Visit 2
TIBC	total iron binding capacity
TIW	three times weekly
TSAT	transferrin saturation
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
[redacted]	[redacted]

3.0 INTRODUCTION

This is an open-label, active-controlled, sponsor-blinded study to determine the safety and efficacy of dose conversion from a long-acting erythropoiesis-stimulating agent (ESA) (Mircera) to three times weekly (TIW) oral vadadustat dosing for the maintenance treatment of anemia in hemodialysis subjects

3.1 Study Rationale

During prior clinical trials, vadadustat has demonstrated dose proportional pharmacokinetic (PK) and dose-dependent pharmacodynamics (PD). Vadadustat showed dose-dependent increases in erythropoietin (EPO) concentrations in Phase 1 and Phase 2 studies. The changes in EPO have been accompanied by an increase in reticulocytes and hemoglobin (Hb) as well as increases in total iron binding capacity (TIBC) and decreases in hepcidin and ferritin. Overall, the safety profile for vadadustat has been acceptable and has supported further development.

Akebia is developing vadadustat as a treatment for anemia associated with chronic kidney disease (CKD) in adult patients. The development program to date included a number of phase 1, 2, and 3 clinical trials in both populations. A majority of trials studied once daily (QD) dosing. TIW dosing is supported by an earlier completed clinical trial involving TIW dosing and PK-PD modelling data.
The rationale for this trial is to obtain additional safety and efficacy data that supports dialysis-dependent (DD)-CKD patients switching from Mircera to vadadustat TIW.

3.2 Background

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

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

- Peritubular fibroblasts, a type of cell in the kidney, are designed to sense the amount of oxygen carried by the blood. These cells produce and 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 production and secretion is significantly decreased, leading to a reduction in RBC production (Iseki 2007; Nurko 2006).

- On average, the RBCs in CKD patients have a shorter lifespan (approximate lifespan of 70 days) compared with the RBCs in healthy people (approximate lifespan of 90 to 120 days) (Ly 2004; Nurko 2006). Such a condition requires 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 (Finkelstein 2019). 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, Metivier 2000). Other consequences from anemia in CKD patients include impaired cognitive function, sleep disorders, and depressed immune function which can impact the quality of life in patients (Iseki 2007; NICE 2011). Overall, anemia contributes to a poorer prognosis in patients with CKD (Iseki 2007; Nurko 2006).

Anemia associated with CKD has been treated with ESAs, blood transfusions, and iron supplementation. The risks associated with ESAs, including an increased risk of death and CV events (Besarab 1998; Drüeke 2006; Pfeffer 2009a; Pfeffer 2009b; Singh 2006), highlight the need for additional therapies that might minimize or avoid these risks when compared to currently available recombinant protein-based ESAs. Therefore, the unmet medical need for the treatment of anemia in 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.

3.3 Hypoxia-Inducible Factor Prolyl-Hydroxylase Inhibitors

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

Vadadustat is a synthetic, orally bioavailable, small molecule being developed as an inhibitor of hypoxia-inducible factor prolyl-hydroxylases (HIF-PHs) for the treatment of anemia associated with CKD. HIF-PH enzymes are also referred to as prolyl 4-hydroxylase domains (PHDs), of which the 2 most commonly expressed isoforms are PHD2 and PHD3. Vadadustat inhibits PHD2 and PHD3. The inhibition of PHD2 and PHD3 stabilizes hypoxia-inducible factor (HIF)-2α and HIF-1α, which in turn stimulates the production of EPO. In vivo animal efficacy and messenger ribonucleic acid (mRNA) data indicate that vadadustat induces the production of EPO from both renal and extra-renal sites (liver and brain), and this increase in EPO results in an increase in RBC production in the bone marrow. In clinical 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 may offer 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.

3.4 Summary of Clinical Experience

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

The efficacy, safety, tolerability, PK, and PD profiles of vadadustat have been characterized in 15 completed Phase 1 studies in healthy subjects including 1 ethno-bridging study in Caucasian and Japanese subjects, 1 completed Phase 1 study in subjects undergoing chronic hemodialysis, 3 completed Phase 2a studies in NDD-CKD subjects, 1 completed Phase 2b study in NDD-CKD subjects, and 1 completed Phase 2 study in DD-CKD subjects. The United States (US) Phase 2a studies evaluated Stages 3, 4, and 5 CKD (not on dialysis) subjects in a single-dose PK study, a multi-dose, 28-day, open-label, dose escalation pilot study, and a randomized, double-blind, placebo-controlled study with 5 different dose groups dosed for 42 days. The US Phase 2b, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 20 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated Stages 3, 4, and 5 CKD (pre-dialysis) dosed for 16 weeks. The US Phase 2 open-label study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. The Japanese Phase 2, randomized, double-blind, placebo-controlled study evaluated DD-CKD subjects on chronic hemodialysis dosed for 16 weeks. In the studies completed to date, a total of 1011 subjects have received vadadustat, including 553 healthy subjects, 450 subjects with CKD, and 8 subjects with hepatic impairment. Four additional Phase 3 studies from Akebia's co-development partner, Mitsubishi Tanabe Pharma Corporation (MTPC) have been conducted in Japan with NDD-CKD and DD-CKD subjects. As of 18 Aug 2019, a total of 379 subjects have received vadadustat. Two of these studies (J02 and J04) have been completed and the clinical study reports (CSRs) are final. The other 2 studies (J01 and J03) have reported 24-week primary efficacy and safety data and CSRs for the 24-week data are final. The clinical conduct for the 52-weeks of treatment (J01 and J03) has been completed and CSRs are pending. One pharmacological study in 61 healthy subjects has also been completed (J05).

Vadadustat has shown dose-dependent increases in EPO concentrations in Phase 1 and Phase 2a studies. The changes in EPO have been accompanied by an increase in reticulocytes and Hb as well as increases in TIBC and decreases in hepcidin and ferritin. Data from Japan Phase 3 studies in NDD-CKD and DD-CKD subjects and post-hoc analyses of the US Phase 2 DD-CKD study indicate the potential for an association between higher baseline ESA dose and a lower Hb response among subjects converted from ESA to vadadustat. Overall, the safety profile for vadadustat has been acceptable and has supported further development. Vadadustat has demonstrated consistent bioavailability with area under concentration-time curve (AUC) and maximum observed concentration (C_{max}) in Phase 1 and Phase 2 studies covering the dose range of 80 to 1200 mg after single administration and 500 to 900 mg after repeated daily administration for 10 days. The plasma half-life of vadadustat had a modest increase in subjects with NDD-CKD and DD-CKD. Despite the longer half-life in the CKD group, vadadustat plasma concentrations are not expected to accumulate with repeated QD or TIW administration.

Vadadustat is extensively metabolized and its metabolites are eliminated from the body by dual routes of excretion (both renal and fecal). The urinary excretion of vadadustat and its metabolites has been shown to be less than 60% in healthy human subjects. In a clinical study conducted to evaluate the effect of hemodialysis on the exposures to vadadustat, hemodialysis did not have an

effect on the exposures of vadadustat or its metabolites. Given its short half-life and the dual routes of elimination, vadadustat is unlikely to accumulate in patients with CKD.

Multiple doses of up to 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 dose-dependent serum EPO concentrations that returned to baseline levels with treatment cessation. A higher incidence of adverse events (AEs) in the gastrointestinal System Organ Class (SOC) – nausea, diarrhea, abdominal pain, dyspepsia – was observed in groups treated with 700, 900, or 1200 mg compared with lower vadadustat doses or placebo. Most AEs were mild to moderate, short-lived (1 or 2 days), and assessed as unrelated by investigators. No AEs led to study withdrawal, and no serious adverse events (SAEs) were reported in healthy subjects. No clinically meaningful changes or abnormalities in vital signs, safety laboratory studies, or electrocardiogram (ECG) parameters were reported.

A 16-week, open-label, multicenter, Phase 2 study evaluated vadadustat in 94 subjects receiving chronic hemodialysis previously maintained on epoetin alfa and intravenous (IV) iron from the 3 months prior to Screening. Epoetin alpha was discontinued and subjects were assigned to 1 of 3 vadadustat dose cohorts: 300 mg QD, 450 mg QD, or 450 mg TIW. Dosing was fixed for the first 8 weeks; for the subsequent 8 weeks dose was adjusted from 150 to 600 mg according to Hb response based upon a dose adjustment algorithm. Sixty-nine of the 94 subjects completed the study. The primary endpoint was the mean Hb concentration change from pre-treatment average (Screening Visit 1 [SV1], Screening Visit 2 [SV2], and Baseline Visit) to mid-study (Weeks 7 to 8) and end-of-study (Weeks 15 to 16) and was analyzed using observed Hb values (no imputation for missing data). No statistically significant mean change in Hb from pre-treatment average was observed for either of the 2 time points for any of the three treatment groups.

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

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

A total of 34 Akebia studies spanning Phase 1 through 3 have been completed or are ongoing. In the studies completed to date (Phase 1 and 2 studies), a total of 1011 subjects have received vadadustat, including 553 healthy subjects, 450 subjects with CKD, and 8 subjects with hepatic impairment. In 4 ongoing Phase 3 studies, 7237 subjects have received study medication (vadadustat or comparator).

Generally, in completed vadadustat studies with healthy subjects, there were a low number of AEs. The most frequently reported AEs in healthy subjects were in gastrointestinal disorders (nausea, diarrhea, abdominal pain, flatulence, dyspepsia) and nervous system disorders (headache, dizziness). The majority of the events were mild to moderate in severity. There were

no SAEs, deaths, or withdrawals due to AEs. [redacted] vital signs, or ECGs.

In completed Phase 2 studies, the most frequently reported AEs in subjects with CKD were in gastrointestinal disorders (nausea, diarrhea, vomiting), CV disorders (hypertension, hypotension, coronary artery disease), renal disorders (renal failure chronic, renal failure acute), infections and infestations (gastroenteritis, urinary tract infection, pneumonia), and metabolism and nutrition disorders (hyperkalemia, fluid overload).

The INNO$_2$VATE program is the global phase 3 clinical development program comprised of 2 studies in subjects with DD-CKD in which vadadustat and the comparator ESA, darbepoetin alpha, were studied. In this program, vadadustat was titrated up or down from a starting dose of 300 mg according to Hb response. The primary safety endpoint of the INNO$_2$VATE program was a MACE endpoint and vadadustat demonstrated non-inferiority to darbepoetin alpha in this regard.

Of the 2 studies which made up the INNO$_2$VATE program, the safety data most relevant to this program is the preliminary safety data from Study CI-6548-0017, a study that demonstrated the efficacy and safety of vadadustat compared with darbepoetin alfa for the maintenance treatment of anemia in subjects with DD-CKD. The Conversion and Maintenance Period of this study was from Weeks 0 to 52: conversion to study drug for maintaining Hb (Weeks 0 to 23), primary efficacy period (Weeks 24 to 36), and secondary efficacy period (Weeks 40 to 52).

One thousand seven hundred and seventy-seven subjects were enrolled in the vadadustat arm of Study CI-6548-0017 of which 1768 received vadadustat. Based on these preliminary data, the overall incidence of TEAEs was similar between the vadadustat (88.3%) and darbepoetin (89.3%) comparator arm. Common TEAEs (≥5% for vadadustat-treated subjects) are as below:

Table 2 Treatment-emergent Adverse Events Occurring at ≥5% Incidence in Vadadustat-treated Subjects

Preferred Term	Vadadustat N = 1768 n (%)	Darbepoetin Alfa N = 1769 n (%)
Any TEAEs	1562 (88.3)	1580 (89.3)
Diarrhoea	230 (13.0)	178 (10.1)
Pneumonia	195 (11.0)	172 (9.7)
Hypertension	187 (10.6)	244 (13.8)
Headache	160 (9.0)	135 (7.6)
Hyperkalaemia	160 (9.0)	191 (10.8)
Fluid overload	156 (8.8)	173 (9.8)
Fall	150 (8.5)	159 (9.0)
Nausea	149 (8.4)	134 (7.6)
Hypotension	146 (8.3)	141 (8.0)
Vomiting	120 (6.8)	124 (7.0)
Urinary tract infection	110 (6.2)	117 (6.6)
Arteriovenous fistula thrombosis	106 (6.0)	78 (4.4)
Cough	99 (5.6)	121 (6.8)
Dialysis related complication	99 (5.6)	122 (6.9)
Upper respiratory tract infection	99 (5.6)	112 (6.3)
Arteriovenous fistula site complication	94 (5.3)	120 (6.8)
Dyspnoea	92 (5.2)	119 (6.7)
Hypoglycaemia	92 (5.2)	78 (4.4)
Nasopharyngitis	92 (5.2)	84 (4.7)
Pain in extremity	91 (5.1)	117 (6.6)

Source: Table 14.3.1.2.1. Study CI-6548-0017

Drug-related TEAEs were more frequently reported in the vadadustat treatment group (9.6%) than in the darbepoetin alfa treatment group (3.8%). Compared to the 5.3% incidence of Gastrointestinal disorders SOC in the vadadustat treatment group (with the most common TEAEs being diarrhea [2.2%] and nausea [1.5%]), there was a 0.2% incidence of Gastrointestinal disorders SOC with darbepoetin alpha. With the exception of Gastrointestinal disorders SOC, the incidence of drug-related TEAEs is similar between subjects treated with vadadustat (4.2%) and darbepoetin alfa (3.7%).

There were 266 (15.0%) and 276 (15.6%) subjects that experienced TEAEs resulting in death in the vadadustat and darbepoetin alfa treatment groups, respectively. The most frequent TEAEs by PT resulting in death were similar between both treatment groups, and included cardiac arrest (2.0% and 2.1%), septic shock (1.3% and 1.2%), and cardio-respiratory arrest (1.2% and 1.3%) for the vadadustat and darbepoetin alfa treatment groups, respectively.

In the vadadustat treatment group, all deaths due to TEAEs were considered unrelated. In the darbepoetin alfa treatment group, only 1 death due to TEAE of acute MI was considered related. The TEAEs that resulted in death were similar across both treatment groups.

In addition to Study CI-6548-0017, Study CI-6548-0025, a Phase 2, randomized, open-label study to evaluate vadadustat for the treatment of anemia in hemodialysis subjects converting from epoetin alfa therapy, has recently completed the active patient phase but summary efficacy and data are not available at this time. Subjects who were randomized to vadadustat were treated QD from Day 1 to Week 12 and if Week 12 criteria were met, then vadadustat was administered TIW from Weeks 12 to 20. Dose levels of vadadustat administered in this study include

150, 300, 450, 600, 750 and 900 mg QD or TIW. One hundred twenty-nine subjects were randomized to vadadustat and 36 subjects were randomized to epoetin. All randomized subjects received at least one dose of study drug. Of the randomized subjects, 60.5% of subjects in the vadadustat group and 88.9% of subjects in the epoetin group completed treatment and 76.7% of subjects in the vadadustat group and 94.4% of subjects in the epoetin group completed the study.

Overall, taking into account the entire vadadustat clinical development program, the safety profile to date supports the ongoing clinical development of vadadustat as an orally bioavailable agent for the treatment of anemia associated with CKD.

3.5 Risk/Benefit Assessment

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

3.5.1 Known Potential Risks

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 (Besarab 1998; Pfeffer 2009a; Singh 2006). Post-hoc analyses performed by the Food and Drug Administration (FDA) and others have shown an association between these adverse outcomes and supraphysiologic serum EPO levels and/or Hb oscillations and overshoots (McCullough 2013; Unger 2010).

In vadadustat 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 (i.e., nausea, diarrhea, abdominal pain, flatulence, dyspepsia) and nervous system disorders (i.e., headache, dizziness) SOC. The majority of AEs were mild to moderate in severity.

The most frequently reported AEs in completed Phase 2 studies of NDD- and DD-CKD subjects were in the following SOCs: gastrointestinal disorders (nausea, diarrhea, vomiting), CV disorders (hypertension, hypotension, coronary artery disease), renal disorders (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.

An important identified risk of hepatotoxicity associated with vadadustat therapy has been confirmed. There have been reports of drug-induced liver injury (DILI) possibly or probably related to vadadustat including one case of Hy's Law probably related to vadadustat. All subjects recovered without sequelae.

An important identified risk of drug-drug interactions with some statins has been confirmed based on the results of clinical studies and have resulted in the following dose restrictions in subjects taking vadadustat and concomitant statins: the maximum recommended daily dose of rosuvastatin is 10 mg, and the maximum recommended daily dose of simvastatin is 20 mg. Review of the Phase 3 safety data did not identify any safety signal for myopathy and/or rhabdomyolysis.

Other non-important identified risks include abdominal pain, headache, and increased blood uric acid.

3.5.2 Known Potential Benefits

In studies to date, once-daily oral doses of vadadustat increased mean Hb with fewer excursions above the target range of 10.0 to 11.0 g/dL when compared with darbepoetin alfa. 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 absorption, transport, and utilization. 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 inhibitor hepcidin, and upregulates the iron-mobilizing regulators ferroportin and transferrin (and its receptor) (Peyssonnaux 2007). Potential clinical benefits include enhanced erythropoiesis and decreased exogenous iron requirements.

3.5.3 Overall Benefit: Risk Conclusion

DD-CKD and associated anemia are serious chronic conditions with significant morbidity and mortality due to the underlying disease as well as associated conditions (including diabetes and cardiovascular diseases including hypertension). Subjects enrolled in this study will be receiving chronic, outpatient in-center hemodialysis TIW, requiring maintenance ESA treatment.

The currently known risks of vadadustat most relevant to the study population are those associated with long-term vadadustat treatment in DD-CKD patients as measured in Study CI-6548-0017. In this study, the overall safety profile was similar to that of darbepoetin alpha. The overall incidence of TEAEs was similar between the vadadustat treatment group (88.3%) and darbepoetin comparator group (89.3%). The most common TEAEs (> 10%) in the vadadustat treatment group were diarrhoea, pneumonia and hypertension.

Drug-related TEAEs were more frequently reported in the vadadustat treatment group (9.6%) than in the darbepoetin alfa treatment group (3.8%). With the exceptional of Gastrointestinal disorders SOC (with the most common TEAEs being diarrhea [2.2%] and nausea [1.5%]), the incidence of drug related TEAEs was similar between subjects treated with vadadustat (4.2% and darbepoetin alfa (3.7%).

Adverse events of special interest (AESI, see Section 9.11.8) for vadadustat are malignancy including renal cell carcinoma (also see Section 9.11.1.2), elevation in ALT or AST >3 times ULN (also see Section 9.11.1.1), hepatotoxicity, worsening of hypertension, pulmonary hypertension, thrombotic events, congestive heart failure and adrenal disorders.

This study will evaluate efficacy and safety of different vadadustat dosing strategies in hemodialysis subjects converting from ESAs to further characterize the optimal vadadustat regimen, with an emphasis on TIW dosing in hemodialysis patients. This will be the first study in which DD-CKD subjects will receive vadadustat as TIW treatment from the onset of treatment, will receive TIW doses for more than 20 weeks or receive doses > 900 mg of vadadustat. In addition, this will be first study in which vadadustat will be studied against Mircera.

In studies to date, QD oral doses of vadadustat increased mean Hb with fewer excursions above the target range of 10.0 to 11.0 g/dL when compared with darbepoetin alfa. The results of the global Phase 3 clinical development program have confirmed that vadadustat in oral daily doses between 150 – 600 mg is non-inferior to darbepoetin alpha with respect to achieving and maintaining target Hb concentrations. Potential clinical benefits include enhanced erythropoiesis and decreased exogenous iron requirements.

Based on the totality of available information for vadadustat in the proposed patient population, the benefits outweigh the risks for the proposed study.

4.0 OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

To demonstrate the efficacy and safety of vadadustat administered TIW compared to long acting ESA (Mircera) for the maintenance treatment of anemia in hemodialysis subjects.

4.2 Primary Efficacy Endpoint

Mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive).

4.3 Secondary Efficacy Endpoint

Mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 46 to 52, inclusive).

4.4 Other Endpoints

Other endpoints include the following:

- Proportion of subjects having a Hb value within the target range (10.0 to 11.0 g/dL) during the primary evaluation period (Weeks 20 to 26).
- Proportion of subjects having a Hb value within the target range (10.0 to 11.0 g/dL) during the secondary evaluation period (Weeks 46 to 52).

4.5 Safety Endpoints

4.6 Primary Safety Endpoint

Treatment-emergent AEs and treatment-emergent SAEs.

4.7 Secondary Safety Endpoints

Secondary endpoints include the following:

- Proportion of subjects receiving RBC transfusions from Baseline to Week 26.
- Proportion of subjects receiving RBC transfusions from after Week 26 to Week 52.
- Proportion of subjects with Hb >11.0, Hb >12.0, >13.0, or >14.0 g/dL.
- Proportion of subjects with Hb <7.0, <8.0, <9.0, or <10.0 g/dL.
- Proportion of subjects with Hb increase >1.0 g/dL within any 2-week interval or >2.0 g/dL within any 4-week interval.

4.8 Pharmacokinetic/Pharmacodynamic Endpoints

The PK parameters include the following:

- C_{max}
- C_{tau}

The PD endpoints include the following:

- Erythropoietin (EPO)
- Reticulocyte count
- Markers of iron metabolism (including iron, ferritin, TIBC)
- [redacted]

5.0 STUDY DESIGN

5.1 Overall Design

This is a multi-center, randomized, open-label, active-controlled study of the efficacy and safety of conversion from long-acting ESA (Mircera) to vadadustat TIW for the maintenance treatment of anemia in hemodialysis patients. Following a Screening period of up to 8 weeks (56 days), subjects who meet all inclusion and none of the exclusion criteria will be randomized 1:1:1 to vadadustat 600 mg TIW, vadadustat 900 mg TIW, or to remain on Mircera according to the dialysis center's protocol.

Randomization will be stratified by dialysis organization:

Following randomization, there will be 2 periods during the study:

- **Conversion and Maintenance Period (Weeks 0 to 52)**: conversion to vadadustat TIW or to remain on Mircera (Weeks 0 to 20). There will be a primary efficacy evaluation period (Weeks 20 to 26) and a secondary efficacy evaluation period (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) either in person or via telephone.

5.2 Scientific Rationale for Study Design

This study will evaluate the efficacy and safety of dose conversion from a long-acting ESA (Mircera) to TIW vadadustat for the maintenance of treatment of anemia in hemodialysis patients. Numerous studies have demonstrated that hemodialysis subjects requiring higher ESA

doses to treat their anemia have a higher burden of comorbidities, a more inflammatory state, and a greater risk of adverse outcomes (Besarab 1998; Parfrey 2005; Unger 2010). As described above (Section 3.4) in a Phase 2 hemodialysis study (CI-0011), a post-hoc analysis suggested higher pre-baseline ESA doses were associated with lower observed mean Hb levels. Subjects on higher pre-baseline ESA doses may benefit from a higher starting dose of vadadustat after initial conversion from ESAs.

In this study, Mircera was chosen as an active comparator as it is a long-acting Continuous EPO Receptor Activator (CERA) and therefore can be administered less frequently than short- and middle-acting ESAs, while maintaining equivalent efficacy for the treatment of anemia in patients with CKD (Biggar, 2017; Davey, 2018; Mircera USPI 2018; Palmer, 2014). Patients receiving CERA required less frequent ESA administration, demonstrated smaller decreases in Hb levels, and were less likely to require an ESA dose during hospitalization. Overall, CERA showed comparable clinical performance to shorter-acting ESAs while reducing dose frequency in CKD patients receiving hemodialysis (Davey et al, 2018).

This is particularly relevant in the current medical and regulatory climate given the accumulating study findings that resulted in the FDA revising the prescribing information for the currently marketed ESAs. These study 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 the US, the mortality and CV risks associated with ESAs are outlined in a black-box warning in the prescribing information of ESAs, with a recommendation to use the lowest dose possible to avoid transfusions. While no similar major warnings exist in the European Union (EU) Summary of Product Characteristics (SmPC), there is caution suggested with use of ESAs, and recommendation to keep Hb levels below 12.0 g/dL. Clinical practice guidelines (Locatelli 2013) recommend that risk factors for stroke and malignancy should also be taken into account when making treatment decisions to use ESAs for the treatment of anemia.

5.3 Justification for Dose

In this trial, 2 different vadadustat starting doses will be explored. The starting doses of vadadustat will be 600 mg TIW and 900 mg TIW in subjects converting from Mircera. The dose range for titration is 300 to 1200 mg TIW. Vadadustat 750 and 900 mg QD as titration doses are being studied in an ongoing Phase 2b trial in DD-CKD subjects and as fixed doses in an ongoing Phase 1b trial, DD-CKD subjects. In prior studies, there was minimal accumulation of vadadustat with repeated dosing of up to 900 mg. Given that the half-life of vadadustat in dialysis patients is approximately 8 to 10 hours and the interval between doses will be a minimum of 48 hours (approximately 5 times the half-life), it is expected that during TIW dosing, vadadustat will be eliminated from the systemic circulation without accumulation before the subsequent dose. Therefore, the exposures with 1200 mg single dose is likely to be similar to 1200 mg TIW. Further, per total weekly dosing, 1200 mg TIW (3600 mg/week) is a lower dosing regimen compared to 900 mg QD (6300 mg/week). The starting doses and the proposed vadadustat Dosing and Dose Algorithm (Appendix 1) in this study are designed to maintain Hb in a predictable and controlled manner while minimizing abrupt increases or excessive rises in Hb levels. Based on plasma concentrations and PD measures from previously conducted clinical studies with vadadustat, a population PK/PD model was developed. Using this model and the proposed dosing algorithm, simulations were carried out to evaluate the effects of different starting doses and the resulting Hb responses to support the dosing rationale. Results of the

simulations indicated that the starting doses of 300 and 450 mg QD along with the proposed dosing algorithm are optimal to maintain Hb levels of 10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL outside of the US while minimizing excessive rises. The daily dose of 300 mg equates to a weekly dose of 2,100 mg. That weekly dose would equate to 700 mg TIW. The daily dose of 450 mg equates to a weekly dose of 3,150 mg. That weekly dose would equate to 1050 mg TIW. For dosing simplicity, a single dose strength of 300 mg is being used in this study. Therefore, 600 mg TIW (maximum weekly dosing of 1800) and 900 mg TIW (maximum weekly dosing of 2700 mg) were selected as starting doses for this study.

Hb monitoring, a dose adjustment algorithm (Section 7.1.2 and Appendix 1), 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 8 and thereafter every 4 weeks.
- The dose adjustment algorithm will target a narrow Hb range, 10.0 to 11.0 g/dL.
- 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.

5.4 End of Study Definition

Study Completion

The study will be considered completed after all randomized subjects have completed their final study visit (Week 52/or ET and Safety Follow-Up at Week 56).

Subject Completion

A subject will be considered as having completed the study after completion of their final study visit (Week 52, Safety Follow-Up at Week 56).

5.5 Number of Study Sites

Approximately 50 investigative sites in the US at outpatient hemodialysis center.

5.6 Subject Input on Study Design

No subject input was obtained on the study design.

6.0 STUDY POPULATION

6.1 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. ≥18 years of age.
2. Receiving chronic, outpatient in-center hemodialysis TIW for end-stage kidney disease for at least 12 weeks prior to SV1.
3. Currently maintained on Mircera (≤250 μg/month) with at least 2 doses received within 8 weeks prior to SV2.
4. Mean screening Hb between 8.5 and 11.0 g/dL (inclusive), as determined by the average of 2 Hb values measured by the central laboratory at least 4 days apart between SV1 and SV2.
5. Serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20% during Screening.
6. Folate and vitamin B_{12} measurements ≥ lower limit of normal during Screening.

6.2 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Anemia due to a cause other than CKD (e.g., sickle cell disease, myelodysplastic syndromes, bone marrow fibrosis, hematologic malignancy, myeloma, hemolytic anemia, thalassemia, or pure red cell aplasia).
2. Clinically meaningful bleeding event in opinion of investigator within 8 weeks prior to Baseline.
3. RBC transfusion within 8 weeks prior to Baseline.
4. Having received any doses of darbepoetin alfa (Aranesp®) within 4 weeks prior to Baseline.
5. Having received any doses of epoetin alfa (Epogen®) within 1 week prior to Baseline.
6. Anticipated to discontinue hemodialysis during the study.
7. Judged by the Investigator that the subject is likely to need rescue therapy (ESA administration or RBC transfusion) immediately after enrollment in the study.
8. History of chronic liver disease (e.g., chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver).
9. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), or total bilirubin >2 x upper limit of normal (ULN) during Screening. Subjects with a history of Gilbert's syndrome are not excluded.
10. Current uncontrolled hypertension as determined by the Investigator that would contraindicate the use of an ESA.
11. Acute coronary syndrome (hospitalization for unstable angina or myocardial infarction), surgical or percutaneous intervention for coronary, cerebrovascular or peripheral artery disease (aortic or lower extremity), surgical or percutaneous valvular replacement or repair, sustained ventricular tachycardia, hospitalization for HF or New York Heart Association Class IV HF, or stroke within 12 weeks prior to or during Screening.
12. History of new, active 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 treated cervical carcinoma in situ are not excluded.
13. History of deep vein thrombosis or pulmonary embolism within 12 weeks prior to or during Screening.
14. History of hemosiderosis or hemochromatosis.
15. History of prior organ transplantation (subjects with a history of failed kidney transplant or corneal transplants are not excluded).
16. 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.
17. History of a prior hematopoietic stem cell or bone marrow transplant (stem cell therapy for knee arthritis is not excluded).
18. Known hypersensitivity to vadadustat, Mircera, or any of their excipients.
19. Use of an investigational medication or participation in an investigational study within 30 days or 5 half-lives of the investigational medication (whichever is longer), prior to Screening (subjects may participate in another concurrent study only if that study is a non-interventional, observational investigation).
20. Current exposure to any HIF-PH inhibitor or prior exposure to vadadustat.
21. Subjects with bilateral native nephrectomy.
22. Noncompliance with dialysis session attendance defined as missing more than 1 dialysis session within 8 weeks prior to Baseline.
23. Active Severe Acute Respiratory Syndrome-Related Coronavirus (SARS-CoV-2) during Screening.
24. Females who are pregnant or breastfeeding during Screening or are planning to become pregnant and breastfeeding during the study period, and for 30 days after the final study drug administration.
25. Women of childbearing potential who are unable or unwilling to use 2 acceptable methods of contraception* starting at Screening, throughout the study period and for 45 days after the final study drug administration.
26. Female subjects of childbearing potential who plan to donate ova during the study, and for 30 days after the last dose of study drug.
27. Non-vasectomized male subjects who are unable or unwilling to use an acceptable method of contraception* from time of first dose of study drug until 30 days after the last dose of the study drug.
28. Male subjects who plan to donate sperm during the study and for at least 30 days after the last dose of study drug.
29. Any other reason, which in the opinion of the Investigator, would make the subject not suitable for participation in the study.

**Acceptable forms of contraception include:*

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

6.3 Screen Failures and Retesting/Rescreening

Subjects who fail to qualify for the study based on laboratory tests may be considered for rescreening at the discretion of the Investigator if it is considered that the subject's status has

changed, and the subject may now qualify for the study. 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. Rescreened subjects should be assigned a new subject number.

Subjects who initially fail to qualify for the study based on laboratory test results may be retested once for each laboratory parameter within the 8-week Screening Period, per Investigator discretion.

7.0 STUDY INTERVENTION

7.1 Study Intervention(s) Administration

7.1.1 Study Intervention Description

A multi-center, randomized, open-label, active-controlled study of the efficacy and safety of conversion from long-acting ESA (Mircera) to vadadustat TIW for the maintenance treatment of anemia in hemodialysis patients. Following a Screening period of up to 8 weeks (56 days), subjects who meet all inclusion and none of the exclusion criteria, Mircera will be discontinued and subjects will be randomized 1:1:1 to vadadustat 600 mg TIW, vadadustat 900 mg TIW, or to remain on Mircera according to the dialysis center's protocol.

Randomization will be stratified by dialysis organization:

The minimum dose of vadadustat will be 300 mg TIW and the maximum dose will be 1200 mg TIW.

Following randomization, there will be 2 periods during the study:

- Conversion and Maintenance Period (Weeks 0 to 52): conversion to vadadustat TIW or to remain on Mircera (Weeks 0 to 20). There will be a primary efficacy evaluation period (Weeks 20 to 26) and a secondary efficacy evaluation period (Weeks 46 to 52).
- Safety Follow-up Period (ET and Follow-Up): post-treatment safety follow up visit (ET/EOT +4 weeks) either in person or via telephone.

7.1.2 Dosing and Administration

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

Dosing will be initiated at Baseline and the first dose of vadadustat will be administered at the hemodialysis unit after other Baseline procedures have been completed. Thereafter, vadadustat is anticipated to be administered at the hemodialysis unit. Subjects may take vadadustat with or without food and will be instructed to swallow the tablet(s) whole. Subjects are to take vadadustat at roughly the same time each day.

Mircera will be administered IV at the hemodialysis unit based on according to the dialysis center's protocol.

Note: For all subjects, it is recommended that no additional ESA doses will be administered after SV2 after the subject has met all eligibility criteria and before Baseline. For all subjects, it is required that a minimum of 14 days be observed between the last dose of Mircera and the

Baseline visit. If an ESA other than Mircera was administered during the Screening period, the subject will be a screen failure.

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

For subjects who are randomized to the Mircera treatment arm, the initial dosing regimen in the study (starting from Baseline) will be according to the dialysis center's protocol. The timing of randomization should align with next anticipated dose of Mircera.

Study Drug Guidelines for Dose Adjustment

Dose adjustments will be guided by central laboratory Hb concentrations throughout the study to determine if vadadustat or Mircera doses will be adjusted, interrupted, or maintained. Mircera dosing will be based on standard of care laboratory measures according to the dialysis center's protocol.

Guidelines for vadadustat dose adjustment are as follows (see Appendix 1):

- Dose adjustments are based on the Investigator's clinical discretion, incorporating the protocol guidance below as well as the subject's current Hb level, trajectory, and variability; symptoms; CV risk; and other features of his/her clinical condition(s).
- If a dose increase or decrease is required to achieve and maintain Hb levels within the target range of 10.0 to 11.0 g/dL inclusive, dose is adjusted by 1 dose level (vadadustat 300 mg).
- A one-time dose increase after the first 2 weeks of dosing after randomization is allowed. Thereafter, in general, do not increase the dose more frequently than once every 4 weeks.
    - A subject's dose may be increased by 1 dose level (300 mg TIW) if the subject has a decline in Hb ≥0.5 g/dL from Baseline in the first 2-week period (the initial period from Baseline to Week 2 following conversion from Mircera) and if Hb is <10.0 g/dL.
- Reduce the dose in the setting of a 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).
- Reduce the dose in the setting of Hb >11.0 g/dL.
- Interrupt the dose in the setting of a Hb >12.0 g/dL until Hb value falls below 11.0 g/dL. After Hb falls below 11.0 g/dL, restart study drug at a lower dose.

The minimum dose of vadadustat will be 300 mg TIW (1 tablet TIW) and the maximum dose will be 1200 mg TIW. Subjects whose dose of vadadustat is interrupted due to elevated Hb will continue in the study. Unless contraindicated, treatment will be resumed whenever possible and assessed at every visit following study drug interruption.

Mircera will be administered as standard of care. Dose adjustments will be made according to the dialysis center's protocol.

7.1.3 Study Medication Stopping Rules for Liver Function Test Changes

Vadadustat must be permanently discontinued if a subject meets 1 of the following criteria:

- ALT or AST >3x ULN and total bilirubin >2x ULN

- ALT or AST >3x ULN and international normalized ratio (INR) >1.5
- ALT or AST >8x ULN
- ALT or AST remains >5x ULN over 2 weeks (re-challenge generally should be avoided with ALT or AST >5x ULN unless there are no other good therapeutic options)
- ALT or AST >3x ULN with symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain, fever, rash) or eosinophilia

See Section 9.11 for reporting requirements related to a subject being permanently discontinued based on meeting the laboratory abnormalities listed above.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 Acquisition and Accountability

Vadadustat for oral administration will be provided and shipped by the Sponsor.

The investigator or designated study personnel will be responsible for preparing vadadustat for dispensing to the subject and for vadadustat supply accountability.

Mircera will be supplied by the dialysis unit which will be also responsible for mircera supply accountability.

Refer to the Pharmacy Manual for additional details.

7.2.2 Formulation, Appearance, Packaging and Labeling

Vadadustat will be provided as 300 mg oval, yellow tablets debossed with “VDT” on 1 side and “300” on the other side for oral administration. The tablets will be packaged in high-density polyethylene bottles with child-resistant closures, polypropylene liner, and induction seal. Labeling will be in accordance with current Good Manufacturing Practices (GMP) and local regulatory requirements.

7.2.3 Product Storage and Stability

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

7.2.4 Preparation

Not applicable.

7.3 Measures to Minimize Bias: Randomization and Blinding

Subjects will be randomized 1:1:1 to vadadustat 600 mg TIW, vadadustat 900 mg TIW, or to remain on Mircera.

Randomization will be stratified by dialysis organization:

This will be an open-label study. Treatment assignment will be done through a validated electronic system. The Investigator, Sponsor, and contract research organization (CRO) study teams will not be aware of which treatment will be assigned next. Treatments will be

administered in an open-label fashion. The sponsor and CRO study teams will be blinded to 'by treatment' aggregated analyses except for the unblinded statistician.

7.4 Study Intervention Compliance

Subjects will take the dose of study drug on dialysis days. If a dose is forgotten, the missed dose will not be replaced.

Subjects will be questioned on whether they have experienced any problems related to the dosing of study medication.

7.5 Concomitant Therapy

7.5.1 Erythropoiesis-stimulating Agents

Co-administration of any ESA with vadadustat is prohibited. In the setting of ESA rescue therapy, the initial dose of ESA rescue therapy may be administered on the same day as the last vadadustat dose prior to vadadustat dose interruption (Section 7.5.5.2) if deemed medically necessary at the discretion of the Investigator. Guidelines for ESA administration as rescue therapy are provided in Section 7.5.5.2. All efforts will be made to avoid inadvertent administration of ESAs resulting from adherence to ESA hemodialysis center protocols (e.g., ESA protocols for patients on hemodialysis). If ESA is inadvertently administered to subjects actively receiving vadadustat treatment, vadadustat treatment will be stopped and the event will be reported as a protocol deviation.

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

7.5.2 Iron Supplementation and Phosphate Binders

Investigators will prescribe iron supplementation (IV, oral or intradialytic) as needed throughout the study to maintain ferritin and TSAT according to the Schedule of Activities (SoA) (Section 1.3). The use of iron-based phosphate binders (e.g., 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 and phosphate binders to reduce the bioavailability of vadadustat, the trial medication is not to be administered concurrently with an oral iron supplement (including multivitamins containing iron), iron-containing phosphate binders, non-iron-containing phosphate binders, or any oral medications containing iron.
Subjects will be instructed to take any non-iron-containing phosphate binders with a meal at least 2 hours before or 1 hour after the dose of vadadustat. Subjects will be instructed to take iron-containing supplements and phosphate binders at least 1 hour after the dose of vadadustat.

Investigators will prescribe IV iron as needed with dosing according to the dialysis center's protocol. Iron supplementation details will be captured in the appropriate electronic case report form (eCRF).

7.5.3 OATP1B1/1B3 Substrates (eg, Statins)

Investigators should adjust the dose of these concomitant medication as follows:

- Simvastatin, maximum daily dose of 20 mg.
- Rosuvastatin, maximum daily dose of 10 mg.

7.5.4 Sulfasalazine, Other Breast Cancer Resistance Protein Substrates, and Probenecid

Exposures to sulfasalazine (moderately) and mesalamine (mildly) were increased with co-administration of vadadustat based on a study in healthy adults. In subjects taking vadadustat, sulfasalazine and other clinically relevant substrates of the breast cancer resistance protein (BCRP) transporter (e.g., sulfasalazine, methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, topotecan, tenofovir, glecaprevir, pibrentasir, or sofosbuvir), caution should be taken during the study.

Probenecid, an inhibitor of UDP-glucuronosyltransferase (UGT) and the organic anion transporter (OAT)1/3 transporters, increased vadadustat area under the curve and is prohibited during the study

7.5.5 Rescue Medicine

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

7.5.5.1 Red Blood Cell Transfusion

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

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

7.5.5.2 Erythropoiesis-stimulating Agent Use

ESA Rescue administration will be allowed when medically necessary at the discretion of the Investigator or if a subject is hospitalized. 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 <9.0 g/dL, and ESA rescue will be stopped when Hb ≥9.5 g/dL. ESA therapy will be administered using an approved ESA and dosing as per the local institution's guidelines and per the approved product label.

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

- 2 days after last dose of epoetin alfa

- 7 days after last dose of darbepoetin alfa
- 14 days after last dose of methoxy polyethylene glycol-epoetin beta (Mircera)

Following ESA administration, vadadustat will be resumed at the same dose as previously used or one dose higher and adjusted according to the dose adjustment algorithms (Section 7.1.2 and Appendix 1) at the discretion of the Investigator.

Reasons for ESA Rescue use will be captured in the appropriate eCRF.

8.0 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Intervention

8.1.1 Temporary Interruption of Study Drug

During the study, a subject may interrupt vadadustat for any of the following reasons:

- AE
- Missed hemodialysis visit
- Investigator's discretion
- Rapid rise in Hb (defined in Section 7.1.2)
- Hb above 11.0 g/dL
- ESA use

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

8.1.2 Permanent Discontinuation of Study Medication

Subjects who permanently discontinue study medication prior to study completion will not continue in the study. These subjects are to have their ET visit at the time of permanently discontinuing study medication and perform a 4-week safety follow-up after ET visit.
Subjects may permanently discontinue study medication for any of the following reasons:

- AE
- Investigator's discretion
- Subject withdrawal of consent
- Lack of efficacy
- Lost to follow up despite reasonable efforts by the Investigator to locate the subject
- Death
- Other reasons (pregnancy, kidney transplantation, specific reasons to be documented by the Investigator)

Lack of efficacy is defined as an inadequate response to vadadustat in the Investigator's opinion.

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

8.1.3 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.
Details on the withdrawal of consent from the pharmacogenomic (PGx) assessment and/or optional future biospecimen research (FBR) substudy are provided in the informed consent form (ICF).

8.1.4 Entire Study Termination

The entire study may be suspended or terminated by the Sponsor for safety or other unanticipated reasons or upon request of regulatory agencies. Criteria for premature termination or suspension of the study are detailed in Section 11.8.1.

8.1.5 Individual Study Site Termination

Study participation may be suspended or terminated at an individual investigational site for various reasons. Criteria and procedures for premature termination or suspension of an investigational site are detailed in Section 11.8.2.

8.1.6 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject‘s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator may search publicly available records to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9.0 STUDY ASSESSMENTS AND PROCEDURES

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

9.1.1.1 Informed Consent

Informed consent must be obtained prior to the subject entering into the study and before any protocol-directed procedures are performed (including Screening activities). Additionally, subjects may be asked to provide a separate, optional consent to obtain and store a blood sample(s) for future research.

This study includes 2 screening visits (SV1 and SV2).

9.1.2 Treatment Period

The treatment period of this study includes the following visits:

- A Baseline/randomization visit
- A 52-week treatment period

9.1.3 End of Treatment Visit

Subjects completing the study will undergo a final Week 52 EOT visit according to the SoA (Section 1.3).

9.1.4 Safety Follow-up

The safety follow-up will be conducted 4 weeks after the EOT visit, or 4 weeks after the last dose of study medication for ET.

9.2 Clinical Assessments

The following clinical evaluations will be conducted during the course of the study. If the evaluations will occur on a hemodialysis day, the clinical evaluations should be completed before dialysis, if applicable.

9.2.1 Medical History, Demographics, and Physical Examination

Medical history, demographic information, and physical examination (including height) will be collected according to the SoA (Section 1.3). 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.

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

9.2.2 Vital Sign Measurements

Predialysis temperature, heart rate, blood pressure, respiratory rate, and weight 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.

Dry weight will be collected for all subjects per site standard of care according to the SoA (Section 1.3).

9.2.3 Dialysis Adequacy

Dialysis adequacy, as available from local collection, will be recorded in the eCRF.

9.2.4 Dialysis Treatment

Hemodialysis vascular access type use at baseline; and changes in renal replacement therapy (from in-center hemodialysis) throughout the trial.

9.3 Efficacy Assessments

The primary efficacy endpoint is mean change in Hb between Baseline (average pretreatment Hb) and the primary evaluation period (average Hb from Weeks 20 to 26, inclusive). Laboratory evaluations of Hb levels will be conducted according to the SoA (Section 1.3) and are described in Section 9.4.

9.4 Laboratory and Other Assessments

The following safety and other assessments will be conducted during the course of the study, according to the SoA (Section 1.3).

Samples for laboratory assays will be sent to a central laboratory for analysis. Detailed instructions for the collection, processing, and shipment of laboratory samples will be provided by the sponsor and the central laboratory. If blood is collected on a 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 following laboratory evaluations listed below and will be conducted during the course of the study. For details regarding the timing of these assessments refer to Section 1.3.

- Pregnancy Test: A serum pregnancy test will be performed according to the timepoints in the SoA (Section 1.3) for females of childbearing potential. Additional serum or local urine (if possible) pregnancy tests may be conducted throughout the study in sufficient number, as determined by the investigator to establish the absence of pregnancy during the study. These results must be available and must be negative before the subject takes the first dose of study medication.
- PK Evaluations (samples to be drawn only for subjects randomized to vadadustat): Plasma samples for PK evaluation will be collected to analyze for both the parent compound

(vadadustat) and its metabolites. Collection time points for PK will be obtained according to the SoA (Section 1.3). Vadadustat should be dosed prior to the start of dialysis. The predose PK 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 trial medication will be recorded in the eCRF and the start and stop time of the dialysis session will be recorded in the eCRF. The date and time of dose and PK samples will be recorded in eCRF.

  - 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.

- Laboratory Evaluations: Blood samples for laboratory analysis will be obtained according to the SoA (Section 1.3) and are specified in Table 3.

Table 3 Protocol Required Laboratory Assessments

Complete Blood Count	**Iron Indices**	**Serum Chemistry**
Hb hematocrit RBC MCV MCH MCHC platelets RDW Differential WBC • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	Ferritin Iron TIBC TSAT **Lipid Profile** Total cholesterol LDL HDL Trigylcerides **Liver Function Tests**	Sodium Potassium Bicarbonate Chloride Calcium Magnesium Phosphorus Glucose Creatinine BUN CPK Uric acid Albumin Total Protein
Additional Laboratory Tests	Total bilirubin ALP ALT/SGPT AST/SGOT LDH	[redacted] **Coagulation Tests[b]**
β-HCG Reticulocyte count[a] Folate Vitamin B12 CRP Erythropoietin		PT PTT INR

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 ration; LDH: lactate dehydrogenase; LDL: low density lipoprotein; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; PTT: partial thromboplastin 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; VEGF: vascular endothelial growth factor; WBC: white blood cell.

a. An automated reticulocyte count should include both absolute and percent
b. The coagulation tests will be performed for unscheduled visits only.

[redacted]

[redacted]

9.6 Pharmacodynamic Assessments

Blood samples for EPO, reticulocytes, and iron indices (ferritin, iron, TIBC, and TSAT) analysis will be collected according to the SoA (Section 1.3). Blood samples will be collected and processed according to the Operations/Laboratory Manual. For all PD sampling, the time of the previous dose of trial medication is to be recorded in the eCRF and the timing of administration of trial medication and the start and stop time of the dialysis session will be recorded in the eCRF.

9.7 Pharmacogenomic Assessments

9.7.1 Pharmacogenomic Samples

A separate informed consent will be required to authorize the collection of PGx samples. PGx samples will be collected from consenting subjects according to the SoA (Section 1.3). Blood samples will be collected and processed according to the Operations/Laboratory manual. The date and time of samples collected for PGx analysis will be recorded. All PGx samples will be shipped to the PGx laboratory for analysis. Information will be provided in the Operations/Laboratory Manual.

[redacted]

[redacted]

9.10 Safety and Other Assessments

9.10.1 Adverse Event Assessments

AE collection will begin from time of signing of the Informed Consent Form (ICF) through Safety Follow-up Visit. The investigator and study personnel will review each subject's laboratory and clinical evaluation findings and query the subject directly regarding AEs (see Section 9.11.1.1). 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.

9.10.2 Concomitant Medication Recording

All medications (both prescription and non-prescription, and including vitamins, herbals, topicals, inhaled, and intranasal), taken during the screening period and throughout the study, ending at the final protocol required visit, should be recorded on the appropriate eCRF. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single-use or as-needed medication use. All medications and treatments, including vitamin supplements, over-the-counter medications and oral herbal preparations must be recorded in the eCRFs. Heparin injections or saline flushes, are not required to be recorded unless relevant for an AE or SAE, however other concomitant medications administered in the dialysis unit will be recorded. In addition, the ESA, blood transfusion, and iron treatment regimen prior to randomization and date of last dose will be recorded.

9.10.3 Therapeutic Phlebotomy

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

9.11 Adverse Events and Serious Adverse Events

9.11.1 Definitions of Adverse Events and Serious Adverse Events

9.11.1.1 Adverse Events

For the purposes of this study, an AE is any untoward medical occurrence (including an abnormal laboratory finding) that occurs in the protocol-specified AE reporting period; the event does not necessarily have a causal relationship with that treatment or usage.

An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with pre-existing underlying conditions that were not present prior to the AE reporting period. In addition, any worsening of a pre-existing condition that occurs during the protocol-specified AE reporting period is also considered an AE and will be captured as "worsening" of pre-existing condition

AEs therefore include the following:

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

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

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

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

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

Device related events (failures/malfunctions) should not be reported as AEs; however, the etiology or complication associated with the device failure/malfunction should be reported if it meets the definition of an AE.

Pre-existing Conditions – In this study, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical

examination form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

Abnormal Test Findings – All laboratory test results will be reviewed by the Investigator. The Investigator will utilize his/her judgment in determining if out-of-range laboratory values are clinically significant and will denote this using the abbreviation "CS" on the laboratory report for source documentation. Laboratory tests that are labeled as clinically significant should be reported as AEs, either separately or as part of a description of a symptomatic AE. If there are significant changes in a laboratory report from a previous visit that are determined to be clinically significant, these should also be reported as AEs. Any abnormal laboratory value which requires treatment or further diagnostic testing and/or results in discontinuation from study should be reported as an AE. An expected laboratory abnormality from a condition that is part of the medical history is not considered clinically significant for the purposes of the study unless it represents a worsening of the condition.

Abnormalities in ALT, AST, and Total Bilirubin – Abnormalities in ALT, AST, and total bilirubin should be reported to the Sponsor's Medical Monitor or CRO designee within 24 hours of awareness as an SAE with 'other medically important event' criteria selected, if the following conditions are met:

- New elevation in ALT or AST >3 x ULN

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

- Temporary discontinuation of study medication;
- 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;
- Study 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 Section 7.1.3.

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

Transplantation – During this long-term study, it is anticipated that some subjects may receive a kidney transplant. These events will not be recorded as AEs. Subjects will discontinue study medication for receipt of a kidney, other solid organ, hematopoietic stem cell or bone marrow transplant and should continue with the SoA and safety assessments as described in Section 8.1.2.

Malignancy – During this long-term study, some subjects may develop a newly diagnosed malignancy or a recurrence of a malignancy. At the discretion of the Investigator, these subjects may continue study medication. For reporting of AEs of malignancy, see Section 9.11.1.2.

9.11.1.2 Serious Adverse Events

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

- Death
- Life-threatening (see below for definition)
- In-patient hospitalization or prolongation of existing hospitalization (see paragraph below on hospitalization)
- Persistent or significant disability/incapacity (see paragraph below on disability)
- Congenital anomaly/birth defect
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject, or may require medical or surgical intervention to prevent one of the criteria listed in this definition.

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

- Malignancies – Newly diagnosed malignancies or a recurrence of a malignancy should be reported as an SAE with the seriousness criterion "medically important" if no other seriousness criteria are met. However, if a subject develops basal cell carcinoma of skin, squamous cell carcinoma of skin, or cervical carcinoma in situ during the study, or has worsening of these events from Baseline, the Investigator will determine if the event is reported as an AE or SAE.

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

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

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

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

9.11.2 Classification of an Adverse Event

9.11.2.1 Severity of Event

The Investigator will assess each AE as either mild, moderate, or severe using the following guidelines to describe the maximum severity of the AE:

- Mild: Does not interfere with subject's usual function
- Moderate: Interferes to some extent with subject's usual function
- Severe: Interferes significantly with subject's usual function

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

9.11.2.2 Relationship to Study Intervention

The causal relationship of the AE to vadadustat or Mircera will be assessed by both the Investigator and the Sponsor.

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

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

The causal relationship of the AE is assessed using a binary system, and AEs are classified as either ‘related’ or ‘unrelated’;

- Related: There is ‘reasonable possibility’ that the drug caused the AE. The AE follows a reasonable temporal sequence from the time of drug administration. There is supportive evidence (facts) to suggest a possible causal relationship, irrespective of the degree of certainty between the observed AE and the drug.
- Unrelated: An AE does not follow a reasonable temporal sequence from administration of the product and/or there is no reasonable possibility that the drug caused the AE. This assessment includes situations where the AE is related to other factors such as the subject’s clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

Default assessments using the ‘related’ category without supportive evidence for a causal relationship to study medication is generally uninformative and do not contribute meaningfully to the development of the safety profile of the drug or to subject protection.

Investigators are encouraged to choose the most plausible cause for the event(s) from the following list: medical history, lack of efficacy/worsening of treated condition, study medication, other treatment (concomitant, or previous), withdrawal of study medication, administration error, protocol-related procedure, others (specify).

9.11.2.3 Expectedness

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event exceeds the risk information previously described for the study intervention as described in the current Investigator's Brochure.

9.11.3 Time Period and Frequency for Event Assessment and Follow-up

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

9.11.4 Adverse Event Reporting

9.11.5 Reporting Period

AE collection will begin from time of signing of the Informed Consent Form (ICF) through Safety Follow-up Visit.

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

9.11.6 Reporting Adverse Events

All AEs (serious and non-serious) are to be reported on the AE eCRFs.

9.11.7 Serious Adverse Event Reporting

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

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

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

Information about all SAEs (either initial or follow-up information) should be collected and recorded in English on the electronic SAE Report Form within the EDC system. The Investigator must provide an assessment of causality (relationship to study drug) for all events reported at the time of the report. 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/or death certificates are to be obtained, if possible.

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

The Investigators are responsible for submitting required safety information to their local Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as per local regulations. This information includes, but is not limited to, any safety alert letter received from the Sponsor and any SAEs occurring at their investigative site.

9.11.8 Events of Special Interest

The following are considered to be AESIs for this study:

- malignancy including renal cell carcinoma (see Section 9.11.1.2)
- elevation in ALT or AST >3 x ULN (see Section 9.11.1.2)
- hepatotoxicity
- worsening of hypertension
- pulmonary hypertension
- thrombotic events
- congestive HF
- adrenal disorders

Reporting and classification of these events as SAEs (see Section 9.11.1.2) will be as per usual practice.

9.11.9 Follow-up of Unresolved Events

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

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

9.11.10 Reporting of Pregnancy

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

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

If any subject becomes or is found to be pregnant while receiving a study medication or within 30 days of discontinuing the study medication, the pregnancy must be recorded on the Pregnancy Reporting Form/Exposure in Utero Form in the validated electronic system within 24 hours of awareness of the pregnancy or the investigator will call the CRO SAE hotline within 24 hours of being made aware of the pregnancy.

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

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

The investigator will follow the subject (or female partner of a male subject) until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for classification as an SAE (i.e., 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 study medication should also be reported.
- In the case of a live birth, the “normality” of the newborn can be assessed at time of birth.
- The “normality” of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

9.12 Special Situations

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

- Medication error involving the medicinal product (with or without subject exposure to the sponsor’s medicinal product [e.g., name confusion])

- Drug-drug interaction.
- Overdose (see Section 9.12.1)

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.

9.12.1 Treatment of Overdose

Overdose of the medicinal product is a category of Special Situations:

- Mircera overdose – The United States Prescribing Information (USPI) should be referenced for information on Mircera 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 discontinuation may be implemented as necessary. Withholding subsequent vadadustat doses immediately after a vadadustat overdose should be strongly considered.

  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 (i.e., phlebotomy).
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product

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

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

Not applicable.

10.2 Sample Size Determination

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, Mircera, 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 Mircera). With the 1:1:1 randomization ratio of vadadustat 600 mg TIW, vadadustat 900 mg TIW, and Mircera, approximately 150 subjects in each arm, the noninferiority test will have >90% power with consideration of a 30% drop out rate.

10.3 Populations for Analyses

The following analysis populations will be used in this study:

- Randomized population: defined as all randomized subjects.
- Full analysis population: defined as randomized subjects receiving 1 or more doses of study medication and had at least one post-dose Hb assessment. This population will be analyzed based upon the randomized treatment.
- Per protocol (PP) population: defined as all randomized subjects who received study medication during the primary evaluation period, had at least 1 Hb assessments during the primary evaluation period, and have no protocol deviations affecting the primary endpoint analyses. Protocol deviations leading to exclusion from the PP population will be specified prior to database lock on a blinded basis and recorded in a separate document.
- Safety population: defined as all subjects who received at least 1 dose of study medication. This population will be analyzed based upon the actual treatment received. Subjects who received in error some vadadustat and some mircera (excluding rescue therapy) will be classified by the more frequently received drug.

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

10.4 Missing Data

It is expected that some subjects will discontinue prior to Week 52. The reasons for any missing data will be summarized by treatment arm. Missing Hb values in the primary and secondary evaluation period will be imputed using multiple imputation methods.

10.5 Statistical Analyses

10.5.1 General Considerations

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

mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be tabulated. Summaries will be provided by treatment group within appropriate analysis populations (as defined in Section 10.3) 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 first dose. For other parameters, unless otherwise specified, Baseline will be defined as the last available value prior to the first dose of study medication.

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

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

10.5.2 Analysis of Primary Efficacy Endpoint(s)

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

The primary analysis of the primary endpoint will use the randomized population. Analysis of covariance (ANCOVA) with multiple imputation for missing data will be used to calculate the 95% confidence interval (CI) of the difference in mean change in Hb from baseline to the primary evaluation period between the vadadustat groups and Mircera® control group, with the randomization stratification factor and Baseline Hb as covariates.

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 comparisons of the primary efficacy endpoint: comparison between vadadustat TIW 600 mg versus Mircera and comparison between vadadustat TIW 900 mg versus Mircera.

- Step 1: comparison between vadadustat TIW 900 mg versus Mircera
  If the noninferiority of vadadustat is established in step 1, then move to the step 2;
- Step 2: comparison between vadadustat TIW 600 mg versus Mircera

10.5.2.1 Sensitivity Analyses of Primary Efficacy Endpoint Screening

The following sensitivity analyses will be conducted if necessary:

- Primary analysis will be repeated using the full analysis 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).

- Primary analysis will be repeated with method of mixed model for repeated measures (MMRM).

10.5.3 Analysis of Secondary Efficacy Endpoint(s)

Mean change in Hb between Baseline (average pretreatment Hb) and the secondary evaluation period (average Hb from Weeks 46 to 52, inclusive) 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.

10.5.4 Exploratory Endpoint(s)

A full description of the analyses performed on exploratory endpoints will be provided in the SAP.

10.5.5 Safety Analyses

All analyses of safety data will use the safety population.

10.5.6 Analysis of Adverse Events

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

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent and post-treatment AEs will be summarized by SOC and preferred terms (PT) for each treatment group.

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

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

10.5.7 Remaining Safety Endpoints

The analysis of the safety endpoints will be detailed in the SAP: The analysis of proportion of subjects with Hb >11.0, Hb >12.0, Hb>13.0, or >14.0 g/dL post-Baseline will classify a subject as a "yes" if:

- Any value Hb >11.0 g/dL at any time after Day 1
- Any value Hb >12.0 g/dL at any time after Day 1
- Any value Hb >13.0 g/dL at any time after Day 1
- Any value Hb >14.0 g/dL at any time after Day 1
- Any value Hb <7.0 g/dL at any time after Day 1
- Any value Hb <8.0 g/dL at any time after Day 1
- Any value Hb <9.0 g/dL at any time after Day 1
- Any value Hb <10.0 g/dL at any time after Day 1

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

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

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

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

10.5.8 Baseline Descriptive Statistics

10.5.8.1 Analysis of Demographic and Pretreatment Variables

Descriptive statistics will be generated for demographic and pretreatment variables for each treatment group based on randomized population.

Medical history terms will be coded using the MedDRA and summarized by SOC and PT for each treatment group.

10.5.8.2 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 study medication treatment discontinued from study medication early, and completed or discontinued from the study and reasons for discontinuation will be summarized by treatment group and overall.

10.6 Additional Assessments

10.6.1 Concomitant Medications

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

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

[redacted]

10.6.3 Pharmacokinetic Assessments

Plasma concentrations will be summarized descriptively by dose and analyte, as specified in the SoA (Section 1.3). PK parameters will be summarized descriptively by analyte and dose.

10.6.4 Pharmacodynamic Assessments

The observed and change from Baseline/Day 1 values of all PD (EPO, reticulocytes, and iron indices) assessments will be summarized using descriptive statistics.

[redacted]

10.6.7 Sub-Group Analyses

Analyses of the primary efficacy endpoint and secondary efficacy endpoints will also be performed for subgroups based on the following:

- Age
- Sex
- Race
- Stratification factor: Dialysis Organization

11.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (2013).

In addition, the study will be conducted in accordance with the protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guideline on Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

11.2 IRB and Ethics Committees

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

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

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

11.3 Informed Consent Process

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

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor, auditor, regulatory authorities and/or IRB/Ethics Committees and other applicable individuals upon request.

The ICFs will be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The ICFs used in this study, and any changes made during the course of the study, will be prospectively approved by both the IRB/EC and the sponsor before use.

11.4 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information, as requested, to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.5 Confidentiality and Data Privacy

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of subject personal data.

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

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

11.6 Data Handling and Record Keeping

11.6.1 Data Collection and Management Responsibilities

Data handling and record keeping are detailed in the Pharmacy Manual.

11.6.2 Study Records Retention

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., case report forms (CRFs) and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and

telephone calls reports). The records will be retained by the investigator according to the ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

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

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

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

In addition, the investigator will inform the sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP, defined as a breach that will likely affect the safety or physical or mental integrity of subjects or the scientific value of the trial, that comes to the attention of the investigator.

11.8 Study Discontinuation and Closure

The sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator will contact all participating subjects within a time period specified by the sponsor to inform them of the decision to discontinue the study.

11.8.1 Criteria for Premature Termination or Suspension of the Study

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

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

The sponsor reserves the right to discontinue the study for other valid administrative reasons. If the study has been suspended or terminated, prompt notification will be given to investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

11.8.2 Criteria for Premature Termination or Suspension of Study Sites

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended

termination. Advanced notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator and subsequently provide written instructions for study termination. If the study has been suspended or terminated, prompt notification will be given to Investigators, IRBs, and regulatory authorities in accordance with regulatory requirements.

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

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

11.8.3 Criteria for Premature Termination or Suspension of the Study or Study Sites

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

11.9 Future Use of Stored Specimens and Data

With the subject's approval and as approved by local IRBs, de-identified biological samples will be stored at the biorepository with the same goal as the sharing of data with the biorepository. These samples could be used to research the causes of anemia in subjects receiving hemodialysis in CKD, its complications and other conditions for which individuals with anemia in subjects receiving hemodialysis in CKD are at increased risk, and to improve treatment. The biorepository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each subject, maintaining the blinding of the identity of the subject.
During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the biorepository.

11.10 Key Roles, Committees and Study Governance

Not applicable.

11.11 Safety Oversight

An Independent Data Monitoring Committee (IDMC) will be established to review and discuss the available study data as subjects are enrolled and followed. The IDMC will meet approximately twice per year throughout the course of the study. The IDMC will be unblinded

and will include, at a minimum, 2 physicians and a biostatistician. The discussions of the IDMC will include a review of key safety data (i.e., AEs, vital sign measurements, and laboratory assessments).

AEs and laboratory changes suggestive of possible effects on the liver will be reviewed and adjudicated by a hepatic panel of experts.

11.12 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices [GLP], GMP).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.12.1 Clinical Monitoring

During study conduct, the sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and GCP are being followed. The monitors will review source documents to confirm that the data recorded on the eCRFs is accurate. The investigator/institution will allow the sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject to Quality Assurance audits performed by the sponsor or companies working with or on behalf of the sponsor, and/or review by the IRB, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11.12.2 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not

implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

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

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

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

When one of these deviations from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. If the investigator determines that the deviation impacts the safety of a subject, the investigator must contact the sponsor immediately. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

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

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

12.0 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between sponsor and the investigator and/or the investigator's institution. The sponsor will have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the sponsor as confidential will be deleted prior to submission.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including: Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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